ACUTE POST-EXERCISE CARDIOVASCULAR RESPONSES IN HEALTHY PARTICIPANTS

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ABSTRACT

The overall aim of this project was to investigate the acute cardiovascular post-exercise response in healthy individuals. The aim of the first study was to establish the within day and between day reproducibility of supine and tilt baroreflex sensitivity (BRS) utilising time (sequence) and spectral ($BRS_{\alpha LF}$ and BRS_{TFTG}) indices in 46 healthy adult males employing three repeat measures; baseline, + 60 min and + 24 h. Reproducibility was assessed by the 95% limits of agreement (LOA) to assess the extent of agreement and an alternative approach of estimating the technical error of the measurement (TEM) to assess reproducibility was also undertaken. The LOA indicated same day reproducibility was marginally better than between day reproducibility for spectral parameters while between day reproducibility was marginally better than same day reproducibility for sequence parameters with reproducibility markedly improved across all BRS outcome measures during tilt. Precision expressed by TEM for all spectral outcomes was good in both supine and tilt BRS (< 6 %) although precision was lower, but acceptable, for sequence BRS outcomes in both positions (< 11%). Thus, all BRS outcome measures and the tilt procedure were incorporated into the exercise study. The aim of the second study was to compare the response of supine and tilt BRS following a single bout of moderate intensity exercise and high intensity exercise. Nine healthy adult males, currently undertaking regular chronic exercise training, performed two interval cycle exercise conditions consisting of 40% WR_{max} and 75% WR_{max} of equal work done and a control condition of no exercise. The overall study design included three conditions administered in a counterbalanced order with outcome measures determined pre and post exercise up to + 24 h. R-R interval and BP data was collected over consecutive 10 min periods and analysed by Fast Fourier transformation analysis while participants adopted a supine and tilt position. Sequence and spectral BRS outcome measures were established. A fully repeated measures ANOVA revealed a significant interaction ($p \leq 0.05$) between time and condition in supine for spectral indices $BRS_{\alpha LF}$ (p 0.006) and BRS_{TFTG} (p 0.004) and in tilt for both time indices BRS_{UpUp} (p 0.027) and $BRS_{DownDown}$ (p 0.004) and spectral indices $BRS_{\alpha LF}$ (p 0.001) and BRS_{TFTG} ($p < 0.001$). There were significant differences ($p \leq 0.05$) between all conditions at + 15 min and between control and 75% WR_{max} and between 40% WR_{max} and 75% WR_{max} conditions at + 60 min. At + 15 min BRS was lower in the 75% WR_{max}

condition compared to the 40% WR_{max} condition and the control condition, and the 40% WR_{max} condition was lower than the control condition. No significant differences were found between exercise conditions at baseline, + 120 min, + 180 min and + 24 h and no enhancement in BRS was observed at any time point following exercise. The findings in the present exercise study suggested a possible intensity-dependent relationship in the BRS response following exercise which supported the notion that intensity of exercise may be a determining feature in the acute cardiovascular response following a single bout of exercise. Given the small number of studies that have investigated the BRS response post-exercise, future studies should focus on the time course of the BRS response following exercise, the influence of intensity and duration of exercise and the demographics and fitness of participant groups.

DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of the University of Gloucestershire and is original except where indicated by specific reference to text. No part of the thesis has been submitted as part of any other academic award. The thesis has not been presented to any other education institution in the United Kingdom or overseas.

Any views expressed in the thesis are those of the author and in no way represent those of the University.

Linda Jane Reynolds Date: 27th September, 2013

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ABBREVIATIONS AND ACRONYMS

α	= alpha
acidosis	= increased hydrogen ion concentration
aetiology	= specific causes or origins of disease
aliasing	= where discrete sampling changes the apparent frequency
ANOVA	= analysis of variance
ANS	= autonomic nervous system
AR	= autoregressive
bpm	= beats per minute
BMI	= body mass index
BP	= blood pressure
brpm	= breaths per minute
BRS	= baroreflex sensitivity
$BRS_{\alpha HF}$	= α coefficient in high frequency of baroreflex sensitivity
$BRS_{\alpha LF}$	= α coefficient in low frequency of baroreflex sensitivity
$BRS_{DownDown}$	= sequences of progressive decreases in SBP and shortening of R-R interval
BRS_{TFLF}	= transfer gain of baroreflex sensitivity in the LF band
BRS_{TFTG}	= transfer function/ transfer gain of baroreflex sensitivity
BRS_{UpUp}	= sequences of progressive increases in SBP and lengthening of R-R interval
BRS_{mean}	= the mean of sequences of progressive increases and decreases in SBP and lengthening and shortening of R-R interval
CAD	= coronary artery disease
CHD	= coronary heart disease
CI	= confidence interval
CO_2	= carbon dioxide
CVC	= cardiovascular centre
CVD	= cardiovascular disease
DBP	= diastolic blood pressure
DoH	= Department of Health
ECG	= electrocardiogram

EU	= European Union
FFT	= fast Fourier transform
h	= hour
HF	= high frequency
HR	= heart rate
HR_{max}	= maximum heart rate
HR_{mean}	= mean heart rate
HR_{peak}	= peak heart rate
HRV	= heart rate variability
Hz	= unit of frequency equal to one cycle per second
IHD	= ischaemic heart disease
isodistribution	= estimate of the degree to which observed interactions may be due to random fluctuations (noise) in the data
isospectral	= estimate of the number of observed interactions due to linearly coherent structure of the data
kg	= kilogram
l	= litre
LF	= low frequency
LOA	= limits of agreement
m	= metre
MAP	= mean arterial pressure
MetS	= metabolic syndrome
MI	= myocardial infarction
min	= minute
ml	= millilitre
$ml \cdot kg^{-1} \cdot min^{-1}$	= millilitre per kilogram per minute
mmHg	= millimetres of mercury
mmol	= millimole
mmol/l	= millimoles per litre
ms	= milliseconds
ms/mmHg	= milliseconds/ millilitres of mercury
NHS	= National Health Service
O_2	= oxygen

p	= probability value
pathophysiology	= functional changes that accompany a syndrome or disease
pH	= hydrogen ion concentration: reflecting acidity or alkalinity in which 7 is neutral
pO_2	= partial pressure of oxygen
pCO_2	= partial pressure of carbon dioxide
pH^+	= partial pressure of hydrogen ion concentration
PA	= physical activity
PAD	= peripheral arterial disease
PET	= progressive exercise test
PP	= pulse pressure
PSA	= power spectral analysis
PSD	= power spectral density
$\dot{Q}$	= cardiac output
RPE	= rate of perceived exertion
RRI	= R-R interval
RSA	= respiratory sinus arrhythmia
s	= second
S	= supine
SA	= sinoatrial
SAD	= sino-aortic denervation
SBP	= systolic blood pressure
SD	= standard deviation
SE	= standard error
Seq	= sequence
stochastic	= characterised by a sequence of random variables
SV	= stroke volume
T	= tilt
TEM	= technical error of measurement
time-invariant	= the output does not depend explicitly on time
TPR	= total peripheral resistance
TFTG	= transfer function transfer gain
transmural pressure	= the difference between internal and external pressures

µg	= excretion rate in micrograms
µg/min	= excretion rate in micrograms per minute
UK	= United Kingdom
USA	= United States of America
VLF	= very low frequency
$\dot{V}O_2$	= oxygen uptake
$\dot{V}O_{2peak}$	= peak oxygen uptake
$\dot{V}O_{2max}$	= maximal oxygen uptake
WHO	= World Health Organisation
wk	= week
WR	= work rate
WR_{max}	= maximum work rate
y	= year
<	= less than
≤	= less than or equal to
>	= greater than
≥	= greater than or equal to
%	= percentage

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CHAPTER ONE

INTRODUCTION

CHAPTER 1: INTRODUCTION

Hypertension is a primary risk factor for the metabolic syndrome (MetS) (BHF, 2005) and globally, is a major cause of morbidity and mortality (WHO, 2002). Elevated blood pressure (BP) was responsible for 11% of total disease burden and 13% of total mortality with 7 million premature deaths per annum across the world (WHO, 2002). Due to the global growth of population and ageing, the number of people with uncontrolled hypertension rose from 600 million in 1980 to nearly 1 billion in 2008 (WHO, 2008). On a national scale, approximately one third of adults in England and Scotland have elevated BP and nearly half do not receive treatment (BHF, 2012b). Reduced hypertension is linked to improved health outcomes suggesting a reduction in the status of hypertension in global and national populations could have vast implications for the reduction in the global health burden and in national and regional healthcare provision (WHO, 2002). Importantly, hypertension is a modifiable risk factor which may be prevented or attenuated by lifestyle behaviours (JNCPDETHBP, 2004; Mancia *et al.*, 2007).

One factor associated with the incidence of hypertension is physical inactivity. Early research supported the notion that regular physical activity (PA) and increased fitness was linked with a reduction in the risk for hypertension and cardiovascular diseases and an improvement in BP control (see: sections 2.3; 2.4). Furthermore, the multiple underlying metabolic and structural abnormalities which can accompany hypertension implicated autonomic influences in the causation and progression of the disease (Lever & Boushel, 2000; Somers & Narkiewicz, 2002; Yanai *et al.*, 2008). The autonomic nervous system (ANS) is of particular interest in cardiovascular health related research. The ANS contains two divisions of afferent and efferent nerves comprising of parasympathetic and sympathetic nerves (Hainsworth, 1998; Jordan, 1995; Klabunde, 2005). These nerves innovate the heart and have a key role in the regulation of the cardiovascular system by providing optimal functioning during and following various activities and mediating some indicators for cardiac disease. Improved autonomic regulation following regular PA may enhance vagal tone and reduce sympathetic influence (Buch *et al.*, 2002) having a positive effect on cardiac autonomic status (Billman, 2002; Maron, 2000). Thus because hypertension could be modified by

lifestyle behaviours, one of the major objectives in the prevention and management of hypertension was to reduce levels of physical inactivity (JNCPDETHBP, 2004; Mancia *et al.*, 2007). Physical inactivity was implicated in the causation of ~ 2 million deaths per annum across the world (WHO, 2002). Indeed, due to the role of physical inactivity in the global burden of disease and mortality, the World Health Organisation (WHO) urged countries to provide and adopt national strategies for increased exercise and recommended ≥ 30 min of regular moderate intensity exercise most days of the week (WHO, 2004). In the UK the current public health guidelines are 30 – 60 min of moderate intensity exercise ≥ 5 days/ wk although only ~ 38% of men and ~ 28% of women achieve this level of activity (BHF, 2006, 2012a; Nichols *et al.*, 2012).

Exercise participation is associated with health benefits which include improvements in physiological, metabolic and psychological factors (ACSM, 2006; Kenney & Seals, 1993; Thompson *et al.*, 2001) and reductions in disease incidence, morbidity and mortality (ACSM, 2006; Haskell, 2001; Parr, 2003; Thompson *et al.*, 2003). Thus, exercise and its associated benefits for improved and long term health has become a key message in public health campaigns for clinical and non-clinical populations and, in addition, has a recognised role in rehabilitation strategies for conditions such as cardiovascular disease (CVD) and obesity (BHF, 2012c; DoH, 2000, 2004b). General physiological health benefits include improved BP profile (Kenney & Seals, 1993), improved lipid metabolism (Durstine & Haskell, 1994) and improved glucose tolerance (Kang *et al.*, 1996). Previous exercise recommendations were based around training adaptations thus chronic change with training over time. The current guidelines now recognise there is an acute effect following exercise for a range of different outcomes and these acute effects support the current recommendations for exercise, particularly the need to undertake moderate intensity exercise ≥ 5 days/ wk (ACSM, 2006; DoH, 2004a).

Exercise may be undertaken as a single bout of exercise or as multiple bouts of exercise which accumulate over time to provide a training effect (Haskell, 2001; Thompson *et al.*, 2001). A single bout of exercise provides a transient change in the short term recovery period following the exercise bout while exercise training may elicit tissue and system adaptation via increases in capacity or efficiency (Haskell, 2001), enhancing

exercise scope and permitting more vigorous or more prolonged activity for a greater acute effect (Thompson *et al.*, 2001). Thus the benefits of exercise for health may be achieved by an acute transient effect, a training effect or an interaction between the two effects (Haskell, 2001). The acute response may be augmented via repeated bouts of exercise although any benefits may be fleeting if the exercise is not continued (Haskell, 2001). For example, plasma triglycerides were reduced following a single bout of exercise and further reduced following four consecutive days of exercise (Gyntelberg *et al.*, 1977) but such reduction may be reversed after exercise abstinence of a few days (Oscai *et al.*, 1972).

Physiological beneficial responses following chronic exercise training include reduced lipid profile, increased HDL levels, improved glucose homeostasis and reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Durstine & Haskell, 1994; Thompson *et al.*, 2001). Blood pressure may be reduced following moderate intensity exercise with greater reductions recorded in hypertensive populations compared to normotensive individuals (Fagard, 2001; Hagberg *et al.*, 2000; Whelton *et al.*, 2002). The benefits of exercise usually associated with chronic exercise training may also be achieved following a single bout or several bouts of exercise (Pober *et al.*, 2004) and these include reductions in blood pressure (BP) and plasma triglycerides, increased high density lipids (HDL) and improved glucose homeostasis (Crouse *et al.*, 1997; Durstine & Haskell, 1994; Ferguson *et al.*, 1998; Seals *et al.*, 1997; Thompson *et al.*, 2001). Significant reductions in SBP and DBP acutely following moderate intensity exercise may endure 4 - 13 h in hypertensive individuals while no reduction (Kenney & Seals, 1993; Quinn, 2000; Wallace *et al.*, 1999) or smaller reductions in BP of shorter duration (Forjaz *et al.*, 1998) have been reported in normotensive individuals.

Responses in ANS function following chronic exercise training and a single bout of exercise have been reported (Billman, 2002; Borresen & Lambert, 2008) although full elucidation of the autonomic post-exercise effects has yet to be determined. Chronic exercise training increases vagal tone and reduces sympathetic activity resulting in a slowing of HR at rest and during sub-maximal exercise (Hainsworth, 1998). The assessment of autonomic function has received interest via evidence that links the ANS and cardiac events (Hohnloser & Klingenheben, 1998). For example, alterations in

cardiac autonomic control toward greater sympathetic activity have been associated with increased cardiac arrhythmias and ventricular fibrillation (Billman, 2002; Hartikainen & Camm, 2002) and the risk of sudden cardiac death (Albert *et al.*, 2000; Maron, 2000) and evidence of increased sympathetic outflow have been reported following a single bout of exercise in healthy individuals (Niemelä *et al.*, 2008; Stuckey *et al.*, 2011). Paradoxically, reduced sympathetic outflow with greater vagal tone which is suggestive of improved cardiac electrical stability (Buch *et al.*, 2002; Maron, 2000; Schwartz *et al.*, 1984) has also been reported in healthy individuals following a single bout of exercise (Convertino & Adams, 1991; Pober *et al.*, 2004; Raczak *et al.*, 2005). Increases in parasympathetic activity also reduce resting heart rate (HR) and contractility resulting in economical cardiac workload and reduced myocardial oxygen demand (Raczak *et al.*, 2005). Thus an enhancement in parasympathetic activity following exercise may be considered to provide a cardio-protective effect while conversely increased sympathetic influence may be an indicator for increased cardiac risk. The identification of cardiac autonomic control and the role of the parasympathetic and sympathetic limbs of the ANS in the post-exercise response may provide valuable information regarding the benefits and risks of exercise for health outcomes. The determination of baroreflex sensitivity (BRS) is one method which can be employed to investigate cardiac autonomic control.

Early BRS assessment techniques provided 'spot' quantification of BRS and required external stimulus to the participant which was undertaken in standardised laboratory conditions (Parati *et al.*, 2000). These techniques included invasive procedures and due to the limitations of invasiveness, participant risk and severe interference with neural mechanisms they were discontinued (Parati *et al.*, 2000). The current laboratory techniques employed include intravenous bolus injection of a vasoactive drug and the neck chamber device (Parati *et al.*, 2000) and these techniques have been adopted for clinical and non-clinical research testing.

Some past techniques also incorporated invasive direct arterial measurement of beat by beat blood pressure (BP) thus limiting the scope for research due to participant risk and ethical considerations. The innovation and introduction of a non-invasive system (Finapres/ Portapres) (FMS, Finapres Medical Systems, BV Amsterdam, The

Netherlands) to assess beat by beat BP has provided the opportunity for research of the baroreflex to expand both in and beyond the clinical setting. This system uses servo-plethysmomanometry which employs the volume-clamp technique for measurement of BP at the finger. There is extensive relevant research which provides evidence that the BP values obtained by this method are comparable to intra-arterial BP measurement (Eckert & Horstkotte, 2002; Huang *et al.*, 2000; Imholz *et al.*, 1991; Imholz *et al.*, 1998; Silke & McAuley, 1998) and accurately follow BP oscillations (Parati *et al.*, 1989) thus validating the use of this system for cardiovascular research testing.

Baroreflex sensitivity can be assessed by the reciprocal changes that occur between HR and beat by beat BP. The recording of R-R intervals (ms) and beat by beat BP (mmHg) and subsequent analysis over a specified time period can provide an outcome measure for BRS (ms/mmHg). The recent modern methods for the assessment of BRS are the result of combined computer analysis of continuous HR and BP and do not require any invasive or external intervention to be undertaken by the participant (Parati *et al.*, 2000). BRS is defined through various mathematical models of the cardiovascular system (Di Rienzo *et al.*, 2009). These modern methods may be utilised to assess BRS in both laboratory and daily life conditions and reflect the spontaneous baroreflex i.e. the dynamic features of baroreflex modulation of HR (Parati *et al.*, 1995a; Parati *et al.*, 1996, 2000; Parati *et al.*, 1992). Modes of assessing BRS may be undertaken in the time domain or the spectral domain. Common BRS assessment techniques adopted in recent research include the time sequence technique (BRS_{UpUp} and $BRS_{DownDown}$) and spectral techniques of α coefficient in high frequency (HF) and low frequency (LF) ($BRS_{\alpha HF}$ / $BRS_{\alpha LF}$) and the transfer function transfer gain of BRS (BRS_{TFTG}) (Kuusela, 2007; Parati *et al.*, 2000; Robbe *et al.*, 1987).

The sequence method is based on computer identification in the time domain of ≥ three consecutive beats of either a progressive rise in SBP and the lengthening of R-R interval (+RR/ +SBP sequences) or a progressive decrease in SBP and a shortening of R-R interval (-RR/ -SBP sequences) with a minimal sequence specificity for accepted change of ≥ 1 mmHg for SBP and ≥ 5 ms for R-R interval (Di Rienzo *et al.*, 2001; Hughson *et al.*, 1993; Iellamo *et al.*, 1996; Parati *et al.*, 1988; Parati *et al.*, 2000, 2001; Zöllei *et al.*, 1999). The spontaneous R-R interval/ SBP sequence is based on the joint

incidence of concordant changes in SBP and R-R interval signals (Di Rienzo *et al.*, 2001). The progressive beat-by-beat ramp increases or decreases in SBP are the input to the baroreceptors to be tracked while the concordant progressive ramp changes in R-R intervals reflect the baroreflex response to the SBP input. The index of BRS is taken as the slope of the regression line between linearly related changes between SBP and R-R interval when the coefficient of the determination of the regression between SBP and R-R interval is high (> 0.85) (Bertinieri *et al.*, 1988).

The spectral techniques are based on three main points (De Boer *et al.*, 1987; Pagani *et al.*, 1988; Parati *et al.*, 2000; Robbe *et al.*, 1987). Firstly, the BP and R-R interval data are subdivided into short segments of BP and R-R interval ranging from 128 to 1024 beats. Secondly, the quantification of each segment by either FFT or AR modeling of R-R interval and SBP spectral powers in the LF and HF regions where these signals display a high coherence (> 0.5) i.e., the oscillations in R-R interval and SBP are linearly related. Thirdly, the squared root of the ratio of R-R interval and SBP powers (referred to as the α coefficient in the LF and HF regions) ($BRS_{\alpha LF}$ and $BRS_{\alpha HF}$) (Pagani *et al.*, 1988) or the calculation of the gain of the transfer function between SBP and R-R interval, commonly employed in the LF region only (BRS_{TFTG}) (De Boer *et al.*, 1987; Robbe *et al.*, 1987).

The frequency components are quantified in terms of their relative power (variance) and are collectively known as the power spectrum. There are three main frequency domains; very low frequency (VLF), LF and HF. Long period rhythms are found in the VLF range (0.00 - 0.04 Hz) and are thought to relate to long-term mechanisms but because the origin and frequency of the oscillations in the VLF region are unknown (Kuusela *et al.*, 2003) the fluctuations are often disregarded with the main research interest directed toward the LF and HF regions (Berntson *et al.*, 1997; Malliani *et al.*, 1991; Parati *et al.*, 1995c). The LF range (0.04 - 0.15 Hz) is compiled of both sympathetic and parasympathetic contributions and although LF is not thought to reflect the sympathetic component *per se* due to the vagal influence, in general for BRS assessment the LF band is considered to reflect sympathetic modulation and its changes (Pagani *et al.*, 1986; Pagani *et al.*, 1988) with such variation thought to originate from the characteristics of the BP control system (Cevese *et al.*, 2001; Hyndman *et al.*, 1971;

Robbe *et al.*, 1987). The HF component has a wide range (0.15 - 0.4 Hz) and is synchronized with respiratory rate due to the mechanical variations and intrathoracic pressure changes from breathing activity (Cerutti *et al.*, 1995) and is often referred to as the respiratory frequency (Parati *et al.*, 2000). The HF oscillations are generally considered to be a marker of parasympathetic activity because of its mediation by the vagus nerve on the heart (Cerutti *et al.*, 1995) and only parasympathetic modulation is capable of rapid HF adjustments in HR (Hartikainen *et al.*, 1998).

The assessment of the cardiovascular aspects of autonomic function may be undertaken via a range of tests which includes head-up tilt testing (Mathias & Bannister, 2002). Tilt testing is a widely accepted procedure to assess the human cardiovascular response to orthostatic stress (Benditt *et al.*, 1996; Wieling & Karemaker, 2002) and is particularly useful in clinical research to assess autonomic dysfunction (Mathias & Bannister, 2002). In addition, because the tilt procedure induces activation of the baroreflex to enable maintenance of homeostasis in BP and HR during orthostatic stress, such procedure may also be useful to incorporate when assessing BRS in a non-clinical setting. For example, an upright tilt may induce a different physiological response compared to that obtained from a supine position, a posture commonly adopted in research testing and thus may provide additional evidence for change in the cardiovascular system. Indeed, supine resting measures are under strong vagal influence while tilt induces a sympathetic response that may provide greater opportunity to assess sympathetic influence post-exercise. Secondly, such testing may also result in a more sensitive outcome measure for BRS which may be of benefit in the analysis of cardiovascular control and assist in the interpretation of the findings. For example, the assessment of the short and long term recovery (+ 1 h, + 24 h and + 48 h) in cardiac autonomic indices following a single bout of constant and interval training exercise reported a continuing cardiovascular disturbance which was only evident at + 48 h with an orthostatic manoeuvre (Mourot *et al.*, 2004). The method of BRS assessment may also dictate the usefulness of the incorporation of the tilt procedure. This is because during supine testing (and a less active baroreflex) the recording of data may provide few/ no sequences that are acceptable for sequence assessment. In general, acceptable sequences are only found intermittently due to the specificity of the method (Kuusela, 2007). Previous research has reported baroreflex sequences of ≥ 3 beats account for

only 15% - 27% of all beats in the cardiac cycle (Hughson *et al.*, 1993; Parati *et al.*, 1988; Parlow *et al.*, 1995). Furthermore, as the sequences only contain a small number of beats this may result in limited accuracy for the BRS measure (Bertinieri *et al.*, 1988). Respiratory effect may also compound the issue further as respiration affects the naturally occurring oscillations which modulate BP and HR (Kuusela, 2007). Indeed, if the heart rate is slow (RRI > 1 s) and breathing is set (phased to 4 s beat via metronome) one sequence may never contain three consecutive rising data values thus BRS evaluation would not be possible (Kuusela, 2007). However in healthy individuals, during tilt testing and the subsequent activation of the baroreflex there are more sequences of data and thus an improvement in the ability to achieve a satisfactory BRS sequence outcome measure.

The baroreflex is one of the body's mechanisms for the regulation of cardiovascular control. Ongoing clinical research supports a link between BRS and disease and health (Karemaker, 2002; Smyth *et al.*, 1969). Some of this research has associated diminished BRS with cardiovascular diseases such as hypertension (Bristow *et al.*, 1969; Parati *et al.*, 1988), alterations in HR control in patients with myocardial infarction (MI) (Osculati *et al.*, 1990) and the inability to constrain sympathetic activity in patients with congestive heart failure (Grassi *et al.*, 1995). Evidence has also been found associating reduced BRS with natural events such as ageing (Parati *et al.*, 1995b) and imposed events such as general anaesthesia (Parlow *et al.*, 1999). A marked association between impaired BRS and smoking has also been reported (Mancia *et al.*, 1997a). Investigations assessing BRS in diabetic patients found impairment in baroreflex control while classical autonomic testing yielded normal results (Frattola *et al.*, 1997). This suggests the assessment of BRS may be a superior technique for the assessment of autonomic abnormality in identifying risks which link to mortality and morbidity (Mancia *et al.*, 1997b; Parati *et al.*, 1997; Parati *et al.*, 2000). The assessment of BRS may therefore improve prognosis in diseased states and may also provide increased information for the prevention of disease. Thus, as diminished BRS appears to be linked to unfavourable health outcomes, factors that can enhance BRS may be beneficial to cardiovascular health. One factor which appears to enhance BRS in some circumstances is exercise and particularly the response following a single bout or adaptations following training.

An important quality of an assessment technique is a high degree of intra-subject reproducibility of the measure (Davies *et al.*, 1999). Indeed, there are few studies that have assessed the reproducibility of the various spontaneous BRS methods and the lack of evidence inhibits choice of BRS assessment in further research. Reproducibility testing may be undertaken on the same day and/ or following a specified period ≥ 24 h later thus, it would be beneficial to assess the reproducibility of the measure with reference to the repeated measures protocol to be incorporated in any future research. For example, the second phase of this project assessed BRS at pre and post exercise at + 15, 60, 120, 180 min (same day) and + 24 h (between day) therefore it was useful to have undertaken a reproducibility study which incorporated both same and between day reproducibility to provide insight for estimates such as effect size. Furthermore, the posture position of the participant has also been implicated in the variability of the BRS outcome measure with improved reproducibility reported during standing (Herpin & Ragot, 1997; Iellamo *et al.*, 1996). This finding was interesting as an imposed modification such as an orthostatic manoeuvre during testing procedures may be a useful tool to employ to aid in the attenuation of stimuli which influence the determination of BRS and, ultimately, could impact upon future study design considerations. Indeed, there was very little research that appeared to explicitly examine the effect of an orthostatic manoeuvre on the reproducibility of BRS measures and was thus deemed an area worthy of investigation.

Chronic exercise training, where activity is routinely undertaken for sporting or recreational purposes, causes an adaptive response in the cardiovascular system which includes a lowering of HR and BP at rest and during sub-maximal exercise together with an enhancement of BRS (Hainsworth, 1998; La Rovere *et al.*, 2002). The enhancement of BRS due to regular exercise training produces an inhibitory effect on sympathetic activity which may help to improve outcomes following MI (La Rovere *et al.*, 2002; Mimura *et al.*, 2005). Exercise training may also bestow increased vagal influence on the heart, with decreased sympathetic influence, thus providing improved cardiac electrical stability and improved cardiac mortality (TFESC & TNASPE, 1996). Following exercise training, BRS was improved in patients suffering from diabetes (Loimaala *et al.*, 2003), chronic obstructive pulmonary disease (Costes *et al.*, 2004), postural orthostatic tachycardia syndrome (Galbreath *et al.*, 2011), hypertension (Hua *et*

al., 2009; Laterza *et al.*, 2007; Pagani *et al.*, 1988) and coronary heart disease (Iellamo *et al.*, 2000) and in healthy individuals following moderate intensity (McDonald *et al.*, 1993) and high intensity (Heydari *et al.*, 2013) exercise training. Exercise training has also been found to reduce the age-associated decline in BRS in healthy, older men (Monahan *et al.*, 2000) and women (Bowman *et al.*, 1997). A reduced BRS is a characteristic feature in normotensive children of hypertensive parents and exercise training has been suggested as a means for overcoming this genetic predisposition via enhancing vagal activity and increasing BRS (Lénárd *et al.*, 2005; Parati, 2005). Thus, exercise training and increased BRS appear to be associated with positive outcomes for both clinical patients and healthy individuals.

A few studies have investigated the acute effect of a single bout of exercise on BRS (Convertino & Adams, 1991; Halliwill *et al.*, 1996; Niemelä *et al.*, 2008; Piepoli *et al.*, 1993; Ploutz *et al.*, 1993; Raczak *et al.*, 2005; Somers *et al.*, 1985; Stuckey *et al.*, 2012; Terziotti *et al.*, 2001). The studies of interest were those which reported BRS assessment at time points between + 60 min to + 24 h post-exercise (Convertino & Adams, 1991; Halliwill *et al.*, 1996; Niemelä *et al.*, 2008; Ploutz *et al.*, 1993; Stuckey *et al.*, 2012; Terziotti *et al.*, 2001) because they may reflect better the short and long term changes in BRS following exercise. Studies reporting BRS assessment before + 60 min were not so relevant, as any changes could have been dominated by the disturbance of cardiovascular indices that are found immediately following cessation of exercise. A single bout of exercise was investigated in trained individuals (Convertino & Adams, 1991; Niemelä *et al.*, 2008), untrained active participants (Halliwill *et al.*, 1996; Piepoli *et al.*, 1993; Stuckey *et al.*, 2012; Terziotti *et al.*, 2001), detrained (Raczak *et al.*, 2005), sedentary participants (Convertino & Adams, 1991; Halliwill *et al.*, 1996) and participants where no exercise history was provided (Ploutz *et al.*, 1993; Somers *et al.*, 1985). The exercise interventions included a maximal exercise test (Convertino & Adams, 1991; Piepoli *et al.*, 1993; Somers *et al.*, 1985), Wingate sprint exercise (Stuckey *et al.*, 2012), resistance exercise (Ploutz *et al.*, 1993), a mixture of aerobic and resistance exercise (Niemelä *et al.*, 2008) or a single bout of exercise of one intensity (Halliwill *et al.*, 1996; Raczak *et al.*, 2005). Thus the fitness profile and exercise interventions were highly variable providing comparability issues between studies. Other comparability issues included differences in protocol design and participant age

and gender. Furthermore, variation in the methods of BRS assessment included laboratory techniques of phenylephrine injection and neck chamber device and the modern methods of sequence, $BRS_{\alpha LF}$ and $BRS_{\alpha HF}$ and BRS_{TF} techniques. All of the participants in the various studies were healthy individuals with the exception of one study which included borderline hypertensives (Somers *et al.*, 1985). Thus, none of the studies were easily comparable.

It is interesting that although an orthostatic manoeuvre (standing) has been incorporated into reproducibility testing providing improved reproducibility (Herpin & Ragot, 1997; Iellamo *et al.*, 1996) only one of the studies (Stuckey *et al.*, 2012) investigating the acute effect of a single bout of exercise on BRS has included an orthostatic manoeuvre. Indeed, if the reproducibility of the measure is improved with tilt testing compared to supine testing then it may be useful to assess BRS following an exercise intervention under both posture conditions. An orthostatic challenge may provide evidence for a different physiological response following exercise and a more sensitive outcome measure which may maximise the opportunity of finding an effect if an effect is there. For example, the increase in sympathetic activity from the orthostatic challenge reflects a relative decrease in HF and relative increase in LF of R-R interval and an increase in LF spectrum of BP (Bernardi *et al.*, 1997; Pagani *et al.*, 1986; Radaelli *et al.*, 1994; Saul *et al.*, 1991). Thus an increase in LF dominance post exercise compared to baseline measures may indicate increased sympathetic activity (Bernardi *et al.*, 1997) and this may only be apparent by employing an orthostatic manoeuvre. Such findings could aid in the interpretation of the results and provide further evidence for the acute post-exercise cardiovascular response in healthy participants.

All studies undertaking an early assessment of short term recovery of BRS following exercise consistently found a reduction in BRS during the early stage of recovery (Halliwill *et al.*, 1996; Niemelä *et al.*, 2008; Piepoli *et al.*, 1993; Somers *et al.*, 1985; Terziotti *et al.*, 2001). Thereafter, BRS gradually increased back to baseline levels over $\leq$ 20 min (Halliwill *et al.*, 1996; Somers *et al.*, 1985) to > 2 h (Stuckey *et al.*, 2012) post-exercise providing evidence of an altered autonomic balance which may have been associated to the workload and/ or intensity of exercise. Increased BRS is associated to enhanced vagal tone and reduced sympathetic outflow implying improved cardiac

electrical stability and a cardio-protective effect while reduced BRS is linked to greater vagal withdrawal and greater sympathetic outflow implying a loss in cardiac electrical stability and in the cardio-protective effect (Billman, 2002). Thus, a delayed recovery period may be indicative of a change in autonomic dynamics toward greater sympathetic influence providing a persisting window of risk for an adverse cardiac event (Albert *et al.*, 2000; Maron, 2000) lasting over 2 h following exercise (Stuckey *et al.*, 2012). Following the early depression of BRS and subsequent recovery, a number of studies reported an enhancement in BRS following exercise (Convertino & Adams, 1991; Halliwill *et al.*, 1996; Raczak *et al.*, 2005; Somers *et al.*, 1985). Baroreflex sensitivity was increased following moderate intensity exercise (Halliwill *et al.*, 1996; Raczak *et al.*, 2005) and maximal exercise (Convertino & Adams, 1991; Somers *et al.*, 1985) reflecting an enhancement in parasympathetic activity and a reduction in sympathetic influence suggesting these exercise bouts could provide a health benefit. Other studies including moderate and high intensity/ workload exercise did not observe an augmentation in BRS (Niemelä *et al.*, 2008; Piepoli *et al.*, 1993; Stuckey *et al.*, 2012) suggesting a prevailing influence of sympathetic nervous activity and a possible increase in cardiac risk (Albert *et al.*, 2000; Maron, 2000). Thus, it is unclear how the components of a single bout of exercise influence autonomic dynamics post-exercise (Parekh & Lee, 2005). Discrepancy between study findings may also include issues of variance in the total amount of work undertaken between studies and comparability differences between studies.

Although exercise has been found to provide positive health benefits through both chronic adaptations following exercise training and repeated acute responses following a single exercise bout, exercise recommendations for particular health outcomes have yet to be fully elucidated (Haskell, 2001; Thompson *et al.*, 2001). Exercise recommendations should specify the intensity, the duration and the mode of exercise. Indeed, Haskell (2001) suggested that one key issue in defining the dose-response relationship was the need to establish the acute physiological response to various intensities and durations of exercise. Greater elucidation for the autonomic response following exercise may help to define the acute physiological response post-exercise and provide further evidence for the risks and benefits of exercise for health related

purposes. The determination of BRS is one method which can be employed to assess the cardiac autonomic response post-exercise.

Although the use of spontaneous non-invasive BRS techniques is now routinely used for baroreflex testing, there are still only a few studies that have assessed the reproducibility of the measures. Some of the limitations regarding published studies concerning reproducibility of BRS (Maestri *et al.*, 2009) included low sample size (Davies *et al.*, 1999; Herpin & Ragot, 1997; Iellamo *et al.*, 2001; Lord *et al.*, 1998), limited choice of BRS parameters (Iellamo *et al.*, 1996) and deficient protocols for between day reproducibility (Davies *et al.*, 1999; Gerritsen *et al.*, 2000; Herpin & Ragot, 1997; Lord *et al.*, 1998). However, the one study that did include a large sample size, a wide selection of BRS parameters and a protocol for between day reproducibility did not include same day reproducibility or a tilt procedure (Maestri *et al.*, 2009). Thus to date, current BRS reproducibility studies have not included a comprehensive protocol to include large sample size, a wide BRS parameter selection, same day/ between day reproducibility and an orthostatic challenge. The present reproducibility study would incorporate all of these aspects to assess the reproducibility for BRS. Thus, the aims of the reproducibility study were:

- To investigate the same day reproducibility of the measurement of BRS
- To investigate the between day reproducibility of the measurement of BRS

These aims would be met through exploring the following research questions:

(i) To what extent do the procedures used to determine a series of BRS outcomes result in reproducible findings on the same day?
(ii) To what extent do the procedures used to determine a series of BRS outcomes result in reproducible findings between days?
(iii) To what extent does the tilt procedure influence the reproducibility assessment of BRS outcomes?

Whether BRS may be acutely manipulated following exercise is an important question given the influence of BRS on cardiovascular control. Currently, there is little research

that has investigated the effect of a single bout of exercise on post-exercise BRS and in particular, the influence of intensity of exercise on cardiovascular control. The previous studies had incorporated either a maximal exercise test, Wingate sprint testing, a mixture of aerobic and resistance exercise or a single bout of exercise of one intensity. The two studies which did incorporate two intensities/ workloads of exercise did not accommodate for equal amounts of total work undertaken thus providing a confounding influence of volume of work (Stuckey *et al.*, 2012; Terziotti *et al.*, 2001). Thus no previous studies have explicitly identified intensity of exercise in the intervention procedure. The present exercise study would clearly identify two distinct intensities of exercise. The exercise study would also incorporate a tilt procedure, which had not been undertaken by any of the related studies, a comprehensive range of BRS measures, together with six time points to reflect the immediate to long-term post-exercise responses to track the time course of changes across various BRS outcome measures. These procedures have not been incorporated (*en masse*) in the previous related studies. Thus the aims of the present exercise study were:

- To investigate the effects of intensity of exercise on supine BRS following a single bout of exercise
- To investigate the effects of intensity of exercise on tilt BRS following a single bout of exercise

These aims would be met through exploring the following research questions:

(iv) To what extent does the intensity of exercise influence post-exercise supine BRS as illustrated by using a within subjects repeated measures study design including two counterbalanced exercise conditions and a control condition?

(v) To what extent does the intensity of exercise influence post-exercise tilt BRS as illustrated by using a within subjects repeated measures study design including two counterbalanced exercise conditions and a control condition?

CHAPTER TWO

LITERATURE REVIEW

CHAPTER 2: LITERATURE REVIEW

2.1 The Public Health Context: The Metabolic Syndrome

2.1.1 Definition of the metabolic syndrome

The metabolic syndrome (MetS) was initially described 90 years ago by Kylin, a Swedish physician, as the clustering of hypertension, hyperglycaemia and gout (Kylin, 1923) cited in (Eckel *et al.*, 2005). Later in 1947, obesity was added as a further risk factor (Vague, 1947) cited in (Eckel *et al.*, 2005). In 1998, the World Health Organisation (WHO) proposed criteria to establish a worldwide accepted definition for the syndrome with the premise that any definition would need to be modified when future research provided further information on risk factors (Alberti & Zimmet, 1998). This proposal led to two separate definitions by the Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (Executive Summary of NCEP, 2001) and the European Group for the Study of Insulin Resistance (Balkau & Charles, 1999) who agreed on the main risk factors for the MetS as hypertension, glucose intolerance, dyslipidemia and obesity (Eckel *et al.*, 2005). More recently, because of differences in definition for MetS and global ethnic and inter-ethnic differences with regard to risk criterion which had been highlighted by ongoing research (WHO expert consultation, 2004), it became evident that MetS definition would require periodic updating (WHO, 2000, 2006) to provide better guidance for international clinical practice and global comparability opportunities regarding prevalence and impact of MetS between countries (Eckel *et al.*, 2005).

Due to the various connections between the risk factors, the syndrome has been given various names which include the ‘deadly quartet’ (Kaplan, 1989) and ‘syndrome X’ (Reaven, 1988). It is generally accepted that cardiovascular disease (CVD), morbidity and mortality is increased when the risk factors for MetS act synergistically i.e., CVD morbidity risk associated with the cluster of risk factors is greater than the risks linked to the individual components (Isomaa *et al.*, 2001) although more recently some research has provided evidence to the contrary (Mente *et al.*, 2010). Diagnosis for MetS

is accepted as the identification of ≥ 3 risk factors (Executive Summary of NCEP, 2001) and the two major objectives in the clinical management of the syndrome are to reduce the primary cause of the disorder (i.e., physical inactivity and obesity) and to treat the related risk factors (ACSM, 2006b; NCEP, 2002; WHO, 2002). Cardiovascular and metabolic disorders are implicated in MetS suggesting that neurogenic alterations play a key role in the development of MetS via sympathetic overactivity and increased adrenergic action (Grassi, 2006; Grassi *et al.*, 2004; Grassi *et al.*, 1995a).

2.1.2 Hypertension

Blood pressure (BP) is the measure (millilitres of mercury) (mmHg) of the force that circulating blood exerts on the walls of the main arteries (WHO, 2002). Each heart beat produces a pressure wave of BP which is transmitted along the arteries; the highest pressure is exerted during heart contraction (systolic) and the lowest pressure is exerted during heart filling (diastolic). Elevated BP may cause structural changes to the arteries in various parts of the body which may result in disease states such as stroke, ischemic heart disease (IHD) and renal failure. Ongoing research has provided evidence that the risks of associated BP disease can be found in populations with average and below average BP and not just in high levels (hypertensive) populations and this has resulted in reclassification of BP levels for health (ESCHDCRG, 1998; JNCPDETHBP, 2004; Law & Wald, 2002; WHO, 2002).

The current BP classifications refer to adults ≥ 18 y (BPA, 2012; JNCPDETHBP, 2004) (table 2.1.1). The normal BP values were updated to reflect previous optimal BP values (Appendix I: table A1) (JNCPDETHBP, 1997) because new evidence found lifetime risk of hypertension and the risk for CVD complications were associated with BP levels previously considered to be in the normal range (Franklin *et al.*, 1997; JNCPDETHBP, 2004; Vasan *et al.*, 2002; WHO, 2002). The UK BP classifications which reflect European guidelines provide a more detailed BP classification (Appendix I: table A2).

Table 2.1.1. Current (JNC 7) classification for adult blood pressure

Blood Pressure classification	SBP (mmHg)	DBP (mmHg)
Normal	< 120	and < 80
Prehypertension	120 - 139	or 80 - 89
Stage 1 Hypertension	140 - 159	or 90 - 99
Stage 2 Hypertension	≥ 160	or ≥ 100
Isolated systolic hypertension	≥ 140	< 90

Note: SBP is systolic blood pressure; DBP is diastolic blood pressure; mmHg = millimetres of mercury; JNC is Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Taken from (JNCPDETHBP, 2004)

The previous classifications for normal and borderline hypertension were merged to form a new classification labelled 'prehypertension'. Prehypertension is not a disease state but a designation to identify individuals where the adoption of an early intervention i.e., increased physical activity (PA) would reduce BP, decrease the rate of progression of BP to a hypertensive state with age or prevent hypertension entirely (JNCPDETHBP, 2004). Prehypertension, where BP oscillates between high and low values, may be a predictor for more severe hypertension (Julius, 1991). Commonly in this condition, cardiac output ($\dot{Q}$) is increased with normal vascular resistance while in established hypertension $\dot{Q}$ is normal and vascular resistance is increased. Prehypertension presents with increased sympathetic activity and reduced parasympathetic activity. The increased sympathetic tone may lead to a reduced cardiac response which over time will return $\dot{Q}$ to the normal range. Changes in vasculature may also occur such as hypertrophy and hyper-responsiveness to vasoconstriction and these secondary changes form the basis of the transition from prehypertension to hypertension. The elevated sympathetic activity may have clinical consequences such as inducing insulin resistance and dyslipidemia thus encouraging premature atherosclerosis and increased cardiac disease risk (Julius & Nesbitt, 1998). Insulin resistance has been found to be directly correlated to the severity of the hypertension (Ferrannini *et al.*, 1987; Julius, 1994) and elevated BP is strongly associated to obesity (Grundy *et al.*, 2004a). For example, in 2009 in England, hypertension was recorded in 51% men and 46% women who were obese compared to 20% men and 15% women with normal weight (NHS, 2012).

Approximately one third of adults in England and Scotland have elevated BP and the incidence of hypertension increases with age in both sexes (BHF, 2010, 2012b). In 2008 in England, hypertension was recorded in men (women) as 7% (2%) aged 16 – 24 y compared to 52% (41%) aged 55 – 64 y compared to 62% (62%) aged 65 - 74 y while in the UK, 42% men and 32% women aged ≥ 25 y had raised BP or were taking BP medication (Nichols *et al.*, 2012). Worldwide in the developed countries, elevated BP was responsible for 11% of total disease burden and globally, accounted for 13% of total mortality with 7 million premature deaths per annum. Sub-optimal BP (systolic > 115 mmHg) was responsible for 50% ischemic heart disease (IHD) incidence and 62% of cerebrovascular disease incidence (WHO, 2002) and due to global population growth and ageing, the number of people with uncontrolled hypertension rose from 600 million in 1980 to nearly 1 billion in 2008 (WHO, 2008).

2.1.3 Glucose intolerance

Diabetes is an insidious chronic metabolic disease which is symptomatic of an inability to sufficiently produce or utilise insulin resulting in hyperglycemia (Hornsby & Albright, 2003). There are two main categories for diabetes; Type 1 diabetes which presents as an absolute deficiency of insulin caused by β-cell destruction which affects approximately 5 - 10% of the diabetic population and Type 2 (non-insulin dependent diabetes mellitus) (NIDDM) which is commonly caused by insulin resistance and defective insulin secretion and affects 85 - 90% of the diabetic population (Hornsby & Albright, 2003).

Type 1 diabetes is not modifiable and is purported to involve an auto-immune response in susceptible individuals and usually occurs < 30 y (Hornsby & Albright, 2003). Type 2 diabetes is modifiable and progressive and induced via the pancreas which cannot produce enough insulin to compensate for the insulin resistance causing hyperglycemia (Hornsby & Albright, 2003). The prevalence of Type 2 diabetes increases with age and does not normally affect individuals < 40 y although recently, increasing numbers for Type 2 diabetes have been diagnosed in younger individuals (NHS, 2011). Type 2 diabetes may be caused by a genetic or ethnic influence and a frequent significant factor at onset is obesity because obesity contributes to insulin resistance, with physical

inactivity being an important factor in obesity development (Grundy *et al.*, 2004b; Hornsby & Albright, 2003). Sympathetic overactivity is considered to be dependent on hyperinsulinemia and the related insulin resistance because an acute systemic administration of insulin induces a marked sympathetic action in animals and humans (Grassi, 2006; Landsberg, 1996).

The incidence of diabetes is increasing with > 2 million diagnosed cases in England (NHS, 2011). The disease causes 70,000 – 75,000 deaths per annum and provides an increased risk of mortality; 2.6 times higher in Type 1 diabetes and 1.6 times higher in Type 2 diabetes, compared to the general population (NHS, 2011). Diabetes provides a 2 – 4 times increase in risk of coronary heart disease (CHD) and approximately 80% of diabetics die from CHD (Cardio & Vascular Coalition, 2009). Treatment considerations are medication and lifestyle modifications such as diet and PA interventions.

2.1.4 Dyslipidemia

Dyslipidemia is a condition where genetic, environmental or pathological factors combine to abnormally alter blood lipid and lipoprotein concentrations (Gordon, 2003; Landsberg, 1996). Lipids are converted to lipoproteins and the main forms are very-low density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDH). Secondary forms of dyslipidemia are caused by other diseases i.e., diabetes and/ or by a combination of an individual's genetic profile and lifestyle choices i.e., smoking, diet and physical inactivity. Low-density lipoproteins are the main carrier for cholesterol from the intestine or liver to peripheral tissues with high levels of cholesterol implicated in coronary artery disease (CAD) (Durstine *et al.*, 2003). High-density lipoproteins are synthesised and secreted in the intestines and liver and they have a primary role for the reverse transportation of cholesterol from the tissues to the liver and thus are considered to have a positive effect in the removal of excess cholesterol in the blood (Mann & Skeaff, 2004). Variations of genetic and lifestyle factors may alter the transportation of cholesterol and triglycerides, altering lipid concentrations and influencing the risk for CAD (Durstine *et al.*, 2003). Studies including women may be confounded by menopausal status, birth control medication and oestrogen replacement therapy because oestrogen causes an increase in HDL

(Shephard & Balady, 1999). One lifestyle modification that may alter lipid concentration profile is PA due to the regulatory effect on lipid status with an association between lipid profiles, fitness levels and PA (Durstine & Haskell, 1994).

Cholesterol is measured in millimoles per litre of blood (mmol/l). The current UK guidelines for individuals at risk of cardiovascular disease (CVD) are: LDL < 2 mmol/l; HDL > 1 mmol/l and total cholesterol < 4 mmol/l (JBS, 2005) with an audit trail of total cholesterol 5 mmol/l for tracking high cholesterol levels (BHF, 2010). In 2008 in England, mean total blood cholesterol levels and mean HDL levels were 5.2 mmol/l; 1.3 mmol/l for men and 5.4 mmol/l; 1.6 mmol/l for women respectively. LDL cholesterol was not measured. The proportion of men and women with cholesterol levels ≥ 5.0 mmol/l was 58% and 61% respectively (JHS, 2009).

2.1.5 Obesity

Obesity is categorised as a body mass index (BMI) of > 30 kg/m^2 or morbidly obese BMI > 40 kg/m^2 (McArdle *et al.*, 2000a). The primary cause for obesity is a chronic imbalance between levels of energy input (diet) with energy expenditure (PA) (Abdel-Hamid, 2003). Obesity increases both the risk and severity of disease (Klein *et al.*, 2004) and is implicated in diabetes, CAD, hypertension and dyslipidemia and a possible increase of premature mortality (Wallace, 2003). For example, an obese woman is 13 times more likely to develop Type 2 diabetes than a woman of normal weight (NHS, 2012). The pattern of fat distribution may also affect the risk of disease as central or upper body obesity results in a higher risk for diabetes and CHD than lower body obesity due to the increased activity in the abdominal area of the enzyme lipoprotein lipase which regulates fat storage and increases the level of fat in this body area (Parr, 2003). Another important factor in body fat distribution is the discrimination between visceral fat and subcutaneous fat because visceral fat is implicated with a higher risk for diabetes than subcutaneous fat (Parr, 2003). Sympathetic overactivity is linked to obesity via adrenergic action i.e., elevated plasma noradrenalin levels (Grassi, 2006; Troisi *et al.*, 1991) although the magnitude of the sympathetic activity may differ depending of the pattern of the fat distribution with greater sympathetic activity accompanying visceral fat deposits compared to subcutaneous fat distribution (Grassi,

2006; Grassi *et al.*, 2004). The treatment for obesity is decreased energy input (diet modifications) or increased energy output (increased PA) or a combination of both strategies and long-term PA is important to maintain weight reduction (Miller *et al.*, 1997).

Obesity levels in England have risen with the prevalence of obesity in men doubled from 13% in 1993 to 26% in 2012 while in women from 16% in 1993 to 24% by 2012 (JHS, 2010; NHS, 2012). The prevalence of obesity increases with age in both adults and children (JHS, 2010). In children (age 2 – 15 y), the levels of obesity rose in both boys and girls from 11% and 12% respectively in 1995 to 17% and 15% respectively by 2010 (NHS, 2012). In 2010/ 2011, obesity rates doubled between reception children (age 4 – 5 y) (9%) compared to Year 6 children (age 10 – 11 y) (19%) (NHS, 2012).

2.1.6 Evidence for risk factors for disease from epidemiologic studies

An important emphasis in public health studies is to reveal the components of disease which are amenable to intervention thus identifying the interrelated and interacting factors that influence risk for disease (Lucas & McMichael, 2005). The initial evidence for the association between risk factors and CVD was achieved via longitudinal research from data gathered over extended periods of time with large numbers of participants living in their own environment thus inherently rendering less control than would normally be expected in clinical trials or laboratory based research (Lucas & McMichael, 2005). These studies are called 'epidemiologic' and the various study designs and statistical techniques have inherent properties that imbue a classification for evidence (JNCPDETHBP, 1997, 2004) which aids in the interpretation of findings (Appendix II). The development of these studies has provided the opportunity to explore and extrapolate findings from local and global populations over a wide range of cardiovascular research (Appendix III: table A3). The main advantage of epidemiologic research is long term changes in a particular population can be tracked during the development of change and thus be attributed to certain factors, albeit the need for caution in causal inference due to potential confounding variables (Lucas & McMichael, 2005). The main disadvantages include cost, time considerations and the large stable cohort size which is required to ensure the population is accurately represented.

2.1.7 Epidemiologic studies

Since the beginning of the 20th century, death rates from CVD had been steadily rising in the United Kingdom (UK) and the United States of America (USA) but very little was known about the general causes of heart disease and stroke. In 1948, a research study was launched to identify the common factors or characteristics that were responsible for CVD under the direction of the National Heart Institute (now known as the National Heart, Lung, and Blood Institute) (NHLBI) which was called the Framingham Heart Study (FHS, 2012). The main objective of this study was to follow the development of CVD in a local population who did not have any symptoms or had suffered CVD or stroke. The participants underwent detailed physical examinations, laboratory tests and lifestyle interviews which were repeated every two years with the data analysed in an attempt to find any common patterns relating to CVD development. Over time further cohorts have been enrolled which include the children and grandchildren of the original cohort and an additional cohort to reflect a greater diversity within the community.

More than a thousand research articles have been published from the Framingham Heart Study over the last 50 y providing evidence that hypertension, elevated blood cholesterol, smoking, obesity, diabetes and physical inactivity are risk factors for CVD together with information on the effects of related features such as blood triglycerides and HDL cholesterol levels, age, gender and psychosocial issues that also influence CVD (FHS, 2012). This evidence has aided in the diagnosis and management of MetS (Grundy *et al.*, 2005; Grundy *et al.*, 2004b), supported the development of recommended guidelines for risk factors i.e., BP levels for health and disease and improved disease prediction functions for multi-variant disease risk such as CHD (Wilson *et al.*, 1998). Strong, collaborating evidence for hypertension as a major risk factor in CVD has been consistently found from data gathered over 20 – 30 y which includes findings for age related changes in BP leading to hypertension and a risk differential in the development of hypertension between men and women providing evidence for an increasing risk for CVD with increasing age (Franklin *et al.*, 1997; Vasan *et al.*, 2002).

Many other epidemiologic studies have investigated the risk from MetS and the associated risk factors for CHD and CVD. The NHANES I and II studies have investigated mortality risk with MetS and found a significant increased risk of CHD, CVD and total mortality compared to those without MetS (Domanski *et al.*, 2001; Malik *et al.*, 2004). The combined risk factors of MetS provided a greater risk than the independent risk factors for mortality and increases in pulse pressure (10 mmHg) provided 26% increase in CVD mortality risk (Domanski *et al.*, 2001; Malik *et al.*, 2004). A NHANES III study found a strong association between MetS and myocardial infarction (MI) and stroke in men and women, with hypertension independently and significantly related to MI and stroke incidence (Ninomiya *et al.*, 2004).

The INTERHEART Study assessed the importance of risk factors for MI across a global population and identified nine risk factors which provided > 90% risk for an initial acute MI and these included hypertension, abnormal lipids, smoking, diabetes, abdominal obesity, psychosocial factors, diet, alcohol and physical inactivity (Yusuf *et al.*, 2004). The risk factors were consistent in both men and women, across different geographic regions and ethnicity and a quarter of the overall risk was attributed to elevated BP. Individuals with a history of hypertension had nearly twice the risk of having MI compared to those without hypertension history. A later study, using INTERHEART data investigated the risk of acute MI conferred by MetS and the individual risk factors in multiple ethnic populations (Mente *et al.*, 2010). The presence of ≥ 3 risk factors was predictive for MI in men and women, across age, geographic regions and ethnicity. However, this study suggested that the risk for future MI was no greater in individuals with MetS than in those individuals with hypertension or diabetes alone which suggested that preventive and treatment options should be focused on individual risk factors and is contrary to evidence from the NHANES II study which found multiple risk in MetS was greater than the sum of the individual risk factors (Malik *et al.*, 2004).

Hypertension was also indicated in the Copenhagen Heart Study with a greater incidence for CHD in men than women in middle-age and the main risk factors associated with CHD were diabetes, hypertension, smoking and physical inactivity. Although these risk factors were found to be independent this study also provided

evidence for the potential overlap between risk factors i.e. hypertension, obesity, physical inactivity and for the interaction between primary risk factors with lifestyle choice (Schnohr *et al.*, 2002). Additional lifestyle factors have also been implicated in MetS. Regular PA was found to be inversely and independently associated with the prevalence of MetS (Yang *et al.*, 2008), smoking was found to increase the risk of mortality in those with greater abdominal obesity (Pischon *et al.*, 2008), conflicting outcomes were found in saturated fat intake between different ethnic populations (Gartside *et al.*, 1998), alcohol increased the risk for hypertension with significantly increased DBP but not SBP (Wang *et al.*, 2006) and an inverse association between education and high SBP was found over a 30 y life course span (Loucks *et al.*, 2011).

Early epidemiologic research investigating the risk for MetS was undertaken in white Caucasian populations but later research included more diverse racial and ethnic minority populations which found the health risks applied in different racial and ethnic minority populations although distribution patterns varied (WHO, 2000, 2006). These populations included Hong Kong Chinese (Thomas *et al.*, 2005); eastern Asian Chinese and Japanese (ESCHDCRG, 1998); African American and Mexican American (Greenlund *et al.*, 2004; Jones *et al.*, 2002); American Indian (Wang *et al.*, 2006) and European Mediterranean (Mancia *et al.*, 2007). Findings from international populations have provided evidence for the global risk burden for disease and the proportional impact of individual risk factors to that burden (WHO, 2002). For example, the estimated total number of people with hypertension in 2000 was 972 million; 639 million in the developing countries and 333 million in the economically developed countries (Kearney *et al.*, 2005). By 2025, these figures were projected to rise by 60% to 1.56 billion with nearly 75% of this total estimated to occur in the economically developing countries.

Summary

The main risk factors for MetS are hypertension, glucose intolerance, dyslipidemia and obesity and each factor implicates increased sympathetic activity as a common feature in the aetiology and progression of the disease. Epidemiologic studies have provided compelling evidence for the influence of MetS and its related risk factors for CVD in

regional, national and global populations and identified mortality and morbidity trends over time together with confounding factors such as ethnicity, age, gender and lifestyle. The evidence from these studies has become an integral part of diagnostic and prognostic medicine and risk reduction strategies in global health promoting behaviour. One of the most influential factors for disease has been uncontrolled and high BP which leads to the diseased state of hypertension. Hypertension is a persistent characteristic of MetS, indicated in causation, effect and severity in multiple diseases and has been identified as a leading cause in the global health burden.

2.2 Blood pressure

2.2.1 Blood pressure components

The cardiovascular system has two primary components; the heart and the vasculature. The main function of the heart is to propel blood into the systemic system while the vasculature transports and distributes blood around the body. Blood is expelled from the heart via the contraction of muscular walls which enclose the left ventricle thereby generating pressure to eject blood (Klabunde, 2005e). The amount of blood expelled into the aorta during each contraction is the stroke volume (SV) (ml/beat) and the amount of blood expelled over one min (HR) (bpm) is the $\dot{Q}$ (l/min^{-1} or ml/min^{-1}). Any changes in either SV or HR will affect $\dot{Q}$. The vasculature offers resistance to blood flow (total peripheral resistance) (TPR). The resistance is increased during vasoconstriction of the blood vessels and decreased during vasodilation. Thus, BP is the product of $\dot{Q}$ and TPR. Persistent changes in $\dot{Q}$ or TPR are indicators for CVD risk.

The ejection of blood into the aorta results in a pressure pulse of characteristic shape; the peak is termed systolic blood pressure (SBP), the lowest pressure before blood ejection is termed diastolic blood pressure (DBP) and the mean arterial blood pressure (MAP) is calculated according to the shape and size of the pressure pulse (Klabunde, 2005e) (figure 2.2.1). The difference between SBP and DBP is termed pulse pressure (PP) and a change in either SBP or DBP affects PP. All four BP components have been indicated in the risk for CVD (Franklin *et al.*, 1997; Franklin *et al.*, 2009).

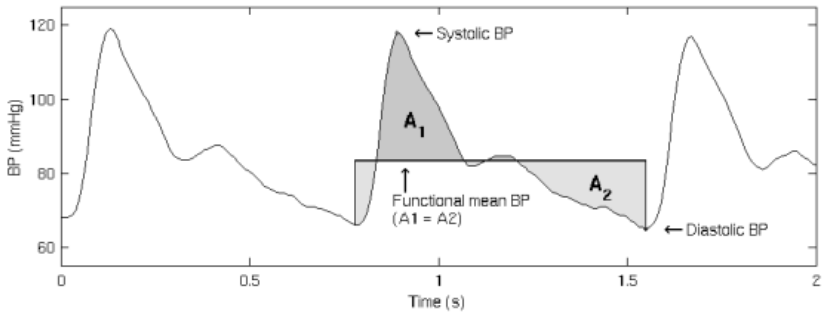

Figure 2.2.1. Blood pressure wave contour (BSAMIG, 2007)

2.2.2 Blood pressure control

Blood pressure is controlled by homeostatic short-term and long-term processes. The short-term processes include the baroreflex, chemoreceptors and circulating catecholamines. The cardiovascular centre for short-term regulation consists of a mass of interconnecting neurons within the medulla and pons of the brain. Input information is received, integrated and co-ordinated from peripheral receptors, chemoreceptors and higher centres of the brain to bring about change via autonomic nerves in the heart and blood vessels (figure 2.2.2) (Waugh & Grant, 2001).

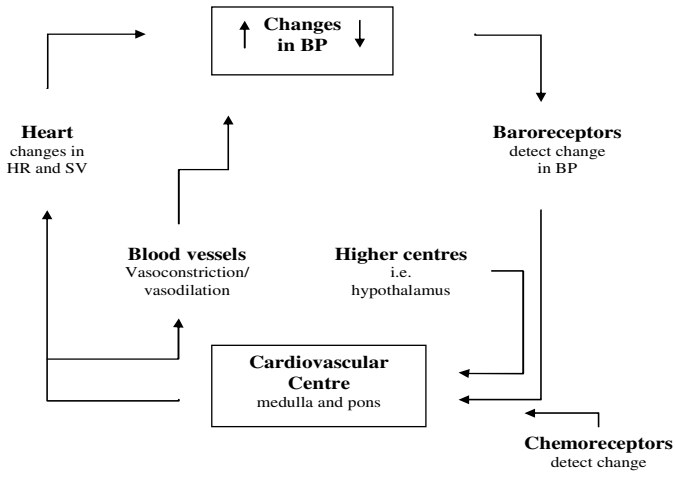

Figure 2.2.2. Summary of the main mechanisms in short-term blood pressure control. Taken and adapted from (Waugh & Grant, 2001)

The baroreflex is the primary mechanism for short-term regulation of cardiovascular control (Levick, 2003a). Sympathetic and parasympathetic nerves which innovate the heart and vasculature are regulated by the brain from sensory information initially received from baroreceptors, which detect changes in BP via distortion in the blood vessels. The relaying of information from afferent fibres, central relays and efferent fibres form the baroreflex, a negative feedback system, to bring about stabilisation in BP. Enhanced levels of sensitivity of the baroreflex (baroreflex sensitivity) (BRS) is implicated in health while reduced BRS has been found in diseased states (see: section 2.5). Other reflexes involved in BP control i.e., chemoreceptors and circulating catecholamines are excitatory as they raise rather than stabilise BP.

Peripheral chemoreceptors are specialised nerve endings found within the carotid and aortic bodies. Their primary purpose is to regulate respiratory function to maintain blood gases; pO_2, pCO_2 and pH^+ (Waugh & Grant, 2001). During rest at normal gas tensions, chemoreceptors have little influence over cardiovascular circulation but during exercise and conditions of hypoxamaemia, hypercapnia and acidosis, the change in gas tensions results in vasoconstriction of blood vessels, increased BP (figure 2.2.3), and indirectly, increased HR (Levick, 2003a; Waugh & Grant, 2001). During spontaneous respiration in dynamic conditions, chemoreceptors stimulate respiration, which in turn stimulate lung stretch receptors and lung inflation reflex, which overpowers the bradycardia of the arterial chemoreflex and results in tachycardia (Levick, 2003a).

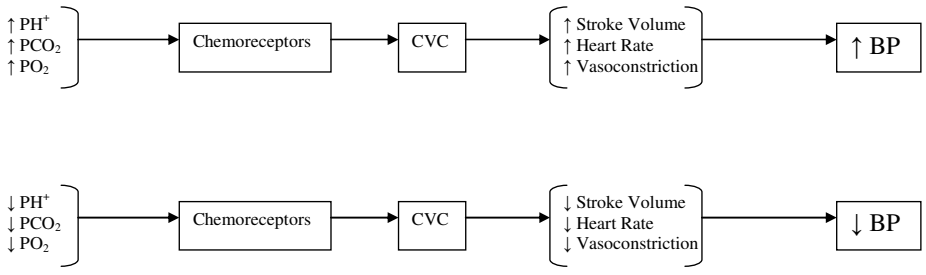

Figure 2.2.3. The relationship between chemoreceptor stimulation and arterial blood pressure. Taken from (Waugh & Grant, 2001).

The circulating catecholamines have two main sources; the adrenal medulla and sympathetic nerves (Levick, 2003d). Activation of the adrenal medulla stimulates the release of the catecholamines adrenalin (80%) and noradrenalin (20%) into the blood circulation. The two hormones have a similar effect and depending on plasma concentrations they can increase HR and BP. Adrenalin has a greater cardiac effect while noradrenalin has more influence over blood vessels (Waugh & Grant, 2001). Sympathetic nerves primarily release noradrenalin, which in normal circumstances is largely taken back by the nerves and metabolised resulting in small amounts entering the blood circulation (Klabunde, 2005a). However, during high levels of sympathetic nerve activity the amount of noradrenalin entering the blood circulation is greatly increased. The excessive secretion of catecholamines is implicated in hypertension, arteriosclerosis and stroke (Waugh & Grant, 2001).

The long-term processes for BP control include the regulation of blood volume, cardiac and vascular function and arterial BP by the renin-angiotensin-aldosterone system (Klabunde, 2005d). This system is largely responsible for the excretion of sodium and water from the kidneys which influence BP via blood volume. The release of renin by the kidneys and its subsequent actions ultimately forms angiotensin II. Angiotensin II produces the actions of sodium retention, thirst stimulation, vasoconstriction of blood vessels, enhancement of sympathetic activity, and cardiac and vascular hypertrophy (Levick, 2003b). The comprehensive effect of angiotensin II is increased blood volume and increased BP. Renal disease is the major cause of secondary hypertension. Indeed due to the actions of angiotensin II, drug therapy has targeted the prevention of formation of angiotensin II because of its potential involvement in hypertension and CVD (Moorman & West, 2005).

Thus, disruption to regulatory short-term and long-term functions for BP control may induce elevated levels of BP leading to hypertension and disease. Epidemiologic research (Appendix IV: table A4) has provided evidence for the relationship between BP and interrelated factors relating to health outcomes.

2.2.3 Blood pressure and age

Epidemiologic studies provided initial evidence of a link between elevated SBP and DBP with CVD and more recently from the emergence of systolic hypertension as a major risk factor for disease (Franklin *et al.*, 1997; Franklin *et al.*, 2001; Williams *et al.*, 2008). One of the main reasons for the recognition of high incidence systolic hypertension was longevity (Williams *et al.*, 2008) because worldwide data estimating the global burden of hypertension in 2000 and the projected burden in 2025, suggested the prevalence of hypertension was predicted to rise by 9% in men and 13% in women, due in part to the projected changes in the age distribution of the population (Kearney *et al.*, 2005).

Blood pressure profiles change with increasing age (Williams *et al.*, 2008). Systolic BP and PP increase progressively with age, while DBP increases until the age of ~ 50 y and then decreases and it is at this age the incidence for CVD starts to rise (Burt *et al.*, 1995; Franklin *et al.*, 1997). The reason for the decrease in DBP is controversial but it is purported to be caused by stiffness in the large arteries (Franklin *et al.*, 1997). The progressive nature of SBP is suggestive of high disease risk potential. Systolic hypertension is responsible for a high global risk burden for CVD (WHO, 2002) possibly because systolic hypertension is more common than diastolic hypertension in older individuals even though both elevated SBP and DBP are associated with CVD (Franklin *et al.*, 2001; Lewington *et al.*, 2002; Williams *et al.*, 2008). Furthermore, the high incidence of SBP involvement in CVD has evoked debate that the SBP component should be prominent in public health messages, risk stratification and for diagnostic and prognostic purposes for individuals > 50 y (Burt *et al.*, 1995; Escobar *et al.*, 2010; Williams *et al.*, 2008). Evidence for this debate has resulted from studies investigating BP components, disease risk and age. For example, a NHANES III study (Franklin *et al.*, 2001) investigated patterns of systolic and diastolic hypertension by age (≤ 50 y and ≥ 50 y) and found the proportion of individuals with systolic hypertension was progressively higher while the proportion of individuals with diastolic hypertension progressively lower in age in uncontrolled hypertension. Uncontrolled hypertension at age ≥ 50 y, was predominantly systolic hypertension (SBP ≥ 140 mmHg and DBP ≤ 90 mmHg); 54% by the fifth decade rising to 87% by the sixth decade. Overall, 74% of all

hypertensive individuals were middle aged or elderly (≥ 50 y). In younger individuals ≤ 50 y the prevalence of diastolic hypertension was much higher suggesting the importance of both SBP and DBP components in risk assessment for this age group (Williams *et al.*, 2008).

2.2.4 Blood pressure and mortality

Blood pressure is directly related to mortality from hypertension and CVD (Pescatello *et al.*, 2004). The long-term average risk of developing hypertension in middle age (55 – 64 y) and older (≥ 65 y) has been estimated at 90% in both men and women (Vasan *et al.*, 2002). More than half of middle-aged participants and two thirds of older participants developed hypertension over a 10 year period whilst over a 20 – 25 y period 85% of all participants developed hypertension (Vasan *et al.*, 2002). These findings suggest hypertension is strongly implicated in the risk for increased mortality. In 2008, elevated BP was estimated to have caused 7.5 million deaths worldwide, approximately 13% of all death total (WHO, 2008). In the GBD study consisting of 14 global sub-regions, the assessment of major risk factors to global and regional burden of disease found high BP to be the leading contributor for mortality and the third global risk factor for burden of disease in the world (Ezzati *et al.*, 2002). The investigation of the similarities between the relative risk of mortality in relation to SBP, DBP and hypertension in seven countries from North America, Europe and Asia found hypertension to be a significant risk factor for death from CHD over a 25 y period (van den Hoogen *et al.*, 2000). The significant risk for mortality was found where the relative increase in long-term mortality due to CHD to a given increase in BP was similar, although the absolute risk at the same level of BP varied substantially between some populations, possibly due to genetic or lifestyle factors and thus, provided implications for public health regarding the prevention and treatment of hypertension in different parts of the world.

Reductions in mortality rates have also been reported. In Canada over a 10 year period, the increased incidence of hypertension (Tu *et al.*, 2008b) may in part be due to the reduced mortality rate of 15.5% suggesting early detection and appropriate treatment had improved patient survival with diagnosed hypertension (Tu *et al.*, 2008a). Indeed,

Tu et al (2008a) suggested the previous projections reporting increased prevalence rates for hypertension in developed countries (Kearney *et al.*, 2005) may be underestimated due to detection and treatment improvements not being taken into account. A greater prevalence of hypertension requires strategies to prevent hypertension in future populations and should include lifestyle modifications that can reduce BP (Tu *et al.*, 2008b). Projection figures for lower BP suggest a possible reduction in mortality in normotensive middle-aged and older individuals (Lewington *et al.*, 2002). Over the long term, reductions of 10 mmHg SBP may provide 40% and 30% reduction in stroke and IHD mortality respectively while smaller reductions of 2 mmHg in SBP may produce 10% and 7% lower stroke and IHD mortality respectively (Lewington *et al.*, 2002). Reductions in BP of this magnitude may be achieved via lifestyle interventions such as increased PA (Kelley & Kelley, 2000; Whelton *et al.*, 2002) which may provide the opportunity for improved health outcomes and reduced levels of hypertension and mortality.

2.2.5 Blood pressure and disease

Elevated BP is a risk factor for CHD, stroke, IHD, heart failure, peripheral arterial disease (PAD), renal disease and renal failure (APCSC, 2003; Graham *et al.*, 2007; JNCPDETHBP, 2004; Navar & Hamm, 2012; Powell *et al.*, 2011; Psaty *et al.*, 2001; Rosenman *et al.*, 1976; Schnohr *et al.*, 2002; Yusuf *et al.*, 2004). Hypertension has been found to be a robust risk factor for CHD in global and local populations. The INTERHEART study utilising data from 52 countries and multi ethnicities and the Copenhagen City Heart study found hypertension to be a strong risk factor for CHD in men and women (Schnohr *et al.*, 2002; Yusuf *et al.*, 2004) with SBP more strongly associated with the risk for CHD than DBP (Rosenman *et al.*, 1976). Data from the Framingham Heart Study suggested a cumulative doubling of risk for CVD in men and women with BP levels 130 - 139/ 85 - 89 mmHg compared to those with lower BP ≤ 120/ 80 mmHg and many of the individuals with BP ≥ 130/ 85 mmHg also had other risk factors associated with MetS compared to normotensives (Vasan *et al.*, 2001). These findings suggested the synergistic effect of risk factors may further increase their level of risk for CVD (Isomaa et al., 2001; Zhang et al., 2006) although evidence for this effect is controversial (Iribarren et al., 2006; Mente et al., 2010). Evidence also

suggested the risk factors were unbalanced in their contribution for risk, with hypertension and glucose abnormalities being the most prominent (Mancia *et al.*, 2007). A meta analysis of individual data from one million adults indicated a continuous relationship between BP and stroke and IHD mortality across a large age range (40 – 89 y) down to low BP levels of 115 / 75 mmHg (Lewington *et al.*, 2002). The risk for stroke and IHD mortality was doubled for every increase of 20 mmHg SBP and 10 mmHg DBP in both men and women (Lewington *et al.*, 2002). Elevated levels of SBP were also indicated in PAD with increases of 10 mmHg conferring 35% increased risk for PAD in women ≥ 45 y (Powell *et al.*, 2011).

Reduced hypertension has been linked to improved health outcomes for CHD and CVD. Over a thirty year period of cardiovascular monitoring in a Swedish population, reduced BP and cholesterol in men resulted in 37% reduction in CHD (Wilhelmsen, 1997). In Japan, reduced BP levels and reduced prevalence of hypertension from 1965 to 1990 was associated with a reduction in stroke incidence, stroke mortality and CHD incidence (Ueshima, 2007). In 90% of patients, hypertension preceded the development of heart failure while the lowering of SBP (110 – 130 mmHg) was consistently found to be beneficial to health (JNCPDETHBP, 2004). Over ~ 10 y period a MDRD study found the progression of non-diabetic renal disease was slowed with lower BP targets (< 125/ 75 mmHg) compared to the usual higher BP target (140/ 90 mmHg) in patients with kidney disease (Sarnak et al., 2005).

2.2.6 Blood pressure trends

Hypertension usually manifests in middle age and later in life and has been labelled ‘the silent killer’ as it often presents with no apparent symptoms. The initial development of hypertension may be present in early childhood (Raitakari *et al.*, 2003) and in clinical terms, is recognised in the prehypertensive state (see: section 2.1.2). Longitudinal trends in BP have shown that prehypertension and hypertension in young adults is often accompanied by other risk factors of MetS, i.e., glucose intolerance, dyslipidemia and obesity (see: sections 2.1.3; 2.1.4; 2.1.5) which may have originated in childhood to predispose individuals to hypertension at a later age (Srinivasan *et al.*, 2006; Zhang *et al.*, 2006). Enhanced levels of SBP and greater occurrence of hypertension has been

associated with paternal premature mortality and thus may be associated to genetic and environmental risk factors (Zureik *et al.*, 2005). The prevalence, impact and control of hypertension was found to vary across different ethnic minorities suggesting other confounding issues i.e., education, socioeconomic status and poorer health care provision may also be attributing to the hypertensive risk in these populations (Gillum *et al.*, 1998; Greenlund *et al.*, 2004; JNCPDETHBP, 2004; Jones *et al.*, 2002; WHO, 2002).

2.2.7 Blood pressure in childhood and adolescence

Risk factors for CVD may begin in childhood and develop silently over many years before resulting in an adverse event (Raitakari *et al.*, 2003). The Cardiovascular Risk in Young Finns Study investigated childhood and adolescent risk factors (elevated SBP, cholesterol, smoking and BMI) associated with changes in arterial thickness resulting in atherosclerosis in later life. This study suggested that the onset of adolescence (12 – 18 y) may be the point in childhood where exposure to the risk factors starts the association with the increased risk for atherosclerosis in adulthood because in this age group the childhood risk factors were found to predict common carotid artery intima-media thickness (IMT) (a marker of pre-clinical atherosclerosis) in adults (Raitakari *et al.*, 2003). An earlier study found childhood risk factors to be associated with hypertension and the early development of coronary artery calcification in young adults 15 – 20 y later (Mahoney *et al.*, 1996). Ethnic differences in BP levels in children were found to be predictive of hypertension in later life which suggested an ethnic predisposition to hypertension may have the origins of disease operating in childhood (Chen *et al.*, 2011; Manatunga *et al.*, 1993). A trend for increasing BP levels and increasing BMI was observed in children and adolescents over 12 y intimating a strong relationship between the two risk factors (Muntner *et al.*, 2004). Increasing BP and BMI are predictive for hypertension and obesity, two of the main risk factors for MetS, CHD and CVD. Thus, the exposure to risk factors in childhood and adolescence indicate a relationship to disease in later life. These findings are important as they suggest early intervention to prevent or delay risk factor influence for disease is essential for adult health outcomes.

Summary

Hypertension has been identified as a primary risk factor for health and disease because of its prevalence, the association of increasing SBP with ageing, the concomitant increase in the risk for disease and mortality, the association with other increasing risk factors such as obesity and the possibility that its early origins may abide in childhood. Thus, the risk of hypertension provides a major public health challenge. Conversely, reduced hypertension is linked to improved health outcomes. Evidence implies a reduction in the status of hypertension in global populations could have vast implications for a reduction in the global health burden and locally, in the burden of healthcare for individual nations and regions. Importantly, hypertension is a modifiable risk factor which may be attenuated or prevented by changes in lifestyle behaviours. This suggests that changes in lifestyle behaviour if implemented in early childhood and retained throughout adulthood may provide the opportunity for enduring health, improved quality of life and reduced mortality. Lifestyle behaviours include increased PA and evidence for the value of PA and the risk imposed by physical inactivity has been gained by further epidemiologic studies.

2.3 Physical activity, cardiovascular risk and blood pressure

Evidence for the beneficial effects of PA for health and disease have been found from epidemiologic studies over the last seventy years with ongoing research supporting the early indications that PA was an important component for improved health and mortality (Appendix V: table A5).

2.3.1 Physical activity and mortality

Early PA epidemiology attempted to explain the 'modern epidemic' of heart disease by focusing their research on the relationship between CHD and level of occupational work effort in men (Blair & Morris, 2009; Morris, 2009). The initial UK studies found differences in CHD incidence between active (bus conductors/ postmen) and sedentary (bus drivers/ government office workers) occupational effort which suggested a possible causal link between occupational PA levels and CHD (Morris *et al.*, 1953). Those

workers undertaking lower levels of occupational effort had a greater likelihood of CHD mortality than their more active counterparts. In an attempt to seek more diverse evidence for links between activity levels and occupational mortality a national necropsy survey was undertaken (Morris & Crawford, 1958). Post-mortem evidence found less heart damage in the active and heavy occupational effort individuals who had died of causes other than heart disease in comparison to the hearts of light occupational effort individuals. An additional important finding was the evidence for hypertension incidence in CHD, suggesting multiple connections between occupational PA, BP control and disease (Morris & Crawford, 1958).

By the 1960's, technical advances in the workplace and home had resulted in the decline in occupational work effort and increased overall physical inactivity in the general population (Morris, 2009). Consequently, the contribution of PA in public health terms meant that PA would have to be part of leisure time activities and subsequent studies attempted to assess non-occupational PA with the risk of CHD (Morris, 2009; Paffenbarger *et al.*, 2001). In 1976, the association between CHD and mortality rates with PA behaviour was investigated in 9376 British male, office based civil servants (Morris *et al.*, 1990). Habitual vigorous aerobic activity was found to afford greater protection against CHD in middle and early old age with halved mortality rates in comparison to those undertaking less activity. Evidence also suggested that differences in morbidity and mortality outcomes were due to variances in level and regularity of PA. Broad categories attributed levels of PA; vigorous and non-vigorous categories were assigned to sporting activities while vigorous/ heavy, moderate and light were divisions of recreational work (DIY/ gardening). Overall, only regular vigorous aerobic (sporting) activity was associated with improved CHD morbidity and mortality rates suggesting only habitual PA of vigorous level could achieve beneficial outcomes. However, other studies reported moderate activity could also provide benefits. The BRH study in 7,735 British middle-aged men assessed the relationship between PA and CHD and found participation in both moderate and vigorous PA (leisure and sporting) compared to inactivity provided a higher protection against CHD and improved mortality risk (Shaper & Wannamethee, 1991).

Research was also undertaken in the USA. Two early epidemiologic studies assessed the relationship of PA with health and mortality (Paffenbarger *et al.*, 1970; Paffenbarger *et al.*, 1978). The evaluation of occupational activity levels in longshoremen with CHD mortality found reduced levels of mortality in the more active cargo handlers than their work colleagues undertaking more sedentary employment (Paffenbarger *et al.*, 1970). The assessment of PA behaviours with health outcomes in Harvard College alumni (Paffenbarger *et al.*, 1978) from sedentary behaviour to more active alumni provided a 36% higher risk of mortality, with higher levels of PA providing a decreasing risk of mortality. Discontinuation of PA increased the risk for mortality, while participation in moderately vigorous PA in later life by previously less active individuals, reduced their level of risk to nearly that of those who had undertaken habitual PA. Thus early evidence suggested that to reduce and retain a level of protection from CHD mortality, PA needed to be current, ongoing and undertaken at a moderate vigorous level.

The earlier epidemiologic occupational studies used a crude classification in occupational PA behaviour which assumed that all individuals undertaking particular occupation employed a similar level of PA and did not consider non-occupational activity outside the workplace (Lamonte & Blair, 2009). The later studies, assessing leisure PA applied more sophisticated methods to assess PA exposure. For example, the Harvard College alumni study quantified PA levels by PA-related incremental categories of energy expenditure (kcal/ week) (Paffenbarger *et al.*, 1978). This method of assessment provided the opportunity to assess a dose-response between PA energy expenditure and mortality risk, estimate the population mortality burden conferred by sedentary living behaviour and possible threshold levels for PA for future public health messages (Lamonte & Blair, 2009). More recent studies have confirmed that increases in habitual PA subsequently reduced mortality from CHD and CVD relative to inactive individuals (Paffenbarger *et al.*, 1993; Smith *et al.*, 2000a), in both men and women with increased benefits with increasing age (Andersen *et al.*, 2000) and the effect from PA was independent from other risk factors (Rosengren & Wilhelmsen, 1997).

2.3.2 Physical activity and hypertension

The main disease focus in epidemiologic studies investigating associations with PA has been CHD and CVD. A number of reviews and meta-analyses of epidemiologic studies have compiled evidence that suggest a physically active lifestyle lowers the risk for CHD and CVD in both men and women in different populations (Berlin & Colditz, 1990; Sofi *et al.*, 2008; Wannamethee & Shaper, 2001). Fewer epidemiologic studies have been undertaken to assess the association between PA and hypertension.

Early evidence from 14,998 middle-aged male Harvard College alumni (35 – 74 y) over 6 – 10 y found a 35% reduction in hypertension risk in those alumni undertaking regular vigorous PA (1 – 2 h/ wk) across all ages (Paffenbarger *et al.*, 1983). Additional PA of light sports or additional vigorous PA did not provide a greater reduction in risk. Higher individual SBP (> 130 mmHg) or DBP (> 80 mmHg) or both predicted an increased risk for hypertension of 36%, 27% and 92% respectively and alumni with a parental history of hypertension had nearly double (83%) the risk for hypertension compared to alumni without parental history. A positive gradient between PA and obesity was observed. Body mass index of ≥ 32 unit (15% overweight) or ≥ 36 unit (20% overweight) provided a 24% or 78% increase in risk respectively of developing hypertension compared to lighter alumni. Thus, not undertaking vigorous PA, increased BP, increased BMI and parental hypertension were all predictive of hypertension in this study population.

Although fitness was not measured in the Harvard College alumni, vigorous activity requires more strenuous effort and suggests a higher level of fitness in alumni compared to their less active counterparts (Paffenbarger *et al.*, 1983). Physical fitness and hypertension incidence was investigated in 6,039 normotensive men and women (20 – 65 y) (Blair *et al.*, 1984). Fitness was categorised into two groups i.e., high and low, with 72% participants at baseline categorised as low fitness and 28% as high fitness. Low fitness compared to high fitness provided twice the risk for hypertension incidence and baseline BP measurements were strong indicators for hypertension risk. Those with BP measurements of 120 – 129/ 81 – 84 mmHg, had a three fold increase in risk of hypertension over those with lower BP and, unfit individuals had four times the level of

risk compared to high fit individuals with BP ≤ 120/ 80 mmHg. These results suggested physical fitness may be an important component of PA providing protective benefits for the maintenance of BP control and against hypertension risk in fit normotensive men and women.

Later studies have also provided evidence that both physically active and physically fit individuals have a lower risk of developing hypertension than less active and unfit individuals (Barlow *et al.*, 2006; Haapanen *et al.*, 1997; Hu *et al.*, 2004; Pereira *et al.*, 1999; Pescatello *et al.*, 2004) and hypertension risk may also be influenced by excess weight and obesity (Hu *et al.*, 2004). A Finnish study of 17, 441 men and women (25 – 64 y) investigated the single and joint association of PA and BMI on the hypertension risk (Hu *et al.*, 2004). An inverse association between PA and risk of hypertension was found in both normal and overweight individuals and regular PA was independently associated with a significant reduction in risk for hypertension in both men and women. Although overweight and obesity increased the risk for hypertension, a protective effect from regular PA was observed in both men and women regardless of the level of obesity. However, men and women of normal weight and undertaking high level PA had a 56% and 46% lower risk respectively of developing hypertension when compared to those who were overweight undertaking low levels of PA. This study also provided evidence that the beneficial effect of regular PA on hypertension risk was found in both men and women while two other studies have provided inconsistent findings in women (Haapanen *et al.*, 1997; Pereira *et al.*, 1999). One study reported an association between increases in intensity and total amount PA with a reduced risk of hypertension in men but no association was found in women (Haapanen *et al.*, 1997) while no association was observed between leisure PA and reduced hypertension risk in women (Pereira *et al.*, 1999). Furthermore, no relationship between PA and hypertension risk was found in black men and women concluding only white men undertaking leisure PA had a reduced risk of hypertension (Pereira *et al.*, 1999). Interestingly, vigorous activity was not an important predictor for hypertension risk after controlling for total PA level in men, highlighting the influence of a possible confounding factor (Haapanen *et al.*, 1997; Pereira *et al.*, 1999). The weak association between leisure PA and risk of hypertension in women may be due to lower levels of intensity and total PA undertaken by women compared to men and because the protective effect of leisure PA may occur in later

years due to the appearance of CHD in later life and the loss of pre-menopausal protection (Haapanen *et al.*, 1997).

The positive relationship between CVD risk and BP and the doubling of risk with each BP increase of 20/ 10 mmHg has recognised the importance of BP control for public health (Lewington *et al.*, 2002; Pescatello *et al.*, 2004; WHO, 2002). National and international committees have provided BP classifications (see: section 2.1.2) for optimal and diseased states and recommended PA for the prevention and treatment of hypertension via the promotion of healthy lifestyle behaviours (ESH, 2003; JNCPDETHBP, 2004; WHO, 2002, 2005). The reclassification of BP and the introduction of the 'prehypertension' category has recognised recent findings that BP as low as 115/ 75 mmHg is linked to lifetime risk of hypertension and the risk for CVD complications (Franklin *et al.*, 1997; JNCPDETHBP, 2004; Vasan *et al.*, 2002) thus emphasising the need for early interventions i.e., increased PA, to enhance BP control before a prehypertensive designation or clinical state is reached.

2.3.3 Physical inactivity

Although physical fitness can be improved with regular aerobic PA, the strength of the representation for inactivity and lack of fitness on cardiovascular risk factors is obscure (Bassuk & Manson, 2009). Regular PA is associated with reduced mortality, reduced risk of disease and improvement in risk factors that contribute to MetS. These findings suggest that physical inactivity may be linked to unfavourable health outcomes. For example, the effect of physical inactivity on BP control may contribute to sympathetic overactivity because regular exercise enhances vagal tone and inhibits sympathetic outflow (Jennings *et al.*, 1986). Some early studies reported only vigorous PA was beneficial for improved health (Paffenbarger *et al.*, 1978; Paffenbarger *et al.*, 1983). However, benefits from low level PA may not have been found because those individuals undertaking more vigorous activity may have done so from a greater fitness baseline compared to sedentary and less fit individuals, where the gain in benefits would be greater from an initial lower fitness baseline level (Lee, 2004). Later studies have provided evidence that light/ moderate levels of walking are associated with a lower risk for CHD in men (Hayashi *et al.*, 1999) and CHD and CVD in women (Lee *et*

al., 2001; Manson *et al.*, 1999; Sesso *et al.*, 1999). The combination of pace and duration provided a further reduction in risk for CHD with a similar risk between brisk walking and vigorous activity with similar total energy expenditure (Manson *et al.*, 1999). Low energy expenditure in men (≥ 1000 kcal/ wk) either from regular combined activities (walking, climbing stairs, sports and leisure activities) or from 1 – 2 bouts/ wk provided a lower risk of mortality compared to sedentary counterparts (Lee *et al.*, 2004). Thus sufficient energy expenditure undertaken via various activities appears to reduce risk for CHD and premature mortality in men and women. Conversely, a sedentary lifestyle in middle-aged men undertaking leisure activities of < 1 h/ wk compared to ≥ 3 h/ wk had over twice the risk of developing MetS (Lakka *et al.*, 2003). A predictable risk for CVD was found in women whose sedentary behaviour included prolonged sitting of > 16 h/ day compared to sitting for < 4 h/ day (Manson *et al.*, 2002).

The compilation of global evidence regarding risk factors for health has implicated physical inactivity in the causation of ~ 2 million deaths per annum and in the genesis of hypertension, cardiovascular and other metabolic diseases across the world (WHO, 2002). Indeed, the recognised role of physical inactivity in the global burden of disease and mortality, provoked the World Health Organisation (WHO) to urge countries to provide and adopt national strategies for increased exercise and recommended ≥ 30 min of regular moderate intensity exercise most days of the week (WHO, 2004). In the UK the current public health guidelines for adults include 30 – 60 min of moderate intensity exercise ≥ 5 days/ wk although recent evidence suggests only ~ 38% of men and ~ 28% of women achieve this level of activity (BHF, 2006, 2012a; Nichols *et al.*, 2012). In 2009 - 2010 in Great Britain, the compliance by children (11 y – 15 y) for 1 h/ day of moderate/ vigorous exercise was poor; only 24% (range 29% to 20%) of boys and 14% (range 18% – 10%) of girls achieved recommended guidelines with exercise participation decreasing with age (Nichols *et al.*, 2012). In Wales and Scotland exercise participation was lower than figures from previous years and only marginally improved in England (Nichols *et al.*, 2012). Thus, research findings that low level PA in some populations has been found to be beneficial for improved health outcomes are important as they largely reflect recommendations for PA in public health guidelines and may provide the opportunity for greater compliance via daily life activities. However, there is inconsistent epidemiologic evidence regarding the appropriate intensity level and

amount of PA required for improved health benefits for men and women. Indeed, following the establishment that PA was associated with a decreased risk of mortality and disease, the focus of epidemiologic research diverted to examine the different components within the association itself (Lee, 2009). These components consisted of frequency, intensity, duration and type of PA and were collectively termed the 'dose response'.

2.3.4 Dose response

A major question regarding the dose response was: *'What was the optimal dose of PA required to produce a specific health benefit?'* (Haskell, 2001). The answer to this question has important public health implications. For example, an understanding of the minimal dose of PA required for improved health outcomes could be related to enhance PA recommendations in public health messages. Currently in the UK, adult participation in recommended levels of PA is low (BHF, 2006) thus future PA recommendations must be realistic and achievable to encourage compliance. Evidence for recommendations may be achieved by a greater understanding of the singular and inter-relationship of the various components of a dose response of PA for various health outcomes and this information may be achieved via research from epidemiologic and experimental studies.

A review of epidemiologic studies has provided evidence for an inverse dose response relationship between volume of PA and all cause mortality rates (Lee & Skerrett, 2001). Energy expenditure of 1000 kcal/ wk, which represents current PA guidelines, provided a 20 – 30% risk reduction in all-cause mortality. There was little evidence in epidemiologic studies concerning the individual components of the dose response although increased amounts of moderate intensity activity were associated with lower rates of mortality, suggesting increasing volume of PA may have been the beneficial factor (Lee & Skerrett, 2001). Evidence for determining the beneficial effects from intensity, duration and frequency of PA was minimal or non-existent (Lee & Skerrett, 2001). The observational nature of epidemiologic research and the inability to measure intensity of PA directly was reflected in the broad categorisation of PA intensity levels which may have resulted in a confounding influence of volume of PA due to unequal

energy expenditure between intensity categories of PA (Lee, 2009; Lee & Skerrett, 2001). In addition, epidemiologic research relied on self reporting questionnaires to provide evidence of PA behaviour which has been shown to be less reliable for light and moderate intensity PA compared to the reporting of vigorous PA (Ainsworth *et al.*, 1993; Chasan-Taber *et al.*, 1996; Lee, 2004) with potential issues of bias when distinguishing between categories of intensity of PA (Shephard, 2003). Thus, epidemiologic studies do not provide evidence of causality but they do provide evidence for the likelihood of a given effect (Lee, 2009). Experimental research via the employment of the randomised controlled trial (RCT) imbues inherent qualities which afford features of control, specificity and accurate measurement and may provide the opportunity to attribute 'cause and effect'. The RCT can accurately differentiate between various intensities of exercise and control volume of exercise thus providing improved ability to elucidate the relationship between the dose response of exercise and health.

Summary

The findings from epidemiologic studies support the notion that regular PA and increased fitness may reduce the risk for CVD, CHD and hypertension and enhance BP control. The findings from early epidemiologic research had limitations because the variability in the findings regarding the beneficial effects from PA may have been due to variance in different participant characteristics i.e., aerobic fitness, rather than real differences between different intensity levels. Indeed, the broad categorisation of PA intensity levels may have been confounded with volume of PA and self reporting of PA may not have reflected actual PA levels. However, regardless of the epidemiologic research limitations, recognition for the value of PA and the associated risks from physical inactivity has resulted in UK national guidelines for increased exercise participation of 30 – 60 min of moderate intensity exercise ≥ 5 days/ wk. Although the epidemiologic research provided some evidence for a dose-response relationship between PA and the risk of disease, the dose response *per se* requires greater elucidation to provide specific evidence of a desired effect for a particular health outcome. Greater specificity requires greater study control which may not be afforded by epidemiologic studies. Evidence for the dose response of exercise via the individual or joint

contribution of components of the dose response may be achieved from experimental studies which may strengthen current epidemiologic findings and promote increased understanding regarding BP control, exercise and health outcomes.

2.4 Exercise and the autonomic nervous system

2.4.1 Dose response and exercise

A key component in the dose response of exercise in relation to health outcomes is intensity of exercise because it has a vital role in producing either favourable adaptations or detrimental health consequences via increased exercise (Haskell, 2001). Key considerations for the role of intensity in defining the response to exercise include the intensity classification for a determined bout of exercise and the increase in intensity needed to provide a critical stimulus for a health related response and outcome (Haskell, 2001). An increased understanding of the physiological benefits or detrimental effects from various levels of intensity of exercise may improve standardisation classifications and aid in establishing the relationship between intensity of exercise and health outcomes (Haskell, 2001).

2.4.2 Intensity

Intensity characterises the overload on the cardiovascular system and in experimental intervention studies the intensity of exercise is based mainly in relative terms i.e., individual capacity (Haskell, 2001). Exercise intensity is traditionally classified into six categories; very light, light, moderate, hard (vigorous), very hard and maximal (Pollock *et al.*, 1998). The reflection of exercise intensity may be expressed in different forms which include a percentage of an individual's $\dot{V}O_{2max}$, a percentage of age related HR_{max}, the percentage of maximal WR and via the individual's subjective perception of their exertion by their rate of perceived exertion (RPE) (ACSM, 2006a; Borg, 1998; Buckley & Eston, 2007). An improvement in cardiovascular endurance requires an overload of the aerobic metabolic pathway and for most individuals this requires undertaking an exercise intensity between 50% - 85% of their $\dot{V}O_{2peak}$ (moderate to high intensity exercise) to bring about adaptation in the cardiorespiratory system for aerobic

capacity to increase (Karvonen *et al.*, 1957) cited in (Ehrman, 2003). In healthy individuals for general exercise prescription, the upper level to improve $\dot{V}O_{2peak}$ is usually set at 85% because beyond this level there is little fitness gain, an increased risk of injury and a possible increase in an adverse cardiovascular event (Ehrman, 2003; Pollock *et al.*, 1998).

In exercise research testing, an individual's $\dot{V}O_{2max}$ or $\dot{V}O_{2peak}$ is often attained because it is considered the gold standard for the criterion of individual fitness providing a measured limit for aerobic work capacity and an individual maximal indicator from which individual exercise intensity levels can be calculated, aiding in the standardisation of procedures and improving study control (ACSM, 2006a; Rowell, 1993a). Ultimately, the research testing exercise intensity level should reflect the desired overload which directly relates to the study purpose, the physiological interest and the testing population undertaking the treatment or intervention. The most common intensity classifications reported in physiological exercise research testing are moderate, high and severe intensities of exercise.

Moderate intensity

Moderate intensity exercise is defined as activity between 40 – 59% $\dot{V}O_{2max}$ or 55 – 69% of age predicted HR and RPE range 12 – 13 (Pollock *et al.*, 1998). Pulmonary $\dot{V}O_2$ uptake is determined by pulmonary blood flow and the increase in $\dot{O}_2$ extraction causes $\dot{V}O_2$ to increase until it reaches a steady state condition i.e., the increase in $\dot{V}O_2$ is equal to the increase in mean rate of muscle $\dot{O}_2$ utilisation (Whipp, 1994). In moderate intensity exercise $\dot{V}O_2$ rapidly achieves a steady state within a relatively short time period with such adaptation dependent on the WR and fitness level of the individual (Whipp & Wasserman, 1972). Moderate intensity exercise is the domain which is incorporated into public health messages for exercise prescription and is reflected in aerobic exercise over durations of 20 – 60 min $\geq$ 5 days per week. The use of a realistic intensity classification and exercise duration period is employed to ensure this system is low risk and amenable to all age groups, in healthy individuals and in clinical populations with limited exercise capacity (Pollock *et al.*, 1998).

High intensity

High intensity exercise is defined as activity between 60 – 84% $\dot{V}O_{2max}$ or 70 – 89% of age predicted HR and RPE range 14 – 16 (Pollock *et al.*, 1998). The upper boundary of high intensity exercise (the fatigue threshold) is related to critical power (i.e., the notion that individuals can maintain a specific submaximal work output without fatigue which represents the upper limit of sustained tolerable work) and other indicators of aerobic fitness such as $\dot{V}O_{2max}$ (Carter *et al.*, 2005; Hill, 1993). The time to exhaustion at the critical power level is limited and work above this level enters the severe intensity domain.

Severe intensity

Severe intensity exercise is defined as activity ≥ 85% $\dot{V}O_{2max}$ or ≥ 90% of age predicted HR with RPE range 17 – 19 (Pollock *et al.*, 1998). Exercise at this intensity has been described as tolerable but predictable for a short duration (~ 5 min to 45 min) (Carter *et al.*, 2005) and individuals cannot achieve a constant WR that provides a specific percentage of $\dot{V}O_{2max}$ because such attainment is transient and cannot be maintained (Whipp, 1994). An individual's $\dot{V}O_2$ cannot be stabilised and continues to rise until fatigue transpires when $\dot{V}O_2$ reaches its maximum level (Gaesser & Poole, 1996).

2.4.3 Acute and chronic effects of exercise on blood pressure

Exercise may be undertaken as a single bout of exercise or as multiple bouts of exercise which accumulate over time to provide a training effect (Haskell, 2001; Thompson *et al.*, 2001). Exercise training provides an increase in the capacity for exercise and permits more prolonged or vigorous exercise with a greater acute effect following exercise which includes reduced SBP and DBP (Thompson *et al.*, 2001). A single bout of exercise provides a transient change in the short term recovery period following the exercise bout while exercise training may elicit tissue and system adaptation via increases in capacity or efficiency (Haskell, 2001), enhancing exercise scope and permitting more vigorous or more prolonged activity for a greater acute effect (Thompson *et al.*, 2001). Thus the benefits of exercise for health may be achieved by an acute transient effect, a training effect or an interaction between the two effects (Haskell, 2001). The acute response may be augmented via repeated bouts of exercise

although any benefits may be fleeting if the exercise is not continued (Haskell, 2001). For example, plasma triglycerides were reduced following a single bout of exercise and further reduced following four consecutive days of exercise (Gyntelberg *et al.*, 1977) but such reduction may be reversed after exercise abstinence of a few days (Oscai *et al.*, 1972).

2.4.4 Chronic exercise training intervention studies

Recent meta-analyses investigating BP responses in men and women following exercise training have reported similar mean BP reductions in normotensive (4/ 3 mmHg) and hypertensive (6/ 5 mmHg) individuals respectively (Fagard, 2001; Whelton *et al.*, 2002). An earlier review reported women experienced a greater BP reduction (15/ 10 mmHg) compared to men (9/ 8 mmHg) with an average combined gender BP reduction of 11/ 8 mmHg (Hagberg *et al.*, 2000). The variance in the magnitude of BP reduction between studies may reflect the variability between trials from numerous dissimilarities such as sample size, participant and exercise training characteristics and methodological issues resulting in design differences that might affect BP reduction values (Hagberg *et al.*, 2000; Whelton *et al.*, 2002).

Dose response relationship and chronic exercise training

Evidence from randomised controlled trials suggested chronic exercise training of 30 – 60 min moderate intensity exercise (≤ 70% $\dot{V}O_{2max}$) undertaken 3 - 5/ wk significantly reduced BP with no significant benefit in BP reduction via increased intensity thereafter (Fagard, 2001; Whelton *et al.*, 2002). For example, no significant differences were observed in the magnitude of BP reductions in normotensive and hypertensive individuals among trials of dissimilar training interventions including frequency (<120; 120 – 150; > 150 min/ wk), intensity (low; moderate; high) or training mode (bike; walk/ jog; mixed; other) (Fagard, 2001; Whelton *et al.*, 2002). The post-exercise BP response was similar for frequencies 3 – 5/ wk and session lengths of 30 – 60 min (Fagard, 2001) and low to moderate intensity exercise (50% - 70% $\dot{V}O_{2max}$) provided a similar or greater reduction in BP compared to high intensity exercise (> 70% $\dot{V}O_{2max}$) with a reduction from moderate intensity exercise training of 11/ 8 mmHg compared to 8/ 7 mmHg from the high intensity exercise training (Hagberg *et al.*, 2000). In

hypertensive middle-aged men and women, SBP and DBP was significantly reduced following 8 wk of 50% intensity exercise training. The exercise training was composed of different programme designs regarding duration/ frequency/ session/ wk (Ishikawa-Takato *et al.*, 2003) with the greatest magnitude of SBP reduction compared to 30 – 60 min/ wk achieved from 60 – 90 min/ wk and, no further significant reductions in SBP from increased exercise volume observed thereafter. There was no significant association between frequency of weekly exercise and reduced BP and no further benefits in BP reduction from > 3 – 4 sessions/ wk. Similar findings were observed in young normotensive men undertaking 4 week blocks of exercise training at 60 – 70% WR_{max} on 3 days/ wk or 7 days/ wk (Jennings *et al.*, 1986). Blood pressure was reduced 10/ 7 mmHg and 12/ 7 mmHg respectively suggesting greater frequency and work load > 3 days/ wk did not provide any further substantial reductions in BP. Thus, these findings suggest there is a ceiling effect in the relationship between the dose response of exercise and reduced BP and that current public health guidelines of 30 – 60 min moderate intensity exercise ≥ 5 days/ wk may be more than adequate to enhance BP control.

2.4.5 Acute effect from a single bout of exercise

Reduced BP has been reported following a single bout of exercise and following three sessions of a training exercise programme (Hagberg *et al.*, 1987; Pescatello *et al.*, 1991), suggesting an acute depressor effect on BP from exercise. The cessation of exercise training has been found to return BP to pre-existing levels within 1 – 2 wk implying the reduction in BP may actually be reflecting an acute post exercise response related to recent exercise exposure rather than a training effect (Kenney & Seals, 1993; Meredith *et al.*, 1990; Seals *et al.*, 1997; Thompson *et al.*, 2001). Systolic BP had greater susceptibility to change over shorter time periods from exercise training compared to DBP which took ≤ five times longer for a reduction to occur (Seals *et al.*, 1997). This is an interesting finding because increased SBP is the key BP component implicated in hypertension with age (see: section 2.2.3). A comparison of acute and chronic training exercise studies investigating the effect of exercise on ambulatory BP suggested chronic exercise training induced greater BP reductions than acute exercise interventions although one reason for this finding may have been because training

participants had higher initial mean BP values (140 ± 11/ 88 ± 6 mmHg) compared to the acute study participants (133 ± -1/ 83 ± 10 mmHg) which could provide a leeway of greater magnitude for BP reduction (Thompson *et al.*, 2001).

Dose response and the acute effect of a single bout of exercise

The dose response parameters to produce a reduction in BP following a single bout of exercise have not been defined. Reductions in ambulatory BP have been reported following a single bout of exercise (Brownley *et al.*, 1996; Guidry *et al.*, 2006; Taylor-Tolbert *et al.*, 2000) particularly in hypertensive individuals. Ambulatory BP pressure reduction following a single bout of low (40% $\dot{V}O_{2max}$) and moderate (60% $\dot{V}O_{2max}$) intensity exercise of short (15 min) and long (30 min) duration was investigated in middle-aged, overweight hypertensive men (Guidry *et al.*, 2006). All exercise conditions reduced SBP (4 – 6 mmHg) for 9 h while DBP was reduced (3 – 5 mmHg) for ≤ 3 h following low intensity exercise and 9 h following moderate intensity exercise. Another study reported BP was reduced (6/ 4 mmHg) in hypertensive individuals but not in normotensive individuals following a single bout of 20 min moderate intensity exercise which persisted for 5 h and thereafter diminished (Brownley *et al.*, 1996).

Greater reductions in BP of longer duration have been achieved following a single bout of exercise of greater intensity (Quinn, 2000; Taylor-Tolbert *et al.*, 2000). In sedentary middle-aged and older hypertensive men three 15 min bouts 70% $\dot{V}O_{2max}$ intensity interval exercise interspersed with 4 min of seated recovery, reduced 24 h ambulatory mean BP by 7 mmHg, reduced SBP by 6 – 13 mmHg for 16 h and DBP by 5 mmHg for 12 h (Taylor-Tolbert *et al.*, 2000). Single bouts of 50% $\dot{V}O_{2max}$ and 75% $\dot{V}O_{2max}$ intensity exercise have yielded significant and sustained reductions in BP in hypertensive middle-aged men and women with average ambulatory SBP reduced by 4/ 9 mmHg and DBP 5/ 7 mmHg respectively (Quinn, 2000). The reduced BP was significantly sustained following the 75% intensity exercise bout for 13 h compared to 4 h from the 50% intensity exercise bout. Similar SBP reductions following single bouts of 50% and 70% $\dot{V}O_{2max}$ intensity exercise were achieved in a laboratory setting in older hypertensive men and women (Hagberg *et al.*, 1987). Following the 50% intensity bout, SBP was reduced 8 mmHg during the first hour of recovery while the 70% intensity bout elicited a reduction of 13 mmHg over an initial recovery of 3 h. Diastolic

BP did not alter significantly in either intensity bout. These findings support the notion that intensity of exercise may be a key determinant in BP responses following exercise in hypertensive individuals however caution should be applied because a confounding influence of volume of exercise may have been present in some studies (Hagberg *et al.*, 1987; Quinn, 2000).

The magnitude of the effect of exercise on BP control may be lower in normotensive individuals compared to the effects in hypertensive individuals. Two studies reported similar findings following a maximal bout of exercise in normotensive young and middle-aged men and women (Coats *et al.*, 1989; Piepoli *et al.*, 1993). Systolic BP was initially elevated immediately following exercise but significantly reduced at 45 - 60 min post exercise while DBP was reduced for the full 60 min. No measures were taken beyond 60 min. Another study observed a significant reduction in SBP and DBP at 30 min following a maximal exercise bout in hypertensive and normotensive individuals but the reduction was not sustained beyond 60 min (Somers *et al.*, 1991). The magnitude of the SBP reduction in hypertensive individuals was twice that compared to the SBP reduction in normotensive individuals while the magnitude of the DBP reduction was the same between both groups. In young normotensive individuals following a maximal exercise bout, SBP was reduced (not significantly) (< 6 mmHg) at 60 min while DBP was significantly reduced (< 10 mmHg) for the full 60 min post-exercise (Piepoli *et al.*, 1994). Following 45 min of 30%, 50% and 80% $\dot{V}O_{2peak}$ intensity exercise (with no containment of volume of exercise), SBP and DBP was significantly reduced 5/ 3 mmHg respectively ≤ 90 min post exercise in young normotensive individuals (Forjaz *et al.*, 1998). During exercise, SBP rose significantly in all three different intensity bouts with greater increases in SBP elicited by greater intensity level while DBP did not significantly change between any of the exercise bouts. Following exercise, there were no significant differences found between BP reduction and intensity of exercise with similar reductions in BP following all three exercise bouts. This finding suggested low intensity of exercise may be as beneficial as high intensity exercise in normotensive individuals for reducing BP however the study was confounded by volume of exercise. Interestingly in contrast to the exercise at 50% and 80% $\dot{V}O_{2peak}$, the exercise at 30% $\dot{V}O_{2peak}$ significantly reduced the rate pressure product during the recovery period reflecting a significant lower HR following exercise

thus a possible enhancement in cardiac vagal tone resulting from greater sympathetic inhibition. These findings have also been reported in rats following mild intensity exercise (Chen *et al.*, 1995) and with reduced muscle sympathetic nerve activity in hypertensive and normotensive individuals (Floras *et al.*, 1989; Halliwill *et al.*, 1996a) intimating improved autonomic status may be achieved in some circumstances following exercise. The reduction in the rate pressure product was also below resting levels suggesting low intensity exercise may also infer cardio-protection following exercise (Forjaz *et al.*, 1998) because cardiac risk is purported to be linked to increased myocardial O_2 demand i.e., the occurrence of angina pectoris at a constant value of rate pressure product (Robinson, 1967) and ST depression is correlated with the rate pressure product (Detry *et al.*, 1970).

Thus, although exercise has been found to reduce BP in hypertensive and normotensive individuals, the findings are inconsistent regarding the minimal dose of exercise required to induce and sustain a reduction in BP which could aid in enhancing BP control and in defining the requisite dose of exercise to ameliorate the risk for hypertension. A greater understanding of the acute physiological responses post-exercise may elucidate current findings and promote novel perspectives for future clinical and non-clinical research to aid in exercise prescription. For example, during and following a single bout of exercise the physiologic systems including the ANS respond to maintain homeostasis (Borresen & Lambert, 2008). Repeated bouts of exercise may produce an accumulated effect and physiological adaptations for improved performance which may be investigated by assessing the responsiveness of the ANS to exercise (Borresen & Lambert, 2008). Indeed, because autonomic dysfunction is implicated in the loss of BP control and increased risk of cardiac and cardiovascular disease (Brook & Julius, 2000), an enhancement in autonomic function suggests a possible improvement in health status providing a further approach to assess the benefits of exercise for health. Some evidence has intimated the mediation of autonomic function via exercise has provided improved autonomic status of greater vagal control resulting in a cardio-protective effect (Billman, 2002; Forjaz *et al.*, 1998) which may be demonstrated by the assessment of the sympathovagal balance in cardiac autonomic activity.

2.4.6 The Autonomic Nervous System

The ANS contains two divisions of afferent and efferent nerves comprising of sympathetic nerves (thoraco-lumbar) and parasympathetic (cranial and sacral outflows) nerves (Hainsworth, 1998). The effects of the two divisions are generally complimentary; the sympathetic nerves excite the heart (increased HR, conduction velocity and contractility), cause vasoconstriction of some blood vessels and decrease gastrointestinal function (as in the fight or flight response) while the parasympathetic nerves produce the opposite effects of reduced HR, conduction velocity and contractility, vasodilation of some blood vessels and increased gastrointestinal function (Hainsworth, 1998; Jordan, 1995).

The heart is innervated with parasympathetic and sympathetic afferent and efferent nerves which have a primary role in the regulation of cardiac function (Klabunde, 2005d). These nerves innovate reflexogenic areas of the heart which by mechanical or chemical stimuli emanate reflexes influencing both the heart and the constriction of the vasculature (Hainsworth, 1998). Thus sympathetic and parasympathetic nerves have a key role in the regulation of the cardiovascular system by providing optimal functioning during and following various activities and mediating some indicators of cardiac disease (Hainsworth, 1998).

2.4.7 Parasympathetic effects

Efferent vagal fibres (preganglionic fibres) which originate in the dorsal vagal nucleus and nucleus ambiguous of the brain stem leave the medulla in the tenth cranial nerves (vagal nerves) and enter the heart within the right and left vagus nerve effecting vagal influence over the heart (Jordan, 1995). The vagal nerves contain the parasympathetic supply to the heart, thus the parasympathetic effect is often referred to as the ‘vagal effect’. The vagus nerves innervate the sinoatrial (SA) node and the atrio-ventricular (AV) conducting pathways and the atrial myocardium (Hainsworth, 1998). The slowing of the heart is achieved via efferent activity of vagal stimulation and the release acetylcholine at the SA node which effectively slows the rate for the pacemaker potential to reach threshold thereby reducing HR (Hainsworth, 1998; Klabunde, 2005b;

TFESC & TNASPE, 1996). During rest, the heart is under vagal tone reducing the intrinsic HR of 110 – 120 bpm to 60 – 80 bpm (Hainsworth, 1998; Jordan, 1995). Heart rate is dependent on the balance of sympathetic and parasympathetic influence; above the intrinsic value the sympathetic nerves are more active while below the intrinsic value the parasympathetic nerves predominate and high levels of parasympathetic influence produce a marked cardiac slowing (Hainsworth, 1998). The parasympathetic responses develop and subside faster than sympathetic influences with the maximum response occurring in 400 milliseconds (ms) (Levy *et al.*, 1970) thus a reflex action with vagal stimulation could influence HR on a beat by beat basis i.e., a delay in the next heart beat (Hainsworth, 1998). Parasympathetic withdrawal can increase HR and $\dot{Q}$ rapidly but only up to the point where sympathetic dominance becomes evident and thereafter the response of HR and $\dot{Q}$ is slowed (Hainsworth, 1998). For example, during progressive exercise the blockade of parasympathetic control of HR with atropine revealed the initial increase in HR ≤ 100 bpm was primarily due to the withdrawal of parasympathetic activity while the sympathetic blockade of cardiac receptors with propranolol provided evidence for a rising sympathetic dominance in heart rates > 100 bpm (Rowell, 1993a). Thus at the onset of exercise ≤ 40% $\dot{V}O_{2max}$, the vagal withdrawal provided rapid changes in HR and $\dot{Q}$ but thereafter the response of HR and $\dot{Q}$ was slowed (Rowell, 1993a) with total parasympathetic withdrawal at 50% – 60% VO_{2max} (Tulppo *et al.*, 1998). At ~ 100 bpm the initial significant leakage of noradrenalin from sympathetic nerve endings into circulating plasma occurs and its presence provides further evidence for a sympathetic influence of the heart and active muscles > 100 bpm (Rowell, 1993c).

2.4.8 Sympathetic effects

Efferent sympathetic fibres which arise from the cells of the intermediolateral column of the spinal cord and in the upper thoracic region innervate the atria, SA node, ventricles and conduction system of the heart (Hainsworth, 1998; Jordan, 1995). Heart rate is increased via an increase in sympathetic activity which increases the rate of the depolarisation of pacemaker cells (Hainsworth, 1998). Sympathetic stimulation increases the stimulus spread rate throughout the heart, increases the contraction force and reduces the duration of systole. The latency response of sympathetic stimulation is

longer than vagal activity because the sympathetic responses develop and decay slowly i.e., up to 5 s for a change to occur with maximal responses taking 20 – 30 s due to the slow response of the heart (Hainsworth, 1998). Sympathetic control of the heart originates from neurons within the medulla where reciprocal activity controls sympathetic and parasympathetic outflow and higher cortical regions and the hypothalamus can alter autonomic function via input into the medullary regions (Klabunde, 2005d). Sympathetic neurons are implicated in tonic stimulation of the heart and vasculature (Klabunde, 2005d). In resting conditions the vasculature is under a state of partial constriction from ongoing sympathetic vasoconstriction innervation activity (Jordan, 1995; Wallin & Fagius, 1988) and the level of sympathetic activity which innervates the vasculature dictates the level of resting BP (Jordan, 1995).

High levels of sympathetic action are responsible for high HR during exercise (Hainsworth, 1998). The onset of exercise causes an increase in HR due to vagal withdrawal with metaboreceptors in exercising muscles contributing to the sustained vagal inhibition (Hainsworth, 1998). An increased sympathetic response and the progression of exercise elicit corresponding reductions in parasympathetic activity and increases in sympathetic activity and HR (Hainsworth, 1998). Exercise training may cause an adaptive response to the cardiovascular system via enhanced parasympathetic control of HR resulting in a reduction in resting HR and during sub-maximal work with little effect on maximal HR (Hainsworth, 1998; Macor *et al.*, 1996; Yamamoto *et al.*, 2001). During exercise, sympathetic activity has been found to increase significantly at different levels of activity (Macor *et al.*, 1996). For example, increased sympathetic activity was reported at relatively low work rates of 20% maximal workload (Macor *et al.*, 1996), with no increases in sympathetic activity below the anaerobic threshold (Yamamoto *et al.*, 1991) and with initial increases in sympathetic activity at 50% – 60% VO_{2peak} followed by significant increases thereafter and corresponding pronounced increased levels of circulating plasma catecholamines (Nakamura *et al.*, 1993).

2.4.9 Heart rate control mechanisms

There are two main mechanisms that control HR; the intrinsic cardiac mechanism and various reflexes which provide complex and interrelated reflex actions (Hainsworth,

1998). The intrinsic cardiac mechanism is the primary control mechanism for cardiac rhythm and the reflexes include the baroreceptors, chemoreceptors, cardiopulmonary receptors and respiratory sinus arrhythmia (RSA) (Hainsworth, 1998; Klabunde, 2005b, 2005d).

2.4.10 Intrinsic control of heart rate

The SA node containing pacemaker cells is located in the posterior wall of the right atrium and is the primary pacemaker site within the heart (Klabunde, 2005b). In the absence of hormonal or neural influences, the intrinsic automaticity of the SA node is 100 – 120 bpm, which decreases with age and is dominated by either sympathetic influence above the intrinsic rate or parasympathetic influence below the intrinsic rate (Coumel *et al.*, 1995; Hainsworth, 1998; Klabunde, 2005b). Parasympathetic influence dominates during rest, is progressively withdrawn during PA and exercise and gradually increased during recovery in normal individuals although this pattern of autonomic activity may vary in diseased states (Arai *et al.*, 1989; Hainsworth, 1998).

2.4.11. Baroreceptors

Baroreceptors detect distortion within the walls of some arteries which include the carotid sinuses and the aortic arch (Hainsworth, 1998). The carotid sinus baroreceptors are located on the internal carotid artery and are innervated by the sinus nerve of Hering which joins the glossopharyngeal nerve while the aortic arch baroreceptors join the vagus nerve and both afferent pathways lead up to the medullary vasomotor centre (Klabunde, 2005d). Increased BP initiates a rapid and increased firing of the individual receptors and nerves while reduced BP results in a low or silent firing response (Hainsworth, 1998; Klabunde, 2005d). The carotid sinus baroreceptors operate in an approximate range of 60 – 180 mmHg thus an increased or decreased firing rate is dependent on the deviation from normal BP (Klabunde, 2005d). A maximal carotid sensitivity occurs at normal mean BP (95 mmHg) and deviation from this ‘setpoint’ results in large changes in baroreceptor firing rate (Klabunde, 2005d). However the setpoint and the response curve is not fixed thus in acute and chronic change the setpoint may be reset to a higher operating level and the resetting may occur in the

brainstem or the receptors (Klabunde, 2005d). For example, during exercise the medullary and hypothalamic centres modulate autonomic efferent responses at a particular level of baroreceptor firing, thereby resetting arterial BP to a higher level to accommodate the transitional change during exertion (Klabunde, 2005d). The resetting of the baroreceptors is achieved primarily by the feed-forward mechanism of central command (Gallagher *et al.*, 2006; Gallagher *et al.*, 2001b; Raven *et al.*, 2002) and modulated predominantly by the feed-back mechanism of the exercise pressor reflex via activation of the sympathetic nervous system (Gallagher *et al.*, 2006; McIlveen *et al.*, 2001; Ogoh, 2008). The baroreflex regulation of sympathetic activity and the corresponding effects of peripheral vasculature regulate arterial BP at rest and during exercise (Norton *et al.*, 1999; Ogoh, 2008). However during chronic shifts i.e., during hypertension or heart failure, the curve shifts to the right to reduce the firing rate for a given level of mean BP (Klabunde, 2005d) and in atherosclerosis, a reduced compliance in the carotid arteries reduces the level of distortion and thus the sensitivity of the response (Klabunde, 2005d).

The stimulation of baroreceptors increases parasympathetic activity and inhibits sympathetic activity (Hainsworth, 1998). Early evidence of a short latency (0.75 s) (sinus node inhibition) following baroreceptor stimulation implied the response was vagally mediated (Eckberg, 1976) because the sympathetic stimulation effect takes longer due to a slow heart response (see: section 2.4.8). The baroreceptors are part of a negative feedback control mechanism which brings about change in the heart and vasculature via changes in autonomic nerve activity and the baroreflex is the primary mechanism for short-term regulation of cardiovascular control (see: section 2.2.2) (Levick, 2003a). A decrease in BP from its normal operating point reduces the firing rate of baroreceptors, stimulating a rapid baroreflex response via efferent pathways which increases sympathetic activity (disinhibits sympathetic action) and reduces parasympathetic activity thereby increasing $\dot{Q}$ and increasing vasoconstriction to restore normal BP levels (Klabunde, 2005c). Conversely increased BP increases the firing rate of the baroreceptors, increasing parasympathetic outflow and reducing sympathetic activity thereby reducing $\dot{Q}$ and decreasing vasoconstriction to restore normal BP levels. The arterial baroreflex response is modulated by simultaneous interactions in the medullary centre via afferent inputs from the heart and vasculature and alterations in

other reflex cardiac control mechanisms and exercise and posture which continuously influence the central response to baroreceptor afferent activity resulting in complex reflex interactions to enable the cardiovascular system to adapt to changing conditions and demands (La Rovere *et al.*, 1995).

2.4.12 Chemoreceptors

The primary function of chemoreceptors is to regulate respiratory activity to maintain blood gases (see: section 2.2.2) but they also influence cardiovascular activity (Hainsworth, 1998; Waugh & Grant, 2001). Central chemoreceptors are located in the medulla and increase sympathetic activity to the heart and vasculature and enhance baroreflex action (Hainsworth, 1998). Peripheral chemoreceptors are located in the arch of the aorta and branches of the carotid arteries and are activated during arterial hypoxia, hypercapnia and acidosis (Hainsworth, 1998; Klabunde, 2005d). The stimulation of carotid chemoreceptors lowers HR and decreases myocardial contraction while stimulation of aortic chemoreceptors has a general sympathetic effect including a possible increase in HR which suggests a possible opposing circulatory effect during exercise, although the net effect of hypoxia and hypercapnia is an increase in sympathetic activity (Hainsworth, 1998). However because HR is also influenced by respiration, the peripheral carotid chemoreceptor effect on HR may be masked by the reflex response caused by the effects from increased respiration (Hainsworth, 1995).

2.4.13 Cardiac receptors

Cardiopulmonary receptors, which are tonically active and innervated by myelinated vagal afferents, are located at the venoatrial junctions of the heart and detect change during atrial filling and contraction (Klabunde, 2005d). Mechanical atrial distortion via increased venous return may increase HR via neural activation of sympathetic efferent activity of the SA node and reduced vagus tone (Bainbridge, 1915; Klabunde, 2005d). This reflex is termed the Bainbridge reflex and increases HR when initial HR is low (Bainbridge, 1915; Klabunde, 2005d). Stimulation of the ventricular receptor function induces a depressor reflex response, termed the Bezold-Jarisch reflex which via afferent and efferent pathways involving the vagus nerves, cause a reduction in HR and a

reduction in BP (Hainsworth, 1995). Ventricular receptor function may have an important function in cardiac diseased states but in normal individuals its role is unclear (Hainsworth, 1995).

2.4.14 Respiratory sinus arrhythmia

Respiratory sinus arrhythmia is a normal variation in HR which quickens during inspiration and slows during expiration resulting in a shortening and lengthening in R-R interval and is caused by changes in lung inflation and pressure changes (La Rovere *et al.*, 1995; Levick, 2003c). Early research provided evidence that HR responses to baroreceptor stimulation was variable throughout the cardiac cycle with virtual inhibition during early inspiration and of maximal magnitude in early expiration (Anrep *et al.*, 1936) cited in (Hainsworth, 1995). The combined effects via lung mechanoreceptors input to the brainstem and central modulation of the baroreflex are deemed to be responsible for the increase in HR during inspiration because the reduction in vagal activity from brainstem neurons inhibit cardiac vagal neurons causing a transient unresponsiveness to baroreceptor input ('gating' of the baroreflex) (Levick, 2003a). Respiratory gating of the baroreflex is influenced by breathing frequency and tidal volume (La Rovere *et al.*, 1995). Respiratory sinus arrhythmia is sustained at breathing frequency rates of 3, 6 and 12 breaths/ min but is expunged at 24 breaths/ min and RSA is increased by 15% following a 50% increase in tidal volume (Eckberg, 1980, 1983; La Rovere *et al.*, 1995). Respiration may be an influential mechanism in the modulation of arterial baroreflex control of HR (La Rovere *et al.*, 1995) because direct recordings of vagus nerve activity in dogs found reduced baroreceptor action and vagal efferent firing during inspiration (Katona *et al.*, 1970) and, in humans, angiotensin administration and neck suction caused pressure changes which resulted in the shortening and lengthening in R-R intervals from inspiration and expiration respectively (Eckberg *et al.*, 1985; La Rovere *et al.*, 1995; Smyth *et al.*, 1969).

2.4.15 Autonomic assessment approaches

Assessment approaches of autonomic function have received interest via evidence that links the ANS and cardiac events (Hohnloser & Klingenheben, 1998). Identification of

dysfunction in autonomic control can be made through various techniques which include computer analysis of spontaneous BP and HR fluctuations (see: sections 2.5.3; 2.5.6; 2.5.10) (Keselbrener & Akselrod, 1998; Parati *et al.*, 2000). Heart rate and BP are positively correlated at all ages and in both genders with a fast HR predictive of future hypertension (Brook & Julius, 2000). A common non-invasive method to assess autonomic activity is HRV which if depressed is a strong indicator for mortality in patients following an MI (Folino *et al.*, 2005). However, the HRV method only employs HR to assess cardiac autonomic function while the determination of BRS employs both HR and BP indices and thus provides a more comprehensive approach. Baroreflex sensitivity provides a measure for the reflex vagal response which has demonstrated a greater correlation with mortality (Folino *et al.*, 2005; La Rovere *et al.*, 1998a; Parati *et al.*, 2000). Perturbations in BP are buffered by the baroreflex and characterised by BRS with the clinical benefits of a high BRS attributed to the vagal effects on the heart rather than effective BP buffering (van de Vooren *et al.*, 2007). Evidence has intimated the ANS has a critical role in triggering ventricular fibrillation (Schwartz *et al.*, 1984; Schwartz *et al.*, 1976) with vagal activity providing a cardio-protective effect while sympathetic activity predisposes the heart to ventricular fibrillation and increased risk of sudden cardiac death (Billman *et al.*, 1982). Thus change in HR mediated by the baroreflex and assessed via BRS provides a meaningful opportunity to assess the ANS and autonomic cardiac status. Modification of the ANS may improve electrical stability of the heart and reduce the risk of sudden cardiac death and one intervention which has been shown to improve autonomic status in some circumstances is exercise (Billman, 2002; Billman *et al.*, 1984). Indeed, BRS has been employed to assess the autonomic reflex responses in HR and BP following exercise with enhanced BRS observed following chronic exercise training and following a single bout of exercise (see: sections 2.5.14; 2.5.15). Therefore, because the baroreflex has an important role in the short-term modulation of BP and in the variability of HR, the joint analysis of these two phenomena via the determination of BRS may provide additional insight into autonomic responses following exercise and provide an opportunity to elucidate the relationship between the dose response of exercise and health.

Summary

Intensity is a key component of the dose response of exercise because it has a pivotal role in producing either favourable adaptations or detrimental health consequences via increased exercise. Chronic exercise training and a single bout of exercise have been shown to reduce BP with greater reductions in hypertensive individuals compared to normotensive individuals and SBP having a greater susceptibility for change compared to DBP. Overall, reduced BP was found following exercise training which incorporated components of 30 – 60 min moderate intensity exercise ≥ 3/ wk while the acute effect on BP was of greater magnitude and of longer persistence with increasing levels of intensity (≤ 75%). However, the dose response parameters to produce a reduction in BP following a single bout of exercise have not been defined. Enhanced understanding for the acute physiological responses following exercise may be achieved by assessing the responsiveness of the ANS to exercise. The ANS contains two divisions of afferent and efferent nerves comprising of parasympathetic and sympathetic nerves. These nerves innovate the heart and have a key role in the regulation of the cardiovascular system by providing optimal functioning during and following various activities and mediating some indicators for disease. Assessment approaches of autonomic function have received interest from evidence that links the ANS and cardiac events with enhanced vagal activity providing a cardio-protective effect while increased sympathetic activity is linked to unfavourable health outcomes. A useful method to evaluate the sympathovagal balance in cardiac autonomic activity may be achieved by the reflex responses in HR and BP and characterised by BRS. Enhanced BRS has been linked to improved health outcomes and has also been found in some circumstances following exercise.

2.5 Baroreflex sensitivity

2.5.1 The baroreflex

Carotid and aortic baroreceptors have a primary role in the reflex adjustments which accompany acute cardiovascular stressors (Fadel, 2008) with the baroreflex being one of the body's mechanisms for the regulation of cardiovascular control. Early research established the precept for the baroreflex by describing the inverse relationship between HR and BP (Marey, 1863) cited in (Fadel, 2008) with subsequent research undertaken in animals and humans in order to identify the components of the baroreflex which has formed the basis for current understanding of baroreceptor anatomy, neural activity and function (see: section 2.4.11) and has been reviewed (Abboud & Thames, 1983; Fadel, 2008; Mancia & Mark, 1983; Sagawa, 1983). Although research on cardiovascular control via baroreceptor activities in humans has been limited due to ethical and technical considerations, evidence has accrued to suggest the importance of the baroreflex in human circulatory regulation and possibly, in a participatory role as a primary or secondary factor in some cardiovascular diseases (Mancia & Mark, 1983), with ongoing clinical research supporting a link between BRS and disease and health (Adamopoulos *et al.*, 1998; Chesterton *et al.*, 2005; La Rovere *et al.*, 1998a; La Rovere & Schwartz, 1997). For example, diminished BRS has been associated with hypertension (Bristow *et al.*, 1969; Parati *et al.*, 1988) and the inability to constrain sympathetic activity in patients with congestive heart failure (Grassi *et al.*, 1995b). Alterations in HR control and a blunted baroreflex response have been reported in patients with MI and myocardial ischemia (Osculati *et al.*, 1990; Parati *et al.*, 1997) and the clinical relevance of baroreflex dysfunction in arterial baroreflex control of HR is supported by findings of an inverse relationship between the risk of mortality following an MI and BRS (La Rovere *et al.*, 1998a; Osculati *et al.*, 1990; Parati *et al.*, 2001a). Indeed, BRS was implicated as a better prognostic marker for MI between patients with and without life-threatening arrhythmias respectively following MI compared to HRV which did not distinguish between the arrhythmia status (Hohnloser *et al.*, 1994). Evidence has also been found associating reduced BRS with natural events such as ageing (Parati *et al.*, 1995b) and imposed events such as general anaesthesia (Parlow *et al.*, 1999). A marked association between impaired BRS and smoking has also been

reported (Mancia *et al.*, 1997b). Investigations assessing BRS in diabetic patients found impairment in baroreflex control while classical autonomic testing yielded normal results (Frattola *et al.*, 1997). These findings suggest the assessment of BRS may be a superior technique for the assessment of autonomic abnormality in identifying risks which link to mortality and morbidity (Mancia *et al.*, 1997a; Parati *et al.*, 1997; Parati *et al.*, 2000). The assessment of BRS may therefore improve prognosis in diseased states and may also provide increased information for the prevention of disease. Thus, as diminished BRS appears to be linked to unfavourable health outcomes, factors that can enhance BRS may be beneficial to cardiovascular health. One factor which appears to enhance BRS in some circumstances is exercise (Billman *et al.*, 1984; Hull *et al.*, 1994; Raczak *et al.*, 2005).

Ethical and theoretical considerations do not allow direct evaluation of the baroreflex in humans thus indirect techniques have evolved to obtain BRS determination which have included invasive and non-invasive procedures (Parati *et al.*, 2000). The different techniques provide the opportunity to investigate various aspects of the baroreflex response under various conditions in order to elicit information on individual components of the baroreflex and the inter-related features that alter baroreflex function via the quantification of BRS, although due to the various individual qualities of each technique the BRS determination may not be superimposed. Currently, the commonly used methods for the assessment of BRS can be categorised broadly into two approaches; laboratory and modern methods (Parati *et al.*, 2000).

2.5.2 Baroreflex sensitivity quantification laboratory techniques

The laboratory techniques include applications of intravenous bolus injection of vasoactive drugs and neck chamber device and manoeuvres such as Valsalva, head-up tilting and lower body negative pressure (Mancia & Mark, 1983; Parati *et al.*, 2000). These techniques provide the opportunity to gain information regarding the sensitivity of the arterial baroreflex control of the circulation via analysis of BP and HR changes induced by the various controlled laboratory applications and manoeuvres (Mancia & Mark, 1983; Parati *et al.*, 1992) and interpretation of the findings is based mainly on the

magnitude of the elicited response and their modifications in various conditions and in participant status (Parati *et al.*, 1985).

2.5.3 Baroreflex sensitivity quantification modern techniques

The laboratory methods provided evidence that BRS was directly related to the variability of HR and inversely related to the variability of BP and following these observations a number of algorithms were developed to provide estimates of BRS from the combined analysis of the spontaneous fluctuations in HR and BP (Parati *et al.*, 1997). This work resulted in new techniques for the computer analysis of baroreflex function. One of the main advantages of the new techniques was the lack of a requirement for an external stimulus to the participant (Parati *et al.*, 1995a; Parati *et al.*, 2000; Parati *et al.*, 1992). The use of the reflex induced changes on HR by BP that spontaneously occurred warranted the term 'spontaneous' as a distinguishing characteristic from the term 'spot' quantification which was employed in the laboratory methods (Parlow *et al.*, 1995). The modern techniques provided a dynamic description of fast BRS modulations which could not be achieved with the traditional methods because the time required to deliver the external stimulus, record the HR reflex responses and reach the baseline condition again would take longer to achieve than the duration of the spontaneous behaviour (Parati *et al.*, 1995a).

The recording of R-R intervals (ms) and beat by beat BP (mmHg) and subsequent computer analysis over a specified time period provides a measure for BRS (ms/mmHg) which can be undertaken in either the time domain or frequency domain (Parati *et al.*, 2000) with the overall efficiency of the baroreflex usually inferred from the baroreflex control of HR (Di Rienzo *et al.*, 2009). Common BRS assessment techniques adopted in recent research include the time sequence technique (BRS_{UpUp}; $BRS_{DownDown}$) and spectral techniques of α coefficient in high frequency (HF) and low frequency (LF) ($BRS_{\alpha HF}$; $BRS_{\alpha LF}$) and the transfer function transfer gain of BRS (BRS_{TFTG}) (Kuusela, 2007; Parati *et al.*, 2000; Robbe *et al.*, 1987). These techniques provide an indirect measure of BRS and only determine BRS from the direct quantification of the effects of SBP on R-R interval changes (Parati *et al.*, 2000, 2001a). The assumptions, advantages

and limitations regarding these spontaneous BRS assessment techniques are summarised (Appendix VI: table A6).

Different approaches in the employment of a particular technique may provide variation in the magnitude of the outcome measure and currently there is no agreed gold standard in the determination of BRS providing difficulties in the validation of a chosen technique and for comparability purposes of the findings between studies. Further techniques are still being devised and updated to improve the determination of BRS (Di Rienzo *et al.*, 2001; Di Rienzo *et al.*, 2010; Pinna & Maestri, 2002; Pinna *et al.*, 2004; Pinna *et al.*, 2002) and some of these techniques include the control and measure of respiration (Hollow *et al.*, 2011; Parkes, 2011). However, the current spontaneous techniques that are commonly employed do not generally control respiration and instead employ the spectral LF component, which is not significantly affected by respiration, to provide a determination of BRS.

The assessment of the spontaneous fluctuations in SBP and reciprocal changes in R-R intervals are the focus in the modern techniques for the determination of BRS (La Rovere *et al.*, 1998b; Parati *et al.*, 2000). The baroreflex is continuously activated by small spontaneous SBP variations around a set point of an individual or condition and controls abrupt changes in BP (La Rovere *et al.*, 1998b) bringing about change in the HR response and vasculature. The relationship between SBP and R-R interval is described schematically by the stimulus response curve.

2.5.4 The stimulus response curve

The arterial baroreflex control of HR has a sigmoidal stimulus response curve (figure 2.5.1) and includes three features; a threshold, a saturation point and between these two points, a linear operating range (Di Rienzo *et al.*, 2001; Mancia & Mark, 1983; Parati *et al.*, 1995c).

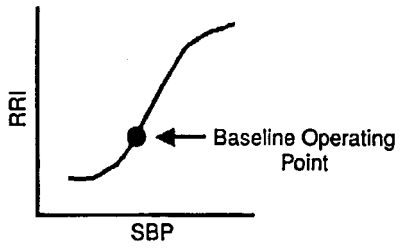

Figure 2.5.1. Stimulus response curve of the baroreflex. Taken from (Di Rienzo *et al.*, 2001)

The curve portrays the relationship between the input (stimulus) to the baroreceptors (SBP) and the reflex changes in the output (response) (R-R interval) with BRS estimated as the tangent at any given point on the curve and dependent on the BP level due to the sigmoidal relationship between BP and R-R interval (Di Rienzo *et al.*, 2001). The baseline operating point is the point of the curve corresponding to the average SBP value during daily life activities and represents the operating point where the baroreflex usually functions during spontaneous behaviour (Di Rienzo *et al.*, 2001). The laboratory techniques with the application of graded input stimuli provide an opportunity to explore the whole of the stimulus response curve of the baroreflex from threshold to saturation during steady-state conditions, while the modern techniques, which evaluate baroreflex function under conditions of spontaneous behaviour, usually only explore around the baseline operating point i.e., the linear portion of the stimulus response curve (Di Rienzo *et al.*, 2001). Indeed, modern techniques rely on an assumption that the responses of the baroreflex are approximately linear providing only limited information on baroreflex function (Parati *et al.*, 1995c).

2.5.5. Signal acquisition and preliminary processing

Electrocardiography

The HR data can be obtained by the use of electrocardiography (ECG) equipment and in the modern techniques, the ECG signal is digitised via an acceptable sampling rate (500 – 1000 Hz) by the computer together with the derivation of the R-R interval data (Berntson *et al.*, 1997; Bragge *et al.*, 2005; TFESC & TNASPE, 1996). This data is visually inspected to identify abnormal beats or artefacts in the recording followed by

manual editing to correct identification of QRS complexes (Hartikainen *et al.*, 1998). Lower resolution of 250 Hz may be adequate for typical levels of RSA in normal healthy humans (Merri *et al.*, 1990) but lower levels < 200 Hz are not desirable because they provide insufficient sampling of the QRS complex (Appendix XVII (a)). Errors in R-wave timing due to noise in the ECG signal may be resolved by smoothing or filtering of the digitised signals before data analysis to enhance the accuracy of the R-wave timing (Berntson *et al.*, 1997) although this could result in a possible dampening of the signal data.

Beat-by-beat blood pressure

Some of the early BRS techniques incorporated invasive direct arterial measurement of beat-by beat BP which limited the scope for research due to the necessity for clinical expertise with accompanying increased ethical considerations and increased participant risk. The recent innovation and introduction of a non-invasive system (Finapres/ Portapres) (FMS, Finapres Medical Systems, BV Amsterdam, The Netherlands) to assess beat by beat BP has provided the opportunity for research to expand beyond the clinical setting with the determination of BRS increasingly being undertaken for non-clinical applications. The Portapres system uses servo-plethysmomanometry which employs the volume-clamp technique (Peñáz, 1969) for measurement of arterial BP at the finger (FMS, 2005). The employment of this system for the collection of beat by beat BP data over time and the issue of BP drift which may be inherent to the study design has been explored (Appendix XVII (b)). Blood pressure values obtained by the Portapres are reported to be comparable to intra-arterial BP measurement (Eckert & Horstkotte, 2002; Huang *et al.*, 2000; Silke & McAuley, 1998) and accurately follow BP oscillations (Parati *et al.*, 1989) thus validating the use of this system for the assessment of complex BP variability components provided by spectral and sequence analysis of the BP signal (Imholz *et al.*, 1998; Omboni *et al.*, 1993). A major practical issue that influences the measurement of finger arterial BP is cold hands (Wesseling *et al.*, 1995). In cold conditions, arteries in the hands and fingers are contracted with a resultant lack of blood circulation to the finger providing an inability to achieve competent BP measurements. This problem can be overcome by providing warming body and hand apparatus and testing in suitable ambient temperatures (Appendix XVII (c)).

WinCPRS data analysis software

The WinCPRS software is a general tool for the analysis of various physiological signals and may be employed for the detection of characteristic signal features such as the R-peaks on ECG signals (Absolute Aliens Oy, 2007). Based on these features the software can generate new signals to produce sets of time domain and spectral domain signals and in addition, calculate statistical results which are typical for each signal type (Absolute Aliens Oy, 2007). The software relies on the mathematical modelling of the human cardiovascular system incorporating algorithms and calculation functions to represent physiological mechanisms that have been based on published methods to ultimately provide a numerical number which is assigned to a specific outcome measure (Absolute Aliens Oy, 2007; De Boer *et al.*, 1987; Di Rienzo *et al.*, 2009). The determination of BRS via the WinCPRS software is founded on various assumptions and limitations and include: the length of RRI is dependent on SBP and the pressure variables are dependent on the length of preceding interval; the relative contributions of sympathetic and vagal activity to the overall value of BRS are equal; following Fourier transformation the resulting frequency scale (cycles per beat) can be converted to cycles per second or Hz by assuming equal spacing between successive beats to be equal to the mean interval length; and, the SBP/ RRI interaction is linear. The limitations for the assessment of BRS via WinCPRS software include the short-term mechanisms characterised in the model cannot predict over the long term and the model is a 'simple' indirect reflection of a complex physiological process.

2.5.6 The time domain: sequence technique

The sequence method is based on computer identification in the time domain of ≥ three consecutive beats of either a progressive rise in SBP and the lengthening of R-R interval (+RR/ +SBP sequences) or a progressive decrease in SBP and a shortening of R-R interval (-RR/ -SBP sequences) with a minimal sequence specificity for accepted change of ≥ 1 mmHg for SBP and ≥ 5 ms for R-R interval (Di Rienzo *et al.*, 2001; Hughson *et al.*, 1993; Iellamo *et al.*, 1996; Parati *et al.*, 1988; Parati *et al.*, 2000, 2001a; Zöllei *et al.*, 1999). Shorter sequences of one or two beats have been found to be randomly distributed between baroreflex and non-baroreflex sequences in humans and animals (Bertinieri *et al.*, 1988; Hughson *et al.*, 1993) thus shorter sequences may not

be able to discriminate between baroreflex or non-baroreflex phenomena (Bertinieri *et al.*, 1988). Sequences lasting 3 beats were most frequent with longer sequences progressively occurring less frequently (Bertinieri *et al.*, 1988; Hughson *et al.*, 1993; Parati *et al.*, 1988). A significantly greater proportion of sequences longer than 3 consecutive beats reflected baroreflex responses compared to non-baroreflex responses and baroreflex and non-baroreflex slopes, sequence length and sequence number did not differ significantly between different conditions of rest, rest with paced breathing or cold pressor test (Hughson *et al.*, 1993). The phase shift equal to one beat i.e., the use of R-R interval signal values moving forward by one beat to compensate for assumed adjustment delay, is commonly employed (Kuusela, 2007).

The spontaneous R-R interval/ SBP sequence is based on the joint incidence of concordant changes in SBP and R-R interval signals (Di Rienzo *et al.*, 2001). The progressive beat-by-beat ramp increases or decreases in SBP are the input to the baroreceptors to be tracked while the concordant progressive ramp changes in R-R intervals reflect the baroreflex response to the SBP input. The index of BRS is taken as the slope of the regression line between linearly related changes between SBP and R-R interval (figures 2.5.2; 2.5.3) when the coefficient of the determination of the regression between SBP and R-R interval is high (> 0.85) (Bertinieri *et al.*, 1988). The relatively strict criterion of the sequence technique provides a high specificity (Parati *et al.*, 2000) which include: the separate identification of spontaneously occurring baroreceptor stimulation and deactivation; the reproducibility of average BRS following standardised behaviour/ conditions of reasonable duration (minimum 10 - 15 min) (Iellamo *et al.*, 1994); the relatively rigorous criteria of the changes in R-R interval in response to changes in SBP have been demonstrated to be dependent on the baroreflex via sino-aortic denervation (SAD) in cats (Bertinieri *et al.*, 1988) and the use of isospectral and isodistribution surrogate data (Blaber *et al.*, 1995); and, the sequence technique reflects mainly the baroreflex control of vagal drive (Parlow *et al.*, 1995) due to sequence length being < 6 beats (Borst & Karemaker, 1983; Saul *et al.*, 1991) and because the sequences were virtually abolished following parasympathetic pharmacologic denervation (Casadei *et al.*, 1992; Glick & Braunwald, 1965).

The technique provides a localised estimate of BRS achieved over a scattered time period of variable assessments via the evaluation of the HR response from short (few seconds) ramps of SBP which may require longer recordings (≥ 10 min) of BP and HR data due to the requirement of variability in SBP and RRI to obtain a sufficient amount of sequences (Di Rienzo *et al.*, 2001). Thus when the whole of the data is analysed, the BRS determination is expressed as a function of time albeit not in a continuous fashion because of the intermittent accepted number of sequences due to the specificity of the method (Kuusela, 2007). In conditions of low BP variability, only a few sequences may be obtained. Previous research has reported baroreflex sequences of ≥ 3 beats account for only 15% - 27% of all beats in the cardiac cycle (Hughson *et al.*, 1993; Parati *et al.*, 1988; Parlow *et al.*, 1995). Furthermore, as the sequences only contain a small number of beats this may result in limited accuracy for the BRS measure (Bertinieri *et al.*, 1988). Respiratory effect may also compound the limitation of this technique because respiration affects the naturally occurring oscillations which modulate BP and HR (Kuusela, 2007). For example, if the HR is slow (RRI > 1 s) and breathing is set (phased to 4 s beat) one sequence may never contain three consecutive rising data values thus, BRS evaluation would not be possible (Kuusela, 2007).

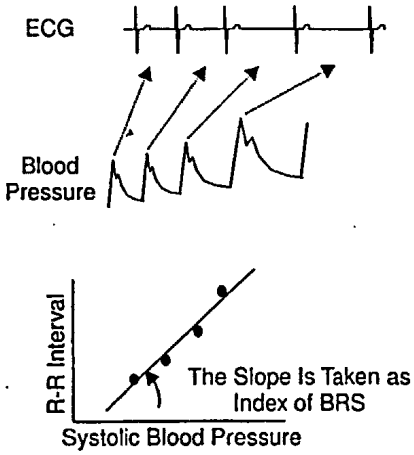

Figure 2.5.2. Steps for the determination of BRS via the sequence method. Taken from (Di Rienzo *et al.*, 2001).

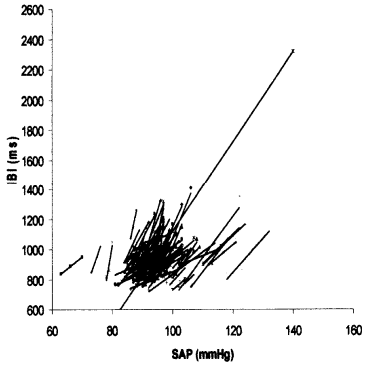

Figure 2.5.3. Plotted sequences with the slope of the regression line providing the determination for BRS.

2.5.7 Spectral domain analysis

Technical advancements for the collection and analysis of continuous BP and HR data have instigated new approaches for circulatory phenomena such as computer generated power spectral analysis (PSA) (Parati *et al.*, 1995c). The spectral methods produce a breakdown of the total variation in the data into frequency components which can be expressed in the form of a spectral density function that depicts spectral power (i.e., variance) (ms^2) as a function of frequency (Hz) (Berntson *et al.*, 1997; Parati *et al.*, 1995c; TFESC & TNASPE, 1996). These are generally accepted as: very low frequency (VLF) (0.00 - 0.04 Hz); LF (0.04 - 0.15 Hz) and HF (0.15 - 0.4 Hz) (see: section 2.5.9), with LF and HF being the two major components of interest. The spectral components may be quantified by either fast Fourier transform (FFT) or autoregressive (AR) modelling (Parati *et al.*, 1995c), which are the two most common approaches for spectral analysis (Berntson *et al.*, 1997). The separation of the components of the signal based on their frequency ranges should discriminate between the faster and slower mechanisms that contribute to regulatory control and may provide additional insight into the associated influences of parasympathetic and sympathetic modulation and activity (Akselrod, 1995).

2.5.8 Fast Fourier transformation or autoregressive modelling

The frequency domain analysis can be undertaken with either nonparametric FFT modelling or parametric AR modelling with the power estimated from the area of power spectral density curve under the corresponding frequency component (Delaney, 2002; Hartikainen *et al.*, 1998).

The FFT is the most common nonparametric model and was developed from the Fourier transform discovered by Jean Baptiste Fourier (1768 – 1830) who found a periodic function of time (signal) could be based on a series of sines and cosines thus the transform moved a calculation from amplitude as a function of time to amplitude as a function of frequency (Delaney, 2002; Priestly, 2001). The FFT spectrum is derived from all data in the recorded signal including both regular oscillations (defined spectral peaks) and irregular oscillations (non-defined peaked broadband powers) thus reflecting

the entire signal variance. This is in contrast with AR modelling which uses the raw data to identify the best fitting model from which a number of peaks and the final spectrum are derived (Berntson *et al.*, 1997; Parati *et al.*, 1995c). Physiological signals may include other interfering signals and such problems may be resolved with filtering and noise reduction techniques to eliminate or attenuate the undesired interference (Winter & Patla, 1997). Smoothing techniques are usually undertaken before the computing of the FFT spectrum from the data segment with the purpose to smooth or shape the resulting spectrum (Delaney, 2002). Smoothing techniques are employed to fit the data to a smooth curve that passes through the middle of the random additive noise and the most common smoothing technique is digital filtering (i.e., Butterworth low-pass filter) which assumes the lower frequency components are signal and the higher frequency components are noise (Winter & Patla, 1997). Smoothing may also help to resolve problems such as spectral leakage; a spectral response that distorts and obscures other inherent responses impacting on power estimation (Kay & Marple, 1981) although such procedure may reduce the frequency resolution i.e., lowers the ability to distinguish between spectral responses of two or more signals (Cerutti *et al.*, 1995; Kay & Marple, 1981). Comparable results may be achieved between FFT and AR modelling when FFT modelling is employed with some degree of signal smoothing and AR modelling is undertaken with sufficient complexity (Hartikainen *et al.*, 1998; Parati *et al.*, 1995c; TFESC & TNASPE, 1996).

2.5.9 Frequency components

The frequency components are quantified in terms of their relative power (variance) and are collectively known as the power spectrum. The unit of frequency is hertz (Hz) and this is defined as the number of cycles or oscillations per second (Clapham & Nicholson, 2005). There are three main frequency domains; VLF, LF and HF.

Very low frequency

Long period rhythms are found in the VLF range (0.00 - 0.04 Hz) and although not fully understood they are thought to relate to long-term mechanisms such as circadian rhythms (Berntson *et al.*, 1997), thermoregulation (Fleisher *et al.*, 1996; Malliani *et al.*, 1991), the renin-angiotensin system (Akselrod *et al.*, 1981; Cerutti *et al.*, 1995) or to the

dynamics of the hormonal systems (Kuusela *et al.*, 2003). The origin and frequency of the oscillations in the VLF region are unknown (Kuusela *et al.*, 2003). Major baroreflex fluctuations and highly variable BRS have been reported at VLF (Eckberg & Kuusela, 2005) and investigation of VLF phenomena may require specific methodologies and long periods of uninterrupted data (Bigger *et al.*, 1992; Cerutti *et al.*, 1995). Although the VLF band is thought to have important clinical applications i.e., high levels of VLF in post-MI is linked to increased mortality risk and is similar to observations in advanced cardiac failure and following heart transplantation (TFESC & TNASPE, 1996), the fluctuations are often disregarded because their origins and mechanisms are unclear thus the main research interest is directed toward the LF and HF regions (Berntson *et al.*, 1997; Malliani *et al.*, 1991; Parati *et al.*, 1995c).

Low frequency

The LF range (0.04 - 0.15 Hz) is compiled of both sympathetic and parasympathetic contributions with increases in LF considered to be a consequence of increased sympathetic activity (Cerutti *et al.*, 1995). In humans, spectral techniques have revealed the presence of spontaneous oscillations of arterial pressure and sympathetic nerve activity at ~ 0.1 Hz (Mayer waves), which are thought to result from an oscillation of sympathetic vasomotor tone because they are markedly attenuated or abolished following α-adrenoceptor blockade (Cevese *et al.*, 2001; Julien, 2006) and are thought to have either a central or baroreflex origin (Berntson *et al.*, 1997; Julien, 2006). However, due to the broad width of the LF band and parasympathetic activity operating at frequency levels as low as 0.05 Hz (Koh *et al.*, 1994) the 0.1 Hz rhythm may be contaminated with VLF and HF rhythms (Berntson *et al.*, 1997). Both parasympathetic and sympathetic pharmaceutical blockades attenuate LF cardiac rhythms by ~ 75% (Pomeranz *et al.*, 1985) suggesting an interaction or degree of non-linearity between sympathetic and parasympathetic activity due to a combination of parasympathetic and sympathetic modulation (Berntson *et al.*, 1997) possibly due to out of phase sympathetic and parasympathetic responses which come into phase at around 0.1 Hz because of the inherent delay in the sympathetic response (Saul *et al.*, 1991). Thus although LF and HF contain parasympathetic tone and LF explicitly is not thought to reflect the sympathetic component *per se* due to the vagal influence, in general for BRS assessment the LF band is considered to reflect sympathetic modulation and its changes

(Pagani *et al.*, 1986; Pagani *et al.*, 1988) with such variation thought to originate from the characteristics of the BP control system (Cevese *et al.*, 2001; Hyndman *et al.*, 1971; Robbe *et al.*, 1987). The dominance of baroreceptor mediated vagal influence of 0.1 Hz R-R interval fluctuations and the central frequency of 0.1 Hz for LF R-R interval and BP rhythms suggest a reflection of baroreflex resonance frequency (Berntson *et al.*, 1997; De Boer *et al.*, 1987; Sleight *et al.*, 1995) and because healthy humans operate along the relatively linear portion of the baroreflex response curve, changes in BP trigger corresponding changes in vagal cardiac efferent activity suggesting a quantitative relationship between the two features (Berntson *et al.*, 1997; Rea & Eckberg, 1987). This evidence supports the use of spectral techniques in the determination of BRS and in particular those measures incorporating the LF domain (Cevese *et al.*, 2001).

High frequency

The HF component has a wide range (0.15 - 0.4 Hz) and is synchronized with respiratory rate due to the mechanical variations and intrathoracic pressure changes from breathing activity (Cerutti *et al.*, 1995) and is often referred to as the respiratory frequency (Parati *et al.*, 2000). The HF oscillations are linked to RSA fluctuations (Altimiras, 1999; Cerutti *et al.*, 1995) and are generally considered to be a marker of parasympathetic activity because of their mediation by the vagus nerve on the heart (Cerutti *et al.*, 1995). The HF oscillations are caused partly by an inhibition of the vagal tone during inspiration via central influences on the cardiovascular centre and via peripheral reflexes arising from thoracic stretch receptors thus both central and peripheral influences contribute to RSA (Altimiras, 1999). Respiratory sinus arrhythmia is considered to be strongly mediated by vagal influences because RSA is abolished in animals following vagotomy and in animals and humans following blockade with atropine (Coker *et al.*, 1984). Animal and human studies also suggest HF fluctuations in HR are mediated almost entirely by fluctuations of efferent parasympathetic activity because only parasympathetic modulation is capable of rapid HF adjustments in HR (Hartikainen *et al.*, 1998). Thus, the power of HF is commonly employed as an index of vagal activity (Altimiras, 1999; Eckberg, 1983; Hayano & Yasuma, 2003).

2.5.10 Spectral BRS techniques

The spectral BRS techniques are based on three main points (De Boer *et al.*, 1987; Pagani *et al.*, 1988; Parati *et al.*, 2000; Robbe *et al.*, 1987): a subdivision of BP and R-R interval data into short segments of BP and R-R interval ranging from 128 to 1024 beats; the quantification of each segment by either FFT or AR modeling of R-R interval and SBP spectral powers in the LF and HF regions where the signals display a high coherence (> 0.5); and, the squared root of the ratio of R-R interval and SBP powers (referred to as the α coefficient in the LF and HF regions) ($BRS_{\alpha LF}$ and $BRS_{\alpha HF}$) (Pagani *et al.*, 1988) or the calculation of the gain of the transfer function between SBP and R-R interval, commonly employed in the LF region only (BRS_{TFTG}) (De Boer *et al.*, 1987; Robbe *et al.*, 1987).

Blood pressure and HR signals should contain the same frequency components and have a correct phase relationship i.e., change should occur firstly in SBP followed by change in R-R interval (Kuusela, 2007). The calculation of the phase difference provides evidence that when the phase difference is negative, the changes in SBP predict changes in R-R interval thus, the phase difference defines the phase relationship between SBP and R-R interval signals with an assumption that the SBP signal is the primary factor (Kuusela, 2007). The signals should also have good coherence indicating similarity in signal behaviour and linearity (Mulder, 1983). Coherence is high at ~ 0.1 Hz in the LF region and over the HF band which suggests at these frequencies SBP and R-R interval oscillate in the same way (Kuusela, 2007; Mulder, 1983). The notion of coherence is to ensure the integration of spectral density only over those frequency regions where coherence exceeds a certain limit (> 0.5) to assure synchronization of signal oscillations (Kuusela, 2007). The coherence value of 0.5 is an arbitrary measure and is employed because at this value the proportion of shared variance in both signals is equal to 50% (Robbe *et al.*, 1987) and is intended to assure the reliability of the output measures (Pinna & Maestri, 2001).

α coefficient technique

The α-coefficient BRS determination is obtained by dividing the amplitude of the R-R oscillation in each frequency band by the amplitude of the corresponding oscillation in

SBP, assuming the transfer from SBP to R-R interval is linear (> 0.5) (La Rovere *et al.*, 1998b). The coherence is computed first to ensure the assumption of linearity followed by the computation of the square root of the ratio between the spectral components of R-R interval spectrum and SBP spectrum in HF and LF to derive $BRS\alpha_{HF}$ and $BRS\alpha_{LF}$ respectively (La Rovere *et al.*, 1998b; Pagani *et al.*, 1988). Thus BRS_{α} can be quantified as:

$$BRS_{\alpha}(f) = \sqrt{(P_t/ P_s)_f}$$

(P = spectral powers, t = R-R interval, s = systolic blood pressure,
f = frequency; when coherence is > 0.5 and phase < 0)

One assumption for the α coefficient method is the ratio between R-R interval and SBP in the frequency region around 0.1 Hz (LF) and in the frequency around 0.3 Hz (HF), where they are coherent, is a reflection of baroreflex function (Di Rienzo *et al.*, 2001; Parati *et al.*, 2000). The validation for this assumption in the frequency domain is taken from animal research where continuous BP and HR recordings were taken before and after SAD in conscious cats and following SAD, there was an overall variance in R-R interval, particularly around the 0.1 – 0.3 Hz region (Di Rienzo *et al.*, 1997; Di Rienzo *et al.*, 1996; Mancia *et al.*, 1999). Interestingly, over LF (~ 0.1 Hz) the SBP power decreased markedly but conversely over HF did not change thus the R-R interval/ SBP coupling in HF region may not originate wholly from the baroreflex but may be due to other central and peripheral mechanisms such as respiration (Di Rienzo *et al.*, 1997; Parati *et al.*, 2000) suggesting the baroreflex is a major determinant of R-R interval/ SBP coupling only in the LF region (Parati *et al.*, 1992). Moreover in both frequency regions, the modifications in SBP and R-R interval powers were accompanied by significant reductions in the α coefficient thus, when coherence is high (> 0.5), the α coefficient is validated as an index of BRS in the frequency domain (Di Rienzo *et al.*, 2001; Parati *et al.*, 2000).

Transfer function transfer gain technique

Transfer function analysis which characterises the response of a linear time-invariant system in terms of gain and phase shift in frequency regions is a commonly employed technique in short-term (< 10 min) investigations of cardiovascular control (Maestri *et*

al., 1998; Pinna & Maestri, 2001; Robbe *et al.*, 1987; Saul *et al.*, 1991). The gain between SBP and R-R interval provides an indication for the transfer from SBP (mmHg) to R-R interval (ms). The basic assumption for the BRS_{TFTG} technique is the modeling of a linear system in which the SBP signal is the input and the R-R interval signal is the output (Kuusela, 2007; Mulder, 1983). The transfer function indicates the gain (ratio of output to input) of the system which represents the strength of the output signal (R-R interval) when a specific change occurs in the input signal (SBP) (Kuusela, 2007). For example, the amplitude of 15 mmHg SBP corresponding to a change of 150 ms R-R interval provides a gain of 10 ms/mmHg. The BRS_{TFTG} can be derived in different frequency regions. However because the gain is assessed where the variability is driven by SBP, the LF region is considered to be the valid stimulus to the baroreflex thus, the TFTG is commonly employed only in LF because this band best satisfies the mathematical assumption for transfer function estimation (Baselli *et al.*, 1995; La Rovere *et al.*, 1998b; Maestri *et al.*, 1998; Taylor & Eckberg, 1996). A minimum measuring period of 5 min of signal data is required to achieve a reliable determination and this technique has provided stable and high coherence values (Robbe *et al.*, 1987). The BRS_{TFTG} can be quantified as:

$$BRS_{TFTG} = (P_t/P_s)_{LF}$$

(P = spectral powers, t = R-R interval, s = systolic blood pressure,
LF is low frequency; when coherence is > 0.5 and phase < 0)

2.5.11 Standardisation procedures

Posture

The stationary collection of resting arterial BP and HR data for cardiovascular research testing is usually undertaken in a supine posture to eliminate orthostatic influences that alter the individual BP and HR indices and the dynamics between BP and HR which require adaptation by the ANS resulting in differences in autonomic modulation between supine, sitting or upright positions (Keselbrener & Akselrod, 1998).

Resting HR and BP measures change in different postures (Acharya *et al.*, 2005; Aubert *et al.*, 2003; Mourot *et al.*, 2004). In healthy individuals following an active change from supine to upright position, blood volume shifts to the lower extremities below the diaphragm resulting in a transient hypotension which is accompanied by a reflex increase in HR, cardiac contractility and vascular tone (Keselbrener & Akselrod, 1998). The mean HR has been reported to rise by 35 bpm (Aubert *et al.*, 2003). The autonomic balance also changes from a parasympathetic predominance in the supine position to increased sympathetic influence when upright (Aubert *et al.*, 2003). The transient decrease in $\dot{Q}$ elicits a reflex activation of the sympathetic nervous system and a withdrawal of parasympathetic tone (Hohnloser & Klingenheben, 1998; Stevens, 1966). The initial response of increased HR to the change in posture results from vagal inhibition (Ewing *et al.*, 1980) followed by a secondary, more gradual increase in HR which may reflect the arterial baroreflex compensation for the transient fall in BP with further vagal inhibition and greater sympathetic enhancement (Keselbrener & Akselrod, 1998). This is reflected in the power spectrum as a reduction in HF and an increase in LF domains (Aubert *et al.*, 2003). Low frequency fluctuations (< 0.12 Hz) in the supine position are mediated almost entirely by parasympathetic activity while following orthostatic change to upright, LF fluctuations are mediated by sympathetic and parasympathetic influences (Pomeranz *et al.*, 1985). Although LF oscillations are thought to reflect both parasympathetic and sympathetic influence, it has been suggested that LF oscillations are mediated mainly by parasympathetic influence (Uusitalo *et al.*, 1996) and reflect sympathetic outflow (Malliani *et al.*, 1991). At ~ 20 s of assuming an upright standing position, HR decreases with the return to normal BP which may also be associated with an initial overshoot of BP causing a rapid vagal stimulation of the sinus node and, within 30 s from the onset of standing, stabilisation of the circulation should be attained (Keselbrener & Akselrod, 1998).

Head-up tilt testing

Head-up tilt testing is a widely accepted procedure to assess the human cardiovascular response to orthostatic stress (Benditt *et al.*, 1996; Wieling & Karemaker, 2002) and is particularly useful in clinical research to assess autonomic dysfunction (Mathias & Bannister, 2002; Parry *et al.*, 2009) via testing protocols outlined in the principle recommendations of the ACC expert consensus document for tilt table testing (Benditt

et al., 1996) and the updated Newcastle protocols (Kenny *et al.*, 2000; Parry *et al.*, 2009). When the tilt procedure is not be required to induce a syncope episode but merely employed to activate an autonomic response to a change in body position, the tilt methodology may be altered to reflect the required outcome. The advantages of employing head-up tilt testing include the passive nature of the manoeuvre for orthostatic stress with improved procedural control during testing although the inducement of a pre-syncope or syncope episode or other adverse event and the evocation of stimuli which produce an unwanted autonomic response are possible disadvantages.

Tilt testing requires the employment of an appropriate tilt angle for autonomic manipulation. Tilt angles between 60º - 80º are routinely utilised in research studies in clinical and non-clinical populations to provoke sufficient orthostatic stress without increasing the incidence of syncope during the assessment of cardiovascular responses (Benditt *et al.*, 1996; Cooper & Hainsworth, 2002; Fu *et al.*, 2005; Kenny *et al.*, 2000; Kurbaan *et al.*, 2003; Lipsitz *et al.*, 1990; Steinback *et al.*, 2005; Tulppo *et al.*, 2001). Investigations regarding the susceptibility to syncope following tilt in healthy adolescents (12 – 18 y) (Lewis *et al.*, 1997) and reproducibility of tilt in healthy adult males (23 – 40 y) (Sumiyoshi *et al.*, 1999) concluded reasonable specificity for tilt could be achieved with tilt angles of 60º. Moreover, tilt > 60º did not provide any substantial additional effect on $\dot{Q}$ or sympathetic activity (Zaidi *et al.*, 2000) and the comparison of tilt between 60º and 80º found no major differences in test outcomes (Benditt *et al.*, 1996). Thus in non-clinical research, the relative stability of haemodynamic effects of tilt at ≥ 60º, suggest tilt angles of > 60º may be unnecessary (Wieling & Karemaker, 2002; Zaidi *et al.*, 2000).

The tilt procedure may be useful to employ in the assessment of autonomic modulation following exercise because the manoeuvre may induce a different physiological response compared to that obtained from a supine position, providing additional evidence for change in the cardiovascular system via the activation of the sympathovagal balance (Aubert *et al.*, 2003; Bloomfield *et al.*, 1997; Iida *et al.*, 1999). Tilt testing may also result in a more sensitive outcome measure for BRS which may be of benefit in the analysis of cardiovascular control because autonomic reactivity

observed under a stressor may provide insight beyond that gleaned from resting measures alone (Lee *et al.*, 2003). For example, following a single bout of constant and interval exercise the recovery of supine cardiac autonomic activity was complete at 24 h, while in upright conditions the autonomic status was still disturbed at 48 h (Mourot *et al.*, 2004). After short-term (2 wk) (Lee *et al.*, 2003) and long term (7 month) (Hedelin *et al.*, 2001) chronic exercise training, a tilt procedure identified autonomic change of greater vagal influence which was not detectable in the supine position. Conversely, evidence of sustained sympathetic dominance during rest with increased LF compared to the detrained state was observed following tilt which coexisted with a training bradycardia in champion athletes suggesting heavy dynamic exercise may have an adverse effect on the neural control of HR (Furlan *et al.*, 1993). Thus the incorporation of a tilt manoeuvre may identify autonomic change which may not be detectable in supine resting conditions and may also help to provide a better description for the autonomic modulation following various exercise activities. The technique for BRS determination may also dictate the usefulness for the incorporation of tilt. For example, during supine testing conditions the sequence technique may provide few/ no sequences that are acceptable for sequence assessment (see: section 2.5.6). However, during tilt with greater BP variability there may be more sequences of data and thus an improvement in the ability to achieve a satisfactory sequence BRS outcome measure (figures 2.5.4; 2.5.5).

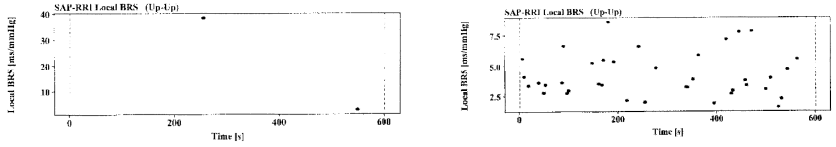

Figure 2.5.4. Accepted BRS sequences in resting conditions for same participant in supine (left panel) and during tilt (right panel) with a progressive rise in SBP and the lengthening of R-R interval (+RR/ +SBP sequences) with a minimal sequence specificity for accepted change of ≥ 1 mmHg for SBP and ≥ 5 ms for R-R interval when the coefficient of the determination of the regression between SBP and R-R interval > 0.85.

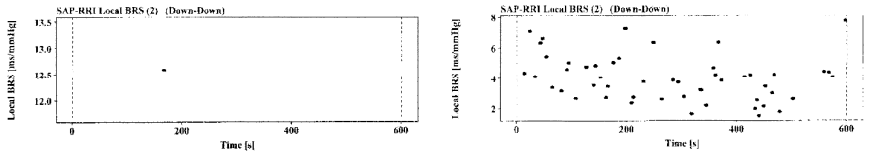

Figure 2.5.5. Accepted BRS sequences in resting conditions for same participant in supine (left panel) and during tilt (right panel) with a progressive decrease in SBP and a shortening of R-R interval (-RR/ -SBP sequences) with a minimal sequence specificity for accepted change of ≥ 1 mmHg for SBP and ≥ 5 ms for R-R interval when the coefficient of the determination of the regression between SBP and R-R interval > 0.85.

Participant aerobic fitness is an important consideration in exercise research testing and there is contradictory evidence regarding the effect of aerobic fitness on orthostatic tolerance (Murrell *et al.*, 2011a, 2011b). Lowered orthostatic intolerance has been observed in young highly trained athletes (Levine *et al.*, 1991; Raven & Pawelczyk, 1993) and has been associated to various features. These include an attenuation of baroreflex responsiveness to tilt from neural inhibition of the baroreflex due to cardiac hypertrophy and a reduced transmission of sympathetic influence in vascular tone (Ogoh *et al.*, 2003) or to increased venous compliance resulting in increased blood pooling (Pawelczyk *et al.*, 1988). In young and older men and women, orthostatic tolerance was unaffected by training fitness, age or a single bout of moderate intensity exercise (Carroll *et al.*, 1995; Hernandez & Franke, 2005; Murrell *et al.*, 2011a, 2011b) while other studies have suggested orthostatic tolerance was improved by aerobic fitness (Convertino, 1993; Murrell *et al.*, 2011a; Winker *et al.*, 2005) and may be an effect from increased blood volume from regular exercise (Convertino, 1991) via maintenance of SV in tilt (Murrell *et al.*, 2011a). Overall, these findings suggest most healthy populations do not suffer from orthostatic intolerance from a tilt procedure with the possible exception of young athletes undertaking high levels of endurance exercise training and thus, this population may be more susceptible to risk during a tilting procedure.

Circadian rhythms

Circadian rhythms are cyclical fluctuations that occur regularly each solar day (Reilly, 2007). Both short term BP and HR display circadian variation (Furlan *et al.*, 1990;

Mancia *et al.*, 1997c) with higher BP and HR values occurring during the day and lower values occur during the night and during sleep (Mancia *et al.*, 1983; Mancia *et al.*, 1997c; Smyth *et al.*, 1969). Autonomic day-night changes were characterised by sympathetic predominance during the day and vagal predominance during the night; the reduction in nocturnal LF activity and increased HF activity was suggestive of reduced sympathetic outflow and increased cardiac vagal tone during night-time hours (Furlan *et al.*, 1990). Following waking, the rapid rise in sympathetic activity with a concomitant simultaneous vagal withdrawal intimated a circadian pattern in the sympathovagal balance (Furlan *et al.*, 1990) which has been proposed as a possible mechanism underlying the increased incidence of acute MI and sudden cardiac death in the early morning hours when changes in cardiac autonomic tone are most rapid (Wennerblom *et al.*, 2001).

The circadian variation exhibited by the ANS suggests the short and long term determination of BRS may be influenced by circadian rhythms (Hossmann *et al.*, 1980). Supine and tilt BRS was increased at 03:00 and 12:00 suggesting a circadian variation for both the vagally mediated baroreflex and the sympathetically mediated baroreflex (Mancia & Mark, 1983; Turton & Deegan, 1974). Over 24 h a pronounced variability in BRS in healthy individuals was observed displaying enhanced nocturnal BRS (Parati *et al.*, 1988). Daytime BRS variability (09:00 – 21:00) was high in healthy individuals undertaking non physical activities although BRS was higher and BP lower in the mornings (09:00 – 12:00) (Cooper *et al.*, 2007). These findings imply the assessment of autonomic regulation via BRS should be undertaken at the same time of day to mitigate any possible confounding circadian influence.

Respiratory control

Respiratory frequency rhythms in autonomic nerves are translated into changes in discharge frequency of the SA node thus RSA frequency differs with breathing rate (Berntson *et al.*, 1997). Respiration influences the cardiovascular system via attenuation of the interbeat interval component of the baroreflex by RSA (see: section 2.4.14) resulting in smaller baroreflex responses and reduced sensitivity during inspiration and greater baroreflex responses and sensitivity during expiration (Eckberg *et al.*, 1980; Mancia & Mark, 1983). The RSA is usually reflected in HF HR

oscillations (0.15 – 0.4 Hz) i.e., the typical frequency range of normal adult respiration (Song & Lehrer, 2003). If the respiratory frequency decreases < 0.15 Hz it becomes measured as LF and not as HF (Brown *et al.*, 1993) thus HF is employed as a measure of parasympathetic activity only if respiratory frequency and volume are carefully controlled, thus paced breathing is a usual practice in measures assessed via HRV (Hartikainen *et al.*, 1998). However, spectral analysis for BRS determination provides an opportunity to avoid most respiratory influence by the selection of frequency bands (LF) below the respiratory frequency and the modern methods for BRS determination do not generally control respiration (Parati *et al.*, 2000). Indeed, the adoption of a different breathing frequency to minimise respiratory effects may require some individuals to increase notably their mental effort of breathing which may introduce an additional experimental control variable (Patwardhan *et al.*, 1995) which could interfere with the reproducibility of the measure (Parati *et al.*, 2001b).

The lack of cardiac respiratory control has been questioned for the determination of sequence BRS (Hollow *et al.*, 2011). Sequence analysis without respiratory control provided a BRS measure (23 ± 3 ms/mmHg) which was 3 ms/mmHg less than the determination achieved employing mean expiratory BRS only (26 ±5 ms/mmHg). However, whether or not either measure was a 'true' BRS value could not be confirmed because currently there is no agreed means of validating any baroreflex measuring technique (Hollow *et al.*, 2011; Laude *et al.*, 2008; Parati *et al.*, 2004). It was suggested that the discrepancy magnitude of 3 ms/mmHg was important because significant changes in BRS (3 ms/mmHg – 6 ms/mmHg) have been found from smoking (4 – 6 ms/mmHg) (Mancia *et al.*, 1997b), ageing (3 – 5 ms/mmHg) (Monahan *et al.*, 2000; Parati *et al.*, 1995b) and by exercise training (3 ms/mmHg) (Costes *et al.*, 2004; Galbreath *et al.*, 2011; Iellamo *et al.*, 2000; La Rovere *et al.*, 2002; Monahan *et al.*, 2000; Pagani *et al.*, 1988) and the removal of the respiratory contamination may increase the sensitivity of the sequence technique to detect important clinical change (Hollow *et al.*, 2011). Although this supposition may be correct, an important caveat for respiratory control and BRS determination was the requirement for a long recording period of 1 h to achieve the necessary amount of inspiratory sequences (mean 18/ h) because inspiration was usually not long enough to accommodate three heart beats. A usual short term sequence analysis length is ~ 10 min and a short recording period may

be an important feature in the research design. Thus in some circumstances, longer recording periods of ≥ 15 min may be highly impractical. Furthermore, the significant differences achieved via the usual application of the modern techniques have provided evidence of significant change and therefore remain of clinical relevance and of practical importance.

Hydration

Exercise increases the metabolic demand resulting in increased body temperature and loss of body fluids, primarily via sweating and reduced plasma volume, the effects of which are increased with the severity of exercise (McArdle *et al.*, 2000b; Sawka *et al.*, 2007). Hot conditions can also increase hydration needs (Sawka *et al.*, 2005) and fluid loss may severely strain circulatory function which may ultimately impact on exercise capacity and thermoregulation (McArdle *et al.*, 2000b) and alter autonomic control of HR (Carter III *et al.*, 2005). Dehydration may have a detrimental effect upon cardiovascular control during and after exercise via a reduction in baroreceptor responsiveness (Charkoudian *et al.*, 2003), a lower ability to sustain arterial BP (Gonzalez-Alonso *et al.*, 1997) and an attenuation of autonomic cardiac stability (Carter III *et al.*, 2005) with the possible consequences of a reduction in BRS, a decrease in orthostatic tolerance and a relative increase in HR at rest (Charkoudian *et al.*, 2003). Exercise induced dehydration may be prevented by adequate pre-hydration and rehydration strategies to maintain plasma volume, provide optimal circulation and sweating capacity, sustain optimal performance and is a requisite for the health and welfare of participatory individuals (Sawka *et al.*, 2007). Various strategies have been incorporated in research studies to furnish adequate hydration, which include monitoring body weight to assess fluid loss following exercise (James & Doust, 1998; James *et al.*, 2010; McArdle *et al.*, 2000b), the consumption of a pre-determined amount of water for all participants following an exercise bout (Nielsen *et al.*, 1986; Niemelä *et al.*, 2008) or self administered fluid strategies to provide euhydration (Carter III *et al.*, 2005; Pober *et al.*, 2004). Hydration *ad libitum* during moderate intensity exercise (65% $\dot{V}O_{2peak}$) and throughout a 22 h study period was considered adequate to avoid plasma loss (Pober *et al.*, 2004). However, self-administered fluid strategies have been criticised because they may result in incomplete fluid replacement as a consequence of thirst being a poor index of body water requirements (Sawka, 1992) and

may be exacerbated in older individuals because ageing attenuates thirst sensitivity (Sawka *et al.*, 2007).

2.5.12 Reproducibility

The basis of testing a physiological system is to provide a disturbance to that system and assess the response which follows (Wieling & Karemaker, 2002) and experimental studies depend on the ability to achieve a statistically relevant finding (if such a finding is there). However, for the finding to be of practical use an understanding regarding the magnitude of error or level of variance present in the outcome measure is required and such error or variance is reflected in a descriptive statistic i.e., the effect size (Lipsey, 1990; Schultz & Sands, 1995). A reproducibility study allows the exploration of the effect size and the influence of characteristics on the sensitivity of the outcome measure thus providing a basis for future testing (Lipsey, 1990).

Reproducibility of the measure refers to the consistency of a test or measure to reproduce findings if similar research was to be repeated and all other considerations were equal and identify the extent of the variance in the measure caused by error (Gratton & Jones, 2004). Thus in the comparison of two samples from a study population, the larger the variance within each sample the larger the effect size would be and the lower the power of the test to detect any statistical change and conversely, the lower the variance within each sample the greater the enhancement in effect size that might be achieved and a corresponding improvement in the power of the test to detect a finding with statistical significance, if such a finding was there (Lipsey, 1990). Variance in the measure is provided by related variance i.e., heterogeneity and unrelated variance (measurement error) and thus accounts for all the variance in the outcome measure (Lipsey, 1990). This relates the reproducibility of a test to be considered in the context of the classical measurement theory which states that an observed score (X for subject i) consists of the true score and error score (Lipsey, 1990; Thomas & Nelson, 2001) and can be formulated as:

$$(X_i = T_i +/- e_i)$$

Observed score = True score +/- Error score

The observed score is that which is obtained from a test and is the sum of the true score and all the measurement error score. Realistically, all observations contain some element of error from several possible sources i.e., from the participant, the testing procedure, the instrumentation and the scoring (Thomas & Nelson, 2001). Thus the aim of the research should be to present the true score, identify the extent and origin of the measurement error and conduct procedures to reduce measurement error to a minimum. The main components of measurement error are random error and systematic bias (Atkinson & Nevill, 1998). Random error is the biological or mechanical variation in the measurement protocol. Systematic bias is a general trend in the data, either positive or negative, between repeated measurements i.e., may be higher due to a learning effect or lower due to a fatigue effect. Measures of higher reproducibility (thus lower measurement error) would provide less variation in the distribution score of the study population (Lipsey, 1990).

Absolute reliability provides information regarding the intra-individual variability of a measurement and is relevant to assess individual changes in test-retest investigations and is expressed in actual units of measurement (i.e., ms/mmHg) or as a proportion of a measured value in a dimensionless ratio (i.e., %) (Atkinson & Nevill, 1998). Consideration for reproducibility testing should include any actions or treatment effects that might impact upon the reproducibility of the measure in future testing. For example, important considerations might include issues of stability of the measure over time and inclusions of specialised testing manoeuvres i.e., tilt testing. Ultimately the reproducibility study should confirm that the measure is suitable for assessment and has the sensitivity to detect any change of interest under the planned research design thus providing insight for estimates such as effect size and statistical power (Lipsey, 1990).

There are various statistical methods to assess absolute reproducibility (Atkinson & Nevill, 1998); the coefficient of variation (CV) (dimensionless ratio) which assesses the difference between two measures and Limits of Agreement (LOA) (actual unit of measure) which assesses the level of agreement between two measures (Bland & Altman, 1986). Correlation assesses the strength of the relationship between the two measures with high correlation (> 0.8) thought to reflect a high level of reproducibility. However the use of the correlation coefficient has been criticised because it is

considered to be too liberal in the estimation of measurement reproducibility (Atkinson & Nevill, 1998; Iga *et al.*, 2006) and high correlation does not always guarantee good agreement between the measures because the correlation coefficient depends on the range of observed measurements and is unable to distinguish between linear relationships lying along the line of identity and any other kind of linear relationship thus it is possible to have high correlation but poor agreement (Bland & Altman, 1986; Maestri *et al.*, 1998). Thus, the employment of LOA to assess the level of agreement between measures has become an increasingly adopted method in reproducibility research testing (Atkinson & Nevill, 1998) with the majority of BRS reproducibility studies utilising LOA for their statistical analysis (Davies *et al.*, 1999; Dawson *et al.*, 1997; Herpin & Ragot, 1997; Lord *et al.*, 1998; Maestri *et al.*, 2009).

The LOA is an alternative approach to correlation using graphical techniques and simple calculations (Bland & Altman, 1986). This method is employed across a range of participants for two repeat measurements of the same units for interval and ratio data. The Bias is the average of the difference between subjects i.e., the mean difference. The Confidence Interval (CI) is the standard deviation of the mean difference with 95% CI's representing the test-retest differences across 95% of the population and provides an estimate for the precision of the error statistic (Atkinson, 2003). The LOA plot provides a schematic measurement of error and a visual examination of the agreement between the measurements; narrow CI's suggest good agreement while wide CI's suggest poor agreement. The LOA is also useful to identify heteroscedasticity and skewness in the data which if present requires logarithmic transformation to provide a more uniform spread of the data (Bland & Altman, 1986). The presence of heteroscedasticity has practical research implications because high scoring individuals may show the lowest change (in units of the measure) in response to an experimental intervention (Atkinson & Nevill, 1998; Schultz, 1989). Indeed, the assumptions for LOA include normal distribution and no relationship between error and size of the measured value (Atkinson, 2003).

The technical error of measurement (TEM) and the standard error of measurement (SEM) are useful to identify the source and extent of error in the measure. The TEM and SEM are identical and can be used interchangeably and they estimate the level of

the precision (or imprecision) associated with the measure i.e., the level of error of the method due to both the biological and technical factors (Norton *et al.*, 2000).

2.5.13 BRS reproducibility

Although the spontaneous non-invasive BRS techniques are now routinely employed for baroreflex testing, there are only a few studies that have assessed the absolute reproducibility of these techniques (Davies *et al.*, 1999; Dawson *et al.*, 1997; Herpin & Ragot, 1997; Iellamo *et al.*, 1996; Lord *et al.*, 1998; Maestri *et al.*, 2009) and the variation between studies has resulted in conflicting findings for the reproducibility of BRS (Appendix VII: tables A7(a; b) and A8(a; b)). Limitations concerning the reproducibility of BRS (Maestri *et al.*, 2009) have included low sample size (Davies *et al.*, 1999; Herpin & Ragot, 1997; Iellamo *et al.*, 2001; Lord *et al.*, 1998), limited choice of BRS parameters (Iellamo *et al.*, 1996) and lack of protocols for between day reproducibility (Davies *et al.*, 1999; Dawson *et al.*, 1997; Herpin & Ragot, 1997; Lord *et al.*, 1998). The one study that has included a large sample size, a wide selection of BRS parameters and a protocol for between day reproducibility did not included same day reproducibility or an orthostatic manoeuvre (Maestri *et al.*, 2009). The participants in previous studies included male and female healthy individuals and cardiac patients over a large age range (20 – 83 y). Baroreflex sensitivity was determined predominantly in supine resting conditions via laboratory and modern methods utilising various techniques and manoeuvres with the employment of CV and LOA in the statistical analysis.

Same day reproducibility was assessed in two studies (Davies *et al.*, 1999; Lord *et al.*, 1998) and reproducibility over various time periods included 24 h (between day) (Iellamo *et al.*, 1996; Maestri *et al.*, 2009); wk (Herpin & Ragot, 1997; Lord *et al.*, 1998); 6 mth (Dawson *et al.*, 1997) and 1 y (Herpin & Ragot, 1997). The differences between studies did not allow direct comparison between studies and thus reproducibility has been compared by either the highest or lowest reproducibility achieved by technique (Appendix VII; table 7(a; b)) with a summary of the findings provided (Appendix VII; table 8(a; b)). Overall, reproducibility assessed via CV (%) ranged from 14 to 52% and the measurement error in LOA (ms/mmHg) ranged from 8

to 26 ms/mmHg in supine BRS measures and 3 to 4 ms/mmHg in standing BRS measures.

Reproducibility assessed via spectral indices was markedly improved in BRS measures incorporating the LF component compared to those measures incorporating HF (Davies *et al.*, 1999; Lord *et al.*, 1998; Maestri *et al.*, 2009) and overall, spectral BRS measures provided better reproducibility than time (sequence) BRS measures. Two studies incorporated patient groups and healthy individuals in the assessment of BRS reproducibility (Davies *et al.*, 1999; Maestri *et al.*, 2009) with one study observing greater variability in the BRS measure and lower agreement between the measures in healthy individuals compared to the patient group (Davies *et al.*, 1999) while the other study reported similar findings between healthy individuals and patient group (Maestri *et al.*, 2009). The sequence technique provided the highest failure rates for BRS determination due to the lack of suitable sequences and, failure to achieve a BRS outcome was substantially higher in patients compared to healthy individuals which suggested BRS determination may not be achieved in one third of patients (Maestri *et al.*, 2009) providing a possible limiting feature in the technique during resting conditions for some populations.

Due to the intrinsic physiological variability in BRS (Parati *et al.*, 1988; Parati *et al.*, 2004; Parati *et al.*, 1995c), the tests employed for investigating the neural cardiovascular control in humans produce responses with limited reproducibility (Parati *et al.*, 1985) thus manoeuvres which improve reproducibility are important. Various manoeuvres in laboratory testing were included in some of the studies and included Valsalva (Dawson *et al.*, 1997; Lord *et al.*, 1998); respiratory control (Davies *et al.*, 1999; Maestri *et al.*, 2009); orthostatic challenge (Herpin & Ragot, 1997; Iellamo *et al.*, 1996; Lord *et al.*, 1998); mental arithmetic and static hand-grip (Iellamo *et al.*, 1996). Reproducibility was markedly different between studies incorporating a Valsalva manoeuvre in the assessment of BRS reproducibility in healthy individuals (Dawson *et al.*, 1997; Lord *et al.*, 1998). One study reported the manoeuvre produced the highest reproducibility (Dawson *et al.*, 1997) while the other study reported the manoeuvre produced the lowest reproducibility (Lord *et al.*, 1998), albeit the difference in respiratory control between studies which may have been an influential feature in the

findings. The inclusion of both spontaneous breathing and paced breathing (Davies *et al.*, 1999; Maestri *et al.*, 2009) reported divergent findings regarding the achievement for the measure of BRS under both conditions. One study reported paced breathing markedly reduced the failure rate in patients with little difference in healthy individuals (Davies *et al.*, 1999) while the other study observed spontaneous breathing was predominantly more consistent with a lower failure rate in both patients and healthy individuals (Maestri *et al.*, 2009). Both studies reported paced breathing provided better reproducibility for $BRS_{\alpha HF}$, probably due to the influence and control of respiration. An orthostatic manoeuvre of standing or tilt was included in three of the studies (Herpin & Ragot, 1997; Iellamo *et al.*, 1996; Lord *et al.*, 1998) with improved BRS reproducibility observed during standing over 24 h (Iellamo *et al.*, 1996) and over 1 wk and 1 y (Herpin & Ragot, 1997). The high BRS reproducibility in standing suggested small significant changes could be detected via small sample size in both the time and spectral domains in follow-up studies with the inclusion of an orthostatic manoeuvre (Herpin & Ragot, 1997). The study which incorporated a head-up tilt manoeuvre assessed BRS prior to and post tilt with no differences found in BRS measures (Lord *et al.*, 1998). This finding suggested the usefulness of an orthostatic manoeuvre for improved BRS reproducibility was only appropriate with data collection during its employment. Mental arithmetic was also found to improve reproducibility while static hand-grip did not alter BRS reproducibility compared to resting measures (Iellamo *et al.*, 1996). Overall, the findings from these studies suggested the highest BRS reproducibility was achieved with the incorporation of spectral LF measures under spontaneous breathing and the inclusion of an orthostatic manoeuvre may markedly improve reproducibility compared to supine resting measures.

2.5.14 Exercise training and baroreflex sensitivity

The oxygen perfusion of bodily tissues at rest and during exercise is achieved via a proportional increase in $\dot{Q}$ to meet the metabolic demand (Ogoh, 2008). This distribution is accomplished by modulating the central and baroreflex mediated sympathetic control of the vasculature to ensure adequate perfusion of the tissues by the maintenance of arterial BP (Ogoh, 2008; Raven *et al.*, 2006; Rowell, 1993b). Human and animal research has established that the baroreceptors reset to a higher BP operating

point during dynamic exercise which is directly related to the intensity of exercise (Gallagher *et al.*, 2006; Gallagher *et al.*, 2001a; Gallagher *et al.*, 2001b; McIlveen *et al.*, 2001).

Exercise training is recommended as a non-pharmacological intervention for cardiovascular disease (Fagard, 2001; Hagberg *et al.*, 1993; Hagberg *et al.*, 2000; Whelton *et al.*, 2002) with the potential for therapeutic use by the alteration of cardiac autonomic function (Winsley, 2002). The adjustment of HR in response to exercise stress via the interplay of parasympathetic and sympathetic modulation enables the cardiovascular system to respond favourably to the exercise challenge (Winsley, 2002). In some circumstances, endurance exercise training may support healthy autonomic dynamics and provide a cardio-protective effect (Buch *et al.*, 2002; Maron, 2000; Schwartz *et al.*, 1984). The identification of cardiac autonomic control and the role of the parasympathetic and sympathetic limbs of the ANS in the post-exercise response may provide valuable information regarding the benefits and risks of exercise for health outcomes. The determination of BRS is one method which can be employed to investigate cardiac autonomic control.

Chronic exercise training increases cardiac vagal tone and reduces sympathetic outflow resulting in a slowing of HR at rest and during sub-maximal exercise together with an enhancement in BRS (Hainsworth, 1998; La Rovere *et al.*, 2002). A reduction in intrinsic HR and altered autonomic balance toward parasympathetic dominance contributes to a training induced resting bradycardia (Chen & DiCarlo, 1998; Katona *et al.*, 1982). The enhancement of BRS from regular exercise training produces an inhibitory effect on sympathetic activity which may help to improve outcomes following MI (La Rovere *et al.*, 2002; Mimura *et al.*, 2005). Exercise training may also bestow increased vagal influence on the heart, with decreased sympathetic influence, thus providing improved cardiac electrical stability and improved cardiac mortality (TFESC & TNASPE, 1996). Following exercise training, BRS was improved in patients suffering from diabetes (Loimaala *et al.*, 2003), chronic obstructive pulmonary disease (Costes *et al.*, 2004), postural orthostatic tachycardia syndrome (Galbreath *et al.*, 2011), hypertension (Hua *et al.*, 2009; Laterza *et al.*, 2007; Pagani *et al.*, 1988) and coronary heart disease (Iellamo *et al.*, 2000) and in healthy individuals following

moderate intensity (McDonald *et al.*, 1993) and high intensity (Heydari *et al.*, 2013) exercise training. Exercise training has also been found to reduce the age-associated decline in BRS in healthy, older men (Monahan *et al.*, 2000) and women (Bowman *et al.*, 1997a). A reduced BRS is a characteristic feature in normotensive children of hypertensive parents and exercise training has been suggested as a means for overcoming this genetic predisposition via enhancing vagal activity and increasing BRS (Lénárd *et al.*, 2005; Parati, 2005). Thus, exercise training and increased BRS appear to be associated with positive outcomes for both clinical patients and healthy individuals.

The beneficial adaptation in cardiac autonomic indices following chronic exercise training has been found with various intensities, durations and frequencies in different patient groups (Appendix VIII: table A9). Patient populations have consisted of male and female young, middle-aged and older adults suffering from cardiovascular, metabolic and respiratory disease. The exercise training protocols have included mild, moderate and high intensity training exercise of 20 – 60 min duration 2 – 6 sessions/ wk over variable training periods lasting 2 wk to 12 month. Baroreflex sensitivity was determined via laboratory and modern methods utilising various techniques. The observed enhancement in BRS ranged from 0.7 ms/mmHg to 9.3 ms/mmHg which related to a relative increase in BRS of 14% - 76% following chronic exercise training. The improved cardiac vagal influence achieved via the exercise training in patient groups may be particularly beneficial in vulnerable individuals due to the cardio-protection and improved cardiovascular control which may reduce the risk of morbidity and mortality in these populations (La Rovere *et al.*, 1998a; Osculati *et al.*, 1990; Parati *et al.*, 2001a).

Beneficial cardiac autonomic adaptation has also been reported in healthy individuals following moderate and high intensity training exercise incorporating laboratory (Valsalva) (Monahan *et al.*, 2000) and modern (sequence) techniques (Heydari *et al.*, 2013; McDonald *et al.*, 1993). Enhanced BRS and lowered resting HR was demonstrated following moderate intensity (60% $\dot{V}O_{2max}$) cycle exercise training 3 days/ wk over a 10 wk period in sedentary young (22 – 34 y) men (McDonald *et al.*, 1993) and following high intensity (80 – 90% HR_{max}) cycle sprint exercise training 3

days/ wk for 12 wk in a similar population (Heydari *et al.*, 2013). Enhanced BRS was also reported following a 3 month walking training programme (65 – 80% HR_{max}) 5 – 7 days/ wk in middle aged and older sedentary men (56 ± 1 y) (Monahan *et al.*, 2000). The average enhancement in BRS in healthy individuals was 3 ms/mmHg relating to a relative increase of 22% - 42%. Although these findings suggest the enhancement in BRS was lower in healthy individuals compared to some patient groups, the average baseline resting BRS measure may be of higher magnitude in healthy individuals. For example, in some patient groups baseline resting BRS was 3 ms/mmHg (Costes *et al.*, 2004; Iellamo *et al.*, 2000) while in healthy sedentary individuals, the lowest baseline resting BRS was 7 ms/mmHg (Monahan *et al.*, 2000) in age-matched individuals. Relative increases following chronic exercise training in BRS are proportional to baseline measures thus small increases in BRS from a low BRS baseline may reflect a large relative increase while conversely larger increases in BRS from a greater baseline level may reflect smaller relative increases in BRS. Thus the magnitude of change in BRS may be dependent on the pre-existing baseline level of BRS.

An enhancement in BRS may be associated to an increase in aerobic fitness. In young healthy adult males the enhancement in BRS following chronic exercise training was associated with an increase in $\dot{V}O_{2max}$ (Heydari *et al.*, 2013; McDonald *et al.*, 1993). Both moderate and high intensity exercise training undertaken over 10 – 12 wk period increased $\dot{V}O_{2max}$ by 10% and 15% respectively indicating the possibility that greater intensity of exercise may provide greater aerobic fitness gains over similar training periods in similar populations. However BRS has not always been linked to fitness gains. For example, BRS was enhanced following 3 mth moderate intensity training in healthy middle aged and older men but no improvement in aerobic fitness was observed (Monahan *et al.*, 2000) while conversely no enhancement in BRS was observed in an older population although $\dot{V}O_{2max}$ was increased by 16% following 6 wk moderate intensity training exercise (Bowman *et al.*, 1997b). Although it could be possible that differences between studies regarding aerobic fitness gains and BRS change may be linked to baseline fitness levels it may be unlikely because no enhancement in BRS was found with a marked increase in $\dot{V}O_{2max}$ from a low fitness baseline (21.7 $ml \cdot kg^{-1}min^{-1}$) (Bowman *et al.*, 1997b) while BRS was enhanced with no increase in $\dot{V}O_{2max}$ (Monahan

et al., 2000) from a higher fitness baseline (30.0 $ml \cdot kg^{-1}min^{-1}$). Thus the relationship, if any, between aerobic fitness and BRS has yet to be elucidated.

Variation in the magnitude of change in BRS following exercise training has been reported utilising different BRS techniques. For example, some studies have reported no change in BRS indices assessed via the neck chamber device following chronic exercise training in healthy individuals incorporating mild and moderate intensity exercise over a 10 - 30 wk period (Convertino *et al.*, 1990; McDonald *et al.*, 1993; Seals & Chase, 1989), regardless of an increase in aerobic fitness (McDonald *et al.*, 1993; Seals & Chase, 1989). Interestingly one of these studies also employed sequence BRS and reported enhanced BRS following the same chronic exercise training in the same population (McDonald *et al.*, 1993). The lack of an observed significant change in BRS assessed via the laboratory technique may be because BRS was investigated over the full range of the stimulus response curve and may provide observations of insufficient magnitude of BRS change while the modern technique evaluated BRS over the smaller physiological range of spontaneous changes in BP (McDonald *et al.*, 1993; Parati *et al.*, 2000). Differences in the magnitude of change in BRS have also been observed in hypertensive individuals following exercise training over 6 mth utilising spectral measures (Pagani *et al.*, 1988). The enhancement in BRS ranged from 5 ms/mmHg ($BRS_{\alpha LF}$) to 9.3 ms/mmHg ($BRS_{\alpha HF}$). These findings corresponded to 48% and 76% of relative change. Thus the method and technique employed for the determination of BRS may influence the magnitude of change in BRS and possibly, the ability to observe a significant change in BRS following chronic exercise training.

Some evidence suggests exercise may acutely alter the cardiac autonomic balance (James *et al.*, 2002; James *et al.*, 2012; James *et al.*, 2010; Mourot *et al.*, 2004). Although there is increasing interest in BRS in exercise and health related fields there has been very little research undertaken for BRS following a single bout of exercise. The investigation of the acute response in BRS following exercise may provide additional insight into the relationship between cardiac autonomic status and exercise.

2.5.15 Single bout of exercise and baroreflex sensitivity

The assessment of autonomic function has received interest via evidence that links the ANS and cardiac events (Hohnloser & Klingenheben, 1998). For example, alterations in cardiac autonomic control toward greater sympathetic activity have been associated with increased cardiac arrhythmias and ventricular fibrillation (Billman, 2002; Hartikainen & Camm, 2002) and the risk of sudden cardiac death (Albert *et al.*, 2000; Maron, 2000) and evidence of increased sympathetic outflow have been reported following a single bout of exercise in healthy individuals (Niemelä *et al.*, 2008; Stuckey *et al.*, 2012). Paradoxically, reduced sympathetic outflow with greater vagal tone which is suggestive of improved cardiac electrical stability (Buch *et al.*, 2002; Maron, 2000; Schwartz *et al.*, 1984) has also been reported in healthy individuals following a single bout of exercise (Convertino & Adams, 1991; Pober *et al.*, 2004; Raczak *et al.*, 2005). Increases in parasympathetic activity also reduce resting heart rate (HR) and contractility resulting in economical cardiac workload and reduced myocardial oxygen demand (Raczak *et al.*, 2005). Thus an enhancement in parasympathetic activity following exercise may be considered to provide a cardio-protective effect while conversely increased sympathetic influence may be an indicator for increased cardiac risk.

A few studies have investigated the acute effect of a single bout of exercise on BRS (Convertino & Adams, 1991; Halliwill *et al.*, 1996b; Niemelä *et al.*, 2008; Piepoli *et al.*, 1993; Ploutz *et al.*, 1993; Raczak *et al.*, 2005; Somers *et al.*, 1985; Stuckey *et al.*, 2012; Terziotti *et al.*, 2001) and these studies may provide greater elucidation for cardiac autonomic control in the short and long term time period following exercise. Findings from these studies are summarised in table 2.5.1 and a summary of the studies is provided (Appendix IX: table A10).

The studies of particular interest are those which report BRS assessment at time points between + 60 min to + 24 h post-exercise (Convertino & Adams, 1991; Halliwill *et al.*, 1996b; Niemelä *et al.*, 2008; Ploutz *et al.*, 1993; Stuckey *et al.*, 2012; Terziotti *et al.*, 2001) because they may reflect better the short and long term changes in BRS following exercise. Studies reporting BRS assessment before + 60 min are not so relevant, as any

changes may be dominated by the disturbance of cardiovascular indices that are found immediately following cessation of exercise (Savin *et al.*, 1982; Terziotti *et al.*, 2001). All studies undertaking an early assessment of short term recovery of BRS following exercise reported a reduction in BRS during the early stage of recovery (> 15 min) (Halliwill *et al.*, 1996b; Niemelä *et al.*, 2008; Piepoli *et al.*, 1993; Somers *et al.*, 1985; Terziotti *et al.*, 2001) which gradually recovered back to baseline levels over ≤ 20 min (Halliwill *et al.*, 1996b; Somers *et al.*, 1985) to > 2 h (Stuckey *et al.*, 2012) providing evidence of an altered autonomic balance which may have been associated to the volume and/ or intensity of exercise. A long recovery period with reduced BRS is associated to decreased vagal tone and increased sympathetic outflow reflecting a possible loss in the cardio-protective effect (Billman, 2002; Schwartz & Vanoli, 1981) and increased cardiac risk (Maron, 2000). During and following acute exercise, the exercise bout has been described to pertain to 'a double-edged sword' because of the risk of sudden cardiac death (Maron, 2000) and is purported to be relate to increased sympathetic activity (Nakamura *et al.*, 1993). Although such risk may be ameliorated in individuals undertaking regular vigorous exercise, the risk was still significantly higher during and following vigorous exercise compared to lighter exertion (Albert *et al.*, 2000).

Following the early depression of BRS and subsequent recovery, a number of studies reported an enhancement in BRS following exercise (Convertino & Adams, 1991; Halliwill *et al.*, 1996b; Raczak *et al.*, 2005; Somers *et al.*, 1985). Baroreflex sensitivity was increased following moderate intensity exercise (Halliwill *et al.*, 1996b; Raczak *et al.*, 2005) and maximal exercise (Convertino & Adams, 1991; Somers *et al.*, 1985) reflecting an enhancement in parasympathetic activity and a reduction in sympathetic influence suggesting these exercise bouts could provide a health benefit with reduced cardiac risk (Albert *et al.*, 2000; Billman, 2002; Maron, 2000). Conversely, other studies including sub-maximal and maximal aerobic exercise, resistance exercise and Wingate sprint exercise did not observe an augmentation in BRS (Niemelä *et al.*, 2008; Piepoli *et al.*, 1993; Stuckey *et al.*, 2012) suggesting a prevailing influence of sympathetic nervous activity and possible health risk. Thus, it is unclear how the components of a single bout of exercise influence autonomic dynamics post-exercise (Parekh & Lee, 2005). Discrepancy between study findings may include comparability

issues of exercise condition protocols, participant characteristics, methods and techniques for BRS determination and post-exercise time points.

The exercise interventions varied between studies and included a maximal graded exercise test (Convertino & Adams, 1991; Piepoli *et al.*, 1993; Somers *et al.*, 1985), Wingate sprint interval exercise (Stuckey *et al.*, 2012), resistance exercise (Ploutz *et al.*, 1993), a mixture of aerobic and resistance exercise (Niemelä *et al.*, 2008) or a single bout of exercise of one intensity (Halliwill *et al.*, 1996b; Raczak *et al.*, 2005) and only half of these studies incorporated a control condition. The exercise interventions that provided evidence of a specified duration length included exercise durations of 20 min (Terziotti *et al.*, 2001), 30 min (Raczak *et al.*, 2005), 40 min (Niemelä *et al.*, 2008) and 60 min (Halliwill *et al.*, 1996b). Greater volumes and load of resistance exercise and Wingate sprint exercise may contribute to a longer recovery of BRS indices following exercise (Niemelä *et al.*, 2008; Stuckey *et al.*, 2012) which may be more apparent during an orthostatic manoeuvre (Stuckey *et al.*, 2012) suggesting a possible greater influence of the sympathetic nervous system in BRS recovery and may also be intensity-dependent. The BRS recovery period following 20 min moderate intensity exercise (80% AT) compared to 20 min light intensity exercise (50% AT) was not significantly different although the R-R interval HF data suggested a greater persisting vagal withdrawal following the moderate intensity exercise condition compared to the light intensity condition (Terziotti *et al.*, 2001). These findings implied a possible change in the autonomic balance of HR control even between lower levels of intensity of exercise (Terziotti *et al.*, 2001). However this study and another study which incorporated two exercise conditions of light and heavy resistance exercise and one condition of aerobic exercise (Niemelä *et al.*, 2008), employed same duration length with no device to equalise work done between the different exercise conditions, providing a confounding influence of volume of exercise. None of the studies explicitly identified intensity of exercise in the exercise intervention. Two studies incorporated a single bout of aerobic exercise of moderate intensity exercise (Halliwill *et al.*, 1996b; Raczak *et al.*, 2005) but did not include a control condition. A control condition is an important consideration in experimental research because its inclusion in the protocol isolates the intervention effect and is useful to negate other possible reasons for an observed significant change, thus enhancing the potential to attribute cause and effect

(Baumgartner & Hensley, 2006; Gratton & Jones, 2004). Thus although these two studies incorporated one intensity of exercise, the lack of a control condition inhibited the explicit identification of intensity of exercise in the intervention procedure reducing the plausibility for a direct association between BRS change and intensity of exercise.

Participant characteristics and exercise history differed between studies. Most of the studies were undertaken by male participants, with the exception of two studies incorporating both male and female participants (Halliwill *et al.*, 1996b; Piepoli *et al.*, 1993). The majority of participants were healthy normotensive non-smoking young (19 – 40 y) adults although one study employed hypertensive individuals and did not provide gender, age or smoking status (Somers *et al.*, 1985). A single bout of exercise was investigated in trained participants (Convertino & Adams, 1991; Niemelä *et al.*, 2008), untrained active participants (Halliwill *et al.*, 1996b; Piepoli *et al.*, 1993; Stuckey *et al.*, 2012; Terziotti *et al.*, 2001), detrained participants (Raczak *et al.*, 2005), sedentary participants (Convertino & Adams, 1991; Halliwill *et al.*, 1996b) and participants with no exercise history provided (Ploutz *et al.*, 1993; Somers *et al.*, 1985). Thus the fitness profiles were highly variable between studies. Only three studies provided evidence of fitness status (Halliwill *et al.*, 1996b; Niemelä *et al.*, 2008; Terziotti *et al.*, 2001) which included profiles ranging from sedentary to high fitness. Aerobic fitness is considered to relate to increased vagal modulation of HR during exercise and a shorter duration of recovery following exercise (Borresen & Lambert, 2008; Javorka *et al.*, 2002; Tulppo *et al.*, 1998) which may be indicative of increased BRS. However, reduced BRS has been reported in young, very fit adults compared to moderately fit adults (Smith *et al.*, 2000b). The reduction in BRS was purported to be due to a greater impact on aortic baroreceptors (Shi *et al.*, 1993a; Shi *et al.*, 1993b) from the increased SV and blood volume induced via a training effect, resulting in an attenuation or reduction in the distortion and/ or aortic baroreceptors, thereby lowering the transduction intensity of the afferent signal to the medulla (Smith *et al.*, 2000b). Ultimately, this would cause a reduction in the aortic baroreflex response reflecting a reduction in BRS in endurance trained, fit individuals (Smith *et al.*, 2000b). Interestingly, reduced BRS was reported following moderate intensity cycle exercise and resistance exercise in young fit healthy adults (54 ± 7 ml·kg^{-1}min^{-1}) (Niemelä *et al.*, 2008) while studies providing evidence of lesser fitness of ≤ 42 ml·kg^{-1}min^{-1} (Halliwill

et al., 1996b) and AT ($W \cdot min^{-1}$): 248 ± 29 W (Terziotti *et al.*, 2001) reported enhanced or no change in BRS respectively following exercise. Other studies reporting lower descriptive fitness participant profiles (Convertino & Adams, 1991; Piepoli *et al.*, 1993; Raczak *et al.*, 2005) have also reported enhanced BRS following exercise. Thus, individual baseline aerobic fitness may influence BRS profile during recovery following a single bout of exercise.

It is interesting that although an orthostatic manoeuvre was incorporated into reproducibility testing providing improved reproducibility (Herpin & Ragot, 1997; Iellamo *et al.*, 1996), only one study (Stuckey *et al.*, 2012) investigating the acute effect of a single bout of exercise on BRS has included an orthostatic manoeuvre. Following exercise, BRS was reduced during standing suggesting a prevailing sympathetic influence while supine measures suggested BRS had returned to baseline levels. This was an important finding because evidence of sustained sympathetic influence on cardiac autonomic dynamics is suggestive of a possible cardiac risk (Albert *et al.*, 2000; Billman, 2002; Maron, 2000). Thus, an orthostatic manoeuvre may provide evidence for a different physiological response following exercise and a more sensitive outcome measure which may maximise the opportunity of observing a change in cardiac autonomic status because during supine resting conditions the sympathetic activity may be obscured by a strong vagal dominance (Hainsworth, 1998; Pomeranz *et al.*, 1985). The increase in sympathetic activity from an orthostatic manoeuvre reflects a relative decrease in HF and relative increase in LF of R-R interval and an increase in LF spectrum of BP (Bernardi *et al.*, 1997; Pagani *et al.*, 1986; Radaelli *et al.*, 1994; Saul *et al.*, 1991). Thus, an increase in LF dominance post-exercise compared to baseline measures may indicate increased sympathetic influence (Bernardi *et al.*, 1997) which may only be apparent by employing an orthostatic manoeuvre. For example, the assessment of short and long term recovery (+ 1 h, + 24 h and + 48 h) in cardiac autonomic indices following a single bout of constant and interval training exercise, demonstrated a continuing cardiovascular disturbance that was only evident at + 48 h during an orthostatic manoeuvre (Mourot *et al.*, 2004).

Evidence from chronic exercise training studies have suggested alternative approaches for the determination of BRS may provide differences in the magnitude for change in

the BRS outcome measure and in the ability to observe a significant effect, if such an effect is there. Thus BRS assessment technique may be implicated in the variance between study findings. Studies investigating supine BRS following a single bout of exercise have employed various methods and techniques to determine BRS and include laboratory techniques of phenylephrine infusion (Piepoli *et al.*, 1993; Raczak *et al.*, 2005; Somers *et al.*, 1985) and neck chamber device (Convertino & Adams, 1991; Halliwill *et al.*, 1996b; Ploutz *et al.*, 1993) and the modern method techniques of BRS_{Seq} (Niemelä *et al.*, 2008; Stuckey *et al.*, 2012), $BRS_{\alpha LF}$ and $BRS_{\alpha HF}$ (Piepoli *et al.*, 1993) and BRS_{TFTG} (Niemelä *et al.*, 2008; Raczak *et al.*, 2005; Terziotti *et al.*, 2001) (table 2.5.1). Interestingly, two of the studies which utilised the neck chamber device in the determination of BRS reported enhanced BRS at 60 min (+ 1.4 ms/mmHg) (Halliwill *et al.*, 1996b) and 24 h (+ 3 ms/mmHg) (Convertino & Adams, 1991) following a single bout of exercise. The previous studies employing the modern methods following a single bout of exercise have generally observed a reduction in BRS at 60 min (- 6 to - 12 ms/mmHg) (Niemelä *et al.*, 2008; Piepoli *et al.*, 1993; Stuckey *et al.*, 2012) with the exception of one study reporting enhanced BRS (BRS_{TFTG}: + 5 ms/mmHg) (Raczak *et al.*, 2005). Three studies utilised the laboratory technique of phenylephrine infusion for BRS determination and all studies reported an enhancement in BRS at + 60 min (+ 6 to + 8.4 ms/mmHg) post-exercise (Piepoli *et al.*, 1993; Raczak *et al.*, 2005; Somers *et al.*, 1985). These findings are contrary to those observed regarding BRS determination technique and BRS outcomes following chronic exercise training where BRS determined via spontaneous techniques was enhanced while conversely, BRS determined via a laboratory technique was not. Thus whether or not the approach for the determination of BRS is an influential feature in the likelihood to observe significant change in BRS post-exercise has not been established.

Time points to reflect the immediate to long term post-exercise responses to track the time course of events over various BRS measures have also differed between studies. For example, three studies reported BRS measures at + 60 min and did not take any measures beyond this time point (Piepoli *et al.*, 1993; Raczak *et al.*, 2005; Somers *et al.*, 1985). One study reported BRS + 60 min and + 120 min (Stuckey *et al.*, 2012), one study at + 10 min, + 55 min, + 100 min and + 145 min (Halliwill *et al.*, 1996b) and two studies at + ≤ 30 min, + 60 min, + 120 min and + 180 min (Niemelä *et al.*, 2008;

Terziotti *et al.*, 2001). Thus, these studies reflected the short term post-exercise BRS responses following a single bout of exercise. The mid to long term responses (+ 180 min to + 24 h) were reported in two studies (Convertino & Adams, 1991; Ploutz *et al.*, 1993) and did not include the short term response following exercise. Thus none of the studies have included both the short and long term BRS post-exercise responses following a single bout of exercise and therefore were unable to track the time-course of change over a comprehensive 24 h time profile.

Summary

Chronic adaptation following exercise training and repeated acute responses following a single exercise bout have been shown to improve physiological health although exercise recommendations for particular health outcomes have yet to be fully elucidated (Haskell, 2001; Thompson *et al.*, 2001). Exercise recommendations should specify the intensity, the duration and the mode of exercise. A key issue in defining the dose response is the need to establish the acute physiological response to various intensities and durations of exercise (Haskell, 2001). Greater understanding for the autonomic response following exercise may help to define the acute physiological response post-exercise and provide further evidence for the risks and benefits of exercise for health related purposes. The determination of spontaneous BRS is a non-invasive, indirect marker to reflect changes in autonomic activity (Mancia & Mark, 1983; Parati *et al.*, 2000) and may be particularly useful for assessing overall cardiovascular control post-exercise. Previous research has provided disparate findings regarding the reproducibility of BRS although overall, findings suggested spectral BRS in the LF domain may provide better reproducibility than other spectral domain measures and time domain measures (Appendix VII; table 7(a; b)). Evidence has also indicated the reproducibility of the measure may be markedly improved during an orthostatic manoeuvre compared to supine resting conditions (Appendix VII; table 8(a)). In some circumstances, BRS may be enhanced following chronic exercise training in patient populations and healthy individuals. Chronic exercise training has been found to enhance BRS in healthy individuals and patient groups providing improved cardiac autonomic status of greater vagal tone and reduced sympathetic influence. Different intensities, durations and frequencies of exercise training have provided beneficial

autonomic adaptation although there is no clear consensus as the relative merits of each component of exercise with regard to the sympathovagal balance in cardiac autonomic activity. Both moderate and high intensity exercise have been associated with an enhancement in BRS while mild and moderate intensity exercise have been implicated with no change in BRS following chronic exercise training. Furthermore the association, if any, between BRS and aerobic fitness has yet to be established. Differences in the magnitude of BRS change have been observed between different methods and techniques for the determination of BRS, intimating the choice of BRS assessment and technique characteristics may influence the likelihood of observing a significant effect following chronic exercise training, if such an effect is there. Whether BRS may be acutely manipulated following exercise is not known. Currently, there is little research that has investigated the effect of a single bout of exercise on BRS and no study has explicitly identified the influence of intensity of exercise in the intervention procedure. Variance between studies investigating the acute BRS post-exercise response include differences in participant characteristics, exercise interventions, BRS determination techniques and in the time course of events over various BRS measures. It is reasonable to assume that such diversity of participant history, exercise mode, duration and intensity of exercise, BRS determination technique and post-exercise time points would have an effect on BRS outcome measures. Thus the lack of consistency between studies may be reflected in the various findings providing difficulties for direct comparison between studies. Due to the acknowledgement by international bodies and other health agencies concerned with public health that exercise participation and in particular moderate intensity exercise participation is an important feature for health related outcomes and disease prevention, it is important that the acute post-exercise responses are fully understood. Greater understanding of cardiac autonomic status following exercise may aid in elucidating the acute post-exercise cardiovascular response which may be beneficial for providing more bespoke exercise prescriptions in public health recommendations. Further evidence for the acute cardiovascular response following exercise may also be of benefit for exercise training and research purposes.

Table 2.5.1: Baroreflex sensitivity following a single bout of exercise: summary of results

Author	Exercise bout	Time point	BRS_{Seq}	$BRS_{\alpha LF}$	$BRS_{\alpha HF}$	BRS_{TFTG}	BRS_{Phen}	BRS_{NP}
Stuckey *et al* (2012)	Single Wingate sprint	60 min	↓	–	–	–	–	–
		120 min	↔	–	–	–	–	–
	Multiple Wingate interval sprints	60 min	↓	–	–	–	–	–
		120 min	↓	–	–	–	–	–
	*Single Wingate sprint	60 min	↓	–	–	–	–	–
		120 min	↓	–	–	–	–	–
	*Multiple Wingate interval sprints	60 min	↓	–	–	–	–	–
		120 min	↓	–	–	–	–	–
Niemelä *et al* (2008)	40 min cycle 50% WR (VO_{2peak})	< 30 min	↓	–	–	↓	–	–
		60 min	↔	–	–	↔	–	–
	40 min resistance light (30% 1RM)	< 30 min	↓	–	–	↓	–	–
		60 min	↔	–	–	↔	–	–
	40 min resistance heavy (80% 1RM)	< 30 min	↓	–	–	↓	–	–
		60 min	↔	–	–	↓	–	–
	All conditions	90-180 min	↔	–	–	↔	–	–
Raczac *et al* (2005)	30 min 65% HR_{max} (220 - age)	60 min	–	–	–	↑	↑	–
Terziotti *et al* (2001)	20 min cycle 50% AT	< 30 min	–	–	–	↓	–	–
		60-180 min	–	–	–	↔	–	–
	20 min cycle 80% AT	< 30 min	–	–	–	↓	–	–
		60-180 min	–	–	–	↔	–	–
Halliwill *et al* (1996)	60 min cycle 60% (VO_{2peak})	< 30 min	–	–	–	–	–	↔
		55 min	–	–	–	–	–	↑
		100-145 min	–	–	–	–	–	↔
						–		
Piepoli *et al* (1993)	Cycle: maximal exercise bout	< 30 min	–	↓	↓	–	↓	–
		60 min	–	–	↓	–	↑	–
Ploutz *et al* (1993)	Resistance supine exercise	3 - 24 h	–	–	–	–	–	↔
Convertino and Adams (1991)	Cycle: maximal supine exercise bout	3 - 24 h	–	–	–	–	–	↑
Somers *et al* (1985)	Cycle: maximal exercise bout	< 30 min	–	–	–	–	↓↑	–
		60 min	–	–	–	–	↑	–

Note: h = hour; min = minute; < 30 min = all time points up to and including 30 min; BRS = baroreflex sensitivity; Seq = sequence; α = alpha index; LF = low frequency; HF = high frequency TFTG = transfer function transfer gain; Phen = phenylephrine; NP = neck pressure; WR = work rate; VO_{2peak} = peak oxygen consumption; 1RM = maximum weight; HR_{max} = maximum heart rate; AT = anaerobic threshold; * = standing measurement position

CHAPTER THREE

METHODS

CHAPTER 3: METHODS

General Procedures

3.1. Participants and recruitment

Participants were recruited from the staff and student body of the University of Gloucestershire on a voluntary basis via direct contact or research presentations during student lecture periods, or through association with research participants from the surrounding community or through communications with local sports/ athletic clubs in the local area. All participants were non smoking males, 18 – 35 y who were deemed healthy with no history of diabetes, hypertension or cardiac disease, who showed no signs of disease and were undertaking regular exercise (moderate exercise 5 ± 2 $h \cdot wk^{-1}$). 46 participants were included in the reproducibility study and 9 participants were included in the exercise study. None of the participants had undertaken studies of this nature previously. Details of recruitment/ retainment numbers are provided in Appendix X (a; b).

Table 3.1 Participant physical characteristics for reproducibility study

Characteristic (n = 46)	Mean ± (SD)
Age (y)	22 (± 5)
Mass (kg)	79.3 (± 11)
Stature (m)	1.80 (± 0.1)
Resting HR (b·min-1)	67 (± 11)
Resting BP (mmHg)	
Systolic	124 (± 9)
Diastolic	69 (± 6)

HR, heart rate; BP, blood pressure

Table 3.2. Participant physical characteristics for the exercise study

Characteristic (n = 9)	Mean (± SD)
Age (y)	26 (± 5)
Mass (kg)	77.9 (± 11.4)
Stature (m)	1.79 (± 0.05)
Resting HR ($b \cdot min^{-1}$)	63 (± 9)
Resting BP (mmHg)	
Systolic	129 (±11)
Diastolic	71 (± 11)
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	52.3 (± 7.5)
HR_{peak} ($b \cdot min^{-1}$)	185 (± 7)

HR, heart rate; BP, blood pressure; VO_{2peak}, peak O_2 uptake

3.2 Ethical considerations

All procedures conformed to those approved and cleared by the University Research Ethics Committee in the Sport & Exercise Laboratory Procedures Manual (UoG, 2008b) which reflects the guidelines as set down by the Declaration of Helsinki (Declaration of Helsinki, 1964).

Participants received no inducement to participate or were offered or recompensed for inconvenience and no reimbursement of expenses was provided. Participants volunteered after completing a health questionnaire (Appendix XI) and providing informed consent (Appendix XII). Informed consent included describing the nature of the study, describing any risks or benefits of participation and the right for the participant to be able to withdraw from the study at any time without negative consequences. Following enrolment onto the study, participants received written study details which included a testing schedule (Appendix XIII; XIV)

Participant data was collected and stored with regard to the Data Protection Act (Data Protection Act, 1988) and in accordance with the University of Gloucestershire guidelines (UoG, 2008a) and any withdrawing participant data was destroyed up to and including the date of withdrawal. All participant data in hard copy form was secured in a locked filing cabinet and individual identification coding was removed and replaced

with number identification that could not be traced to a particular individual. Participants were given access to their data on their request.

3.3 Procedures

Procedures undertaken for the two studies that form the basis for the present thesis conformed to the University of Gloucestershire guidelines as outlined in the Sport & Exercise Laboratory Procedures Manual (UoG, 2008b). All procedures took place in the exercise physiology laboratory of the University of Gloucestershire or the cardiovascular laboratory of the University of Gloucestershire.

3.3.1 Environmental characteristic determination

Environmental characteristics in the exercise physiology laboratory were determined at the start of the progressive exercise test (PET). Air temperature (ºC) was ascertained via a thermometer (Oregon Scientific, Berkshire, UK); humidity (%) was ascertained via a hygrometer (Oregon Scientific, Berkshire, UK) and barometric pressure (mmHg) was ascertained via a mercury barometer (Fisher Scientific, London, UK). Across all tests (mean ± SD): air temperature 21.6 (± 1.8) °C; humidity 31 (± 5) %; barometric pressure 1019 (± 16) hPa.

Environmental characteristics in the cardiovascular laboratory were determined at the start and end of each laboratory visit. Air temperature (ºC), humidity (%) and barometric pressure (hPa) was ascertained via LaCrosse weather station (WS9032U, LaCrosse Technology Ltd., USA). Across all tests (mean ± SD): air temperature 22.8 (± 8) °C; humidity 36 (± 9) %; barometric pressure 1009 (± 13) hPa.

3.3.2 Participant descriptive characteristics

Participant age was self-reported.

Participant stature was determined via a calibrated, wall mounted stadiometer (Holtain, Crymych, UK). Participants were measured wearing appropriate exercise apparel and without shoes or headwear. Feet were positioned together with the back of the heels against the foot plate, the head was placed against the measuring bar and the

participants were requested to look straight ahead and to inspire before measurement acquisition. Participants were measured to the nearest mm.

Participant body mass was acquired via calibrated balance scales (Seca, Medizinsche Waggen und Messsysteme, Hamburg, Germany) to the nearest 0.1 kg. Participants were measured wearing appropriate exercise apparel without shoes.

Body stature and mass acquisition were undertaken in the exercise physiology laboratory at the University of Gloucestershire.

3.3.3 Resting HR determination

Resting HR was determined over 20 min while participants sat quietly reading. Heart rate measurements were made with the placement of a two electrode chest strap and transmitter along with a receiver (T61™, Polar Electro Oy, Kempele, Finland). The chest strap was adjusted for each individual participant to provide comfort and adequate electrode placement and the electrodes were dampened with water to enhance conduction. The chest strap transmitter was placed centrally below the xiphernum. The HR data was transmitted via short-range telemetry to a watch receiver (Polar S610 series) where it was recorded and subsequently downloaded to a desktop computer for storage (Dell, Bracknell, England) via an infrared interface (Polar Electro Oy, Kempele, Finland).

3.3.4 Resting brachial blood pressure determination

Following the 20 min resting HR assessment, resting brachial BP was determined via DynaPulse™ DP-200M clinical grade electronic blood pressure monitor complete with adult arm cuff, hose, bulb pump, valve and communication cable (Pulse Metric Inc, San Diego, USA). This unit was connected to a laptop computer (Sony®, UK) to provide visual instructions and readout for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) and HR (Dynapulse™ software (version 3.8) for Windows™).

Participants were seated with the left palm of the hand upwardly positioned and the elbow flexed and resting on a desk surface at heart level to minimize movement and

gravitational BP changes. The nondistensible cuff with internal inflatable bladder was placed around the bare upper arm and brachial artery and inflated manually to 180 mmHg following visual instructions from the computer software. Blood pressure high range for SBP was set at 160 mmHg and BP low range for DBP was set at 50 mmHg. Three consecutive measurements were undertaken with intervals of 2 min recovery between measures to permit the release of blood trapped in the arm veins (Frohlich *et al.*, 1988). Participants were asked to face away from the computer screen to reduce anxiety during each of the measurements. The average of the three readings was taken as the resting BP measurement.

3.3.5 Beat by beat blood pressure determination

The collection of beat by beat non-invasive BP signal data was determined via the Portapres Model-2 (FMS, Finapres Medical Systems BV, Amsterdam, The Netherlands), an automated system for the measurement of arterial BP. The BP was measured through the middle finger of the left hand using servo-plethysmomanometry which employs the volume-clamp technique. Attachment of the Portapres was undertaken with reference to user guidelines (FMS, Finapres Medical Systems, BV Amsterdam, The Netherlands) (FMS, 2005). The participant was kept warm in room temperature conditions of 21 – 24º C and a blanket was used to cover the participant when necessary. Appropriate hand warming was achieved via hand warmers (Warm Me Ups, Sanford, Florida, USA). Both hands were warmed and the right hand continually warmed throughout the procedure. The left hand was warmed during resting periods and, during recordings, a small hand warmer (Cozy, Pixmania.com) was placed under the palm of the left hand to provide warming properties without interference to the cuffed finger. An appropriate finger cuff size was applied to the middle phalanx of the middle finger and the 'fixed finger' selection (C1) was chosen to avoid interruption of the finger switching procedure during collection of data. The hydrostatic height correction was applied to allow the cuffed finger to be moved away from heart level during data collection even though the cuffed finger was kept at heart level throughout the measurement process via participant instructions. Following input of participant data into control unit and full signal acquisition to 70 beats the physiocal was switched off. Preliminary testing was undertaken to assess BP drift over the 10 min recording period and finger physiology was found to be stable (Appendix XVII (b)).

When signal acquisition to 70 beats was not possible the highest beat number was attained with 40 beats taken as the lowest accepted signal acquisition for all participants. Following BP recording and during data saving the physiocal was switched on. Reinstatement of signal acquisition was achieved before the physical was switched off and the participant was subsequently tilted and data collected. Blood pressure measures were attained from a 10 minute continuously recorded beat by beat BP. No continuous beat by beat BP measure was longer than 10 min to avoid BP drift (FMS, 2005).

3.3.6 R-R interval determination

A three lead ECG chest attachment (Absolute Aliens Oy, Turku, Finland) was attached to the participants to form a triangle around the heart area. When necessary, removal of chest hair with a razor (Tesco, UK) was undertaken to provide adequate attachment of the chest pads. The area was swabbed with a medi-swab (Reliance Medical, Congleton, Cheshire, UK) before and after hair removal. R-R interval measures were attained from a 10 minute continuously recorded ECG.

3.3.7 Supine position

Participants lay on a tilt bed (Model 501, Plinth 2000, Stowmarket, Suffolk, UK) in a horizontal position. A small pillow was positioned under the participant's head for comfort. When necessary, a blanket was placed over the participant to keep the participant warm during testing.

3.3.8 Tilt manoeuvre

The use of a tilt table is an accepted procedure to assess the human cardiovascular response to orthostatic stress (Benditt *et al.*, 1996; Wieling & Karemaker, 2002). The tilt manoeuvre was undertaken on a tilt bed (Model 501, Plinth 2000, Stowmarket, Suffolk, UK) at a 60º upright tilt. Although there is no significant evidence that higher upright tilt angles between 60º to 80º increase the risk of a syncope incident in healthy individuals it was deemed prudent to incorporate a tilt angle of 60º taking into consideration the current tilt angle evidence and because there is no substantial difference in test outcome between upright tilt angles of 60º to 80º (Benditt *et al.*, 1996). All tilt procedures were undertaken with consideration for the principle

recommendations of the ACC expert consensus document for tilt table testing (Benditt *et al.*, 1996) and the updated Newcastle protocols (Parry *et al.*, 2009).

The tilt bed was electronically controlled for smooth and rapid adjustment and participants were supported by straps at the waist and knees for safety and by a footboard for weight-bearing purposes. All tilt manoeuvres were undertaken following supine data collection to ensure cardiovascular variables were not challenged prior to supine conditions.

Measurement of resting HR and resting brachial BP together with beat-by-beat BP and R-R interval during supine and tilt positions were undertaken in the cardiovascular laboratory at the University of Gloucestershire.

3.3.9 Progressive exercise test

Participants undertook a familiarisation procedure with a cycle ergometer (Lode Excalibur Sport, Lode BV Groningen, The Netherlands) in keeping with the mode of exercise for the exercise study. The familiarisation procedure consisted of a full explanation of the equipment, a warm-up of 5 – 10 min and during this period participants were also introduced to the expired gas collection apparatus via Douglas bag collection. The apparatus included Douglas bags (Code 150l, 3000-1043, Cranlea and Company, Birmingham, UK), breathing valve (Three way, Salford type, Cranlea and Company, Birmingham, UK), connecting hose (Hans Rudolph 4Ft, Code 666000, Cranlea and Company, Birmingham), mouthpiece (Code 22243, Cranlea and Company, Birmingham, UK) and nose clip (Code 22939, Cranlea and Company, Birmingham, UK).

The progressive exercise test was undertaken to provide a $\dot{V}O_{2peak}$ parameter and a maximal work rate (WR) parameter for each participant for use in the experimental trials:

- $\dot{V}O_{2peak}$: to describe the fitness level of the participant
- Maximal WR: to provide a percentage WR_{max} for the participant during exercise testing

- Peak HR: to provide a percentage HR_{peak} for the participant during exercise testing

The cycle ergometer seat was individually set for each participant to provide a slight knee bend when the pedal was at the bottom of its stroke with the foot parallel to the floor for maximal muscle efficiency and for comfort of operation (Cooper & Storer, 2005). The seat and handle bar settings were recorded for future testing. The progressive exercise test commenced at 25 W with increments of 25 W every min which was achieved via a progressive exercise ramp protocol to the limit of tolerance. The starting level and increments were chosen to enable participants to reach their peak/ maximal level within 10 ± 2 min as recommended in exercise testing guidelines (ACSM, 2006; Buchfuhrer *et al.*, 1983; Gibbons *et al.*, 2002). Preliminary testing to assess appropriate power and increment levels found the above protocol was the most suitable for the participants forming the sample of the present exercise study.

Participants were asked to undertake a cycle cadence between 60 – 80 $rev.min^{-1}$. This cadence range was chosen as preliminary testing provided evidence for the satisfactory completion of $\dot{V}O_{2peak}$ testing. In addition, previous research undertaken to establish appropriate reference values and predictive equations for gas exchange, ventilatory and cardiovascular variables during maximal incremental cycle ergometry for adults (20 – 80 y) have also incorporated similar protocols (Jones & Carter, 2004; Neder *et al.*, 1999; Neder *et al.*, 2001) as has other research undertaking testing with healthy individuals (Blackie *et al.*, 1991; Neder *et al.*, 1999; Wergel-Kolmert *et al.*, 2002; Wohlfart & Farazdaghi, 2003). Thus, the above protocol was deemed appropriate for $\dot{V}O_{2peak}$ assessment.

A chest strap (Vantage, Polar, Electro Oy, Kempele, Finland) was also applied to the participant for the collection of continuous HR data. The Polar watch was strapped to the cycle handlebars as preliminary testing found this to be a more successful placement for the collection of HR data than participant application.

Expired gas was collected at 1 min intervals for the first 7 min and every 30 s thereafter via Douglas bags. Timings were undertaken using a digital stopwatch (Fasttime,

Cranlea and Company, Birmingham, UK). Analysers were calibrated immediately before gas analysis using different gas mixtures in three stages as follows: firstly, 0% gas mixtures (BOC Gases Limited, Guilford, UK) to set O_2 and CO_2 analysers to zero; secondly, outside air to set the span of the O_2 analyser to 20.94% and check the CO_2 analyser (0.04%); and lastly, certified gas mixtures to check the O_2 analyser (16.11%) and to set the span on the CO_2 analyser to 4.06% (BOC Gases Limited, Guilford, UK). The dry gas meter was calibrated via the retrospective application of a regression equation derived from volumes of gas applied using a 3 L calibration syringe (Hans Rudolf, Cranlea and Company, Birmingham, UK) to fill Douglas bags.

Analysis of expired gases was undertaken off-line with an oxygen analyser (1440 series paramagnetic, Servomex Ltd., Crowborough, UK) and a carbon dioxide analyser (1440 series infra-red, Servomex Ltd., Crowborough, UK). Expired gas volume was measured via a dry gas meter (Harvard Apparatus Limited, Edenbridge, UK) with expired gases drawn through a vacuum pump (Trojun, Bessell, China) which was connected to the meter via polyester elastomer tubing (Dupont™ Hytrel®, Cranlea and Company, Birmingham, UK). Gas temperature was measured via the insertion of a temperature probe (Precision Gold, Maplin, Cheltenham, UK) into the volume meter inlet port.

The familiarisation with exercise equipment and the progressive exercise test were undertaken in the exercise physiology laboratory of the University of Gloucestershire.

3.3.10 $\dot{V}O_{2\,peak}$ determination

The determination of $\dot{V}O_{2peak}$ was taken as the highest value recorded in any full 30 s prior to the participant's volitional termination of the PET or at the point of test termination by the assessor due to a large drop in cadence below 60 rev.min^{-1} and the inability of the participant to cycle proficiently. The fulfillment of a maximum effort was based on other assessment criteria, including the rate of perceived exertion (RPE) (Borg, 1998), 220 – age (± 10 beats) (ACSM, 2006) and the respiratory exchange ratio (RER) > 1.1 (Issekutz *et al.*, 1962). A warm-up and cool down was incorporated into the protocol for the comfort and safety of the participants (Barnard *et al.*, 1973; Shellock & Prentice, 1985) and this was undertaken at a designated power of 60 W for 5 min.

3.3.11 HR_{peak} determination

The determination of HR_{peak} was taken as the maximal HR (five second average) recorded immediately prior to the termination of the PET.

3.3.12 WR_{max} determination

The determination of WR_{max} was taken as the maximal work rate achieved immediately prior to the termination of the PET (Niemelä *et al.*, 2008).

3.3.13 Work done determination

In order to standardise the work done in the two exercise intensity conditions, the total amount of work done by each participant was calculated by multiplying the participant's individual WR (W) by the length in time (s) of each interval exercise bout (adjusted by two decimal places) to provide an index in kilojoules (kJ). This figure was multiplied by the number of exercise bouts (seven) to provide an index of total work done (kJ). Standardisation across exercise conditions was achieved by adjusting length of time (s) appropriately to each of the interval exercise bouts for the 75% WR_{max} and 40% WR_{max} exercise conditions respectively. In practice, the length of each individual exercise bout for the 75% WR_{max} exercise condition was 2 min 18 s (138 s) while the length of each individual exercise bout for the 40% WR_{max} exercise condition was 4 min 18 s (258 s). Preliminary testing was undertaken regarding assessment criteria for the two exercise conditions for the present exercise study to determine a tolerable exercise work load at a heavy intensity (75% WR_{max}) that would be matched to the moderate intensity (40% WR_{max}) work load (Appendix XVII (d)).

3.3.14 75% WR_{max} exercise condition protocol

The 75% WR_{max} for each individual was determined by quantifying 75% from each participant's WR_{max} achieved during the PET. Individual participant 75% WR_{max} exercise condition was calculated and programmed into the cycle ergometer. A 5 min warm up and cool down was undertaken at 60 W at a cadence of 60 – 80 $rev.min^{-1}$ pre and post the exercise condition. Seven bouts at 75% WR_{max} were undertaken interspersed with active recovery of 3 min at 60 W between each bout. The WR was controlled independently of cadence so participants were encouraged to keep a cadence

of 60 – 80 rev.min^{-1} throughout the testing. The RPE data was recorded at the end of each exercise bout. The total length of testing was 44 min 06 s.

3.3.15 40% WR_{max} exercise condition protocol

The 40% WR_{max} for each individual was determined by quantifying 40% from each participant's WR_{max} achieved during the PET. Individual participant 40% WR_{max} exercise condition was calculated and programmed into the cycle ergometer. A 5 min warm up and cool down was undertaken at 60 W at a cadence of 60 – 80 rev.min^{-1} pre and post the exercise condition. Seven bouts at 40% WR_{max} were undertaken interspersed with active recovery of 3 min at 60 W between each bout. The WR was controlled independently of cadence so participants were encouraged to keep a cadence of 60 – 80 rev.min^{-1} throughout the testing. The RPE data was recorded at the end of each exercise bout. The total length of testing was 58 min 06 s.

3.3.16 Rate of Perceived Exertion

At the end of each exercise bout the participants were asked to provide an indication for the RPE (6 – 20 scale) experienced during that particular exercise bout (Appendix XV). The data was manually recorded and stored for later analysis.

3.3.17 Control condition protocol

Participants sat quietly reading. The total time of testing was 51 min which was calculated by taking the mean of the time length of the 75% WR_{max} and 40% WR_{max} exercise conditions.

3.3.18 Hydration strategy

Hydration was provided for the participants during the exercise study for participant comfort and welfare. Following the two exercise conditions 100 ml water was provided at the start of the cool down period and at + 90 min and + 150 min. Following the control condition of no exercise, 100 ml water was provided during the 46th min of the resting period (which had been calculated as the average time for the start of the cool down period between the two exercise conditions) and at + 90 min and + 150 min. The timing of ingestion was controlled to ensure gastric emptying had occurred prior to the measurement of outcomes.

3.3.19 Equipment and tilt familiarisation

A full verbal explanation of the procedures and any possible adverse implications was provided for the participants along with an opportunity for questions.

Following the attainment of resting HR (procedures: see *section 3.3.3*) and BP (procedures: see *section 3.3.4*) the participants undertook an equipment and tilt familiarisation procedure. The beat by beat BP and ECG equipment was attached to the participant and familiarisation took place for 5 min in supine position which was followed by 10 min in 60º upright tilt position. The data was recorded throughout the testing periods.

3.4 Procedures for determination of key outcome measures

Data were gained via the collection of beat by beat BP and HR. Data were analysed via the sequence technique, the α coefficient technique and the transfer function (gain) technique as outlined by Robbe *et al* (1987) and Parati *et al* (2000) (see: sections 2.5.6; 2.5.10).

3.5 Data Analysis

Data analysis was undertaken using dedicated software Microsoft Excel® (version 2003), SPSS® (version 16.01) (SPSS Inc, Chicago, USA), DynaPulse™ (version 3.8), Polar® Precision Performance SW (version 4.03.040), WindowsXP (2003) software packages and WinCPRS (2007) (version 1.610) (Absolute Aliens, Absolute Aliens, Finland).

3.5.1 Analysis of R-R interval and blood pressure

Following the interpolation of beat by beat BP and ECG signals via the WinAcq acquisition system (Absolute Aliens, Absolute Aliens, Finland) the signal data was sent to the receiving computer. The WinCPRS (Absolute Aliens, Absolute Aliens, Finland) dedicated software analysed the physiological signals and detected characteristic signal features such as the R-peaks on ECG signals (Absolute Aliens Oy, 2007). Based on these features the software generated new signals to produce sets of time domain and

spectral domain signals. Following further analysis various BRS indices were produced.

Continuous 10 min collections of R-R interval data (procedures: see section 3.3.6) and beat by beat BP data (procedures: see section 3.3.5) were undertaken while participants were in supine (procedures: see section 3.3.7) and tilt (procedures: see section 3.3.8) positions. The signal data were fed into an acquisition system (WinAcq, Absolute Aliens Oy, Turku, Finland) where the signals were interpolated and relayed to a laptop computer (Tecra S1, Toshiba, Finland) using a sampling rate of 800 Hz and stored for later analysis. To localize the fiducial point which identifies a QRS complex on an ECG, a sampling rate substantially < 200 Hz may cause an error for R-R interval measurement due to problems in the recognition of the QRS complex fiducial point (TFESC & TNASPE, 1996). However, interpolation of low sampling rates may alleviate this problem. Previous research investigating baroreflex sensitivity has applied different sampling rates from 250 Hz up to 1000 Hz (Lénárd *et al.*, 2005; Lucini *et al.*, 2004; Niemelä *et al.*, 2008; Studinger *et al.*, 2003) and to date there is no standard recognized rate. Thus, a sampling rate of 800 Hz was chosen for this project as (i) preliminary testing at 200 Hz, 400 Hz and 800 Hz provided evidence for a more defined tip for the QRS complex fiducial point at 800 Hz (Appendix XVII (a)) ; (ii) interpolation was not undertaken; (iii) more recent studies have incorporated higher sampling rates (Niemelä *et al.*, 2008; Terziotti *et al.*, 2001) or used interpolation to increase the precision for R point detection to 1 ms (i.e. 1000 Hz) (Raczak *et al.*, 2005) and (iv) in practical terms, 800 Hz was the highest level of sampling rate possible using WinCPRS software. The data was processed with dedicated software (WinCPRS, Absolute Aliens Oy, Turku, Finland) and both time (BRS_{UpUp} and $BRS_{DownDown}$) and spectral ($BRS_{\alpha LF}$ and BRS_{TFTG}) analyses of BRS were undertaken.

3.5.2 Baroreflex sensitivity determination

Baroreflex sensitivity is defined as the change in R-R interval following change in BP and is determined via HR and BP components. R-R interval is an expression of HR and measured as the time interval between the consecutive R peaks in milliseconds (ms) while BP is measured in millimeters of mercury (mmHg) thus the measure for BRS is denoted by units of ms/mmHg.

The analysis software (WinCPRS) was utilised to calculate the moving average of the signal over the data range (0.05 s) for the BP data. The ECG data was filtered using a Butterworth low pass filter at 45 Hz. These procedures were undertaken to reduce noise and minimize any measurement error. R-R intervals were calculated from the clean ECG signals and data was visually inspected to identify and correct any irregular or missing R-R intervals. Individual BP data signals (SBP, DBP, MAP and PP) were generated. The R-R interval signal data and SBP signal data was utilised to produce BRS measurements. The time range of interest was taken as follows:

(i) If no artifact was present then the whole of the recording (10 min) was chosen

(ii) If an artifact was present at the beginning or end of the recording then the time range was chosen to exclude the artifact

(iii) If the artifact was 'centrally placed' then the BRS measurements were calculated both before and after the artifact and the average of the two was taken as the BRS measure

No BRS measure was calculated from a time length < 3 min due to a lack of statistical relevance (Robbe *et al.*, 1987) and no measure was calculated from a time length > 10 min to ensure stationarity and reduce the risk of BP drift (FMS, 2005; Kuusela, 2007; TFESC & TNASPE, 1996).

Three analysis techniques for BRS determination were undertaken. One technique was undertaken in the time domain (sequence) and two techniques were undertaken in the spectral domain (α coefficient and transfer gain) (Parati *et al.*, 2000; Robbe *et al.*, 1987). During the initial project setup preliminary trialing of equipment and procedures was undertaken. Following these trials it was decided that the data analysis would be undertaken utilising three of the modern spontaneous BRS techniques (Kuusela, 2007; Parati *et al.*, 2000; Robbe *et al.*, 1987):

(i) Sequence technique (BRS_{UpUp} and $BRS_{DownDown}$): specified naturally occurring sequences of systolic blood pressure (SBP) changes coupled with baroreflex-mediated R-R interval changes in the time domain

(ii) α coefficient in low frequency (LF; 0.1 Hz) ($BRS_{\alpha LF}$): squared ratio of R-R interval/ SBP spectral powers in LF region

(iii) Transfer function in LF (BRS_{TFLF}): indicates the gain of the system in the LF band thus indicating the strength of R-R interval (output signal) when a specific change occurs in SBP (input signal)

The three techniques were chosen because:

- The techniques have been frequently adopted for BRS assessment in related research and therefore allow comparison with other investigations in this area
- The techniques include both time and spectral analysis
- The spectral techniques have been undertaken in LF to attenuate respiratory influence
- Each technique may provide evidence for change in the cardiovascular system which may not be apparent via the other techniques
- Each technique has unique assumptions, advantages and limitations (Appendix VI; table A6)
- An analysis incorporating three techniques may provide more extensive information regarding the outcomes than that found with the incorporation of one technique only

3.5.2(i) Time: Sequence BRS_{UpUp} and $BRS_{DownDown}$

The software detected and identified spontaneously occurring sequences in the time domain in which SBP and R-R interval concurrently increased or decreased over three or more consecutive beats. Sequences were calculated from increasing SBP and lengthening of R-R interval indices (BRS_{UpUp}) and decreasing SBP and shortening of R-R interval indices ($BRS_{DownDown}$) with minimal sequence specificity for accepted change of 1 mmHg for SBP and 5 ms for R-R interval together and a correlation of > 0.85. The slope of the regression line of all accepted sequences was taken as an index of BRS and this technique is known as the 'sequence' method.

The BRS frequency domain assessment was undertaken in accordance with recent literature (De Boer *et al.*, 1987; Pagani *et al.*, 1988; Parati *et al.*, 2000; Robbe *et al.*, 1987). The assessment of spontaneous BRS by the frequency techniques is derived from (Parati *et al.*, 2000):

(i) Sub-division of BP and R-R interval signal data into short segments ranging from 128 – 1024 beats

(ii) Quantification of each segment by FFT in the LF region where the signals displayed a high coherence (> 0.5 i.e., the oscillations of R-R interval and SBP were linearly related)

(iii) Calculation of the α coefficient (square root of the ratio of R-R interval and SBP powers in LF region) (Pagani *et al.*, 1988) or calculation of the transfer function gain between changes in SBP and R-R interval (De Boer *et al.*, 1987; Robbe *et al.*, 1987)

The software sub-divided the SBP and R-R interval signals into segments and each segment was quantified using non parametric modeling of FFT. This was undertaken in the frequency region of LF where the signals displayed a high coherence (> 0.5) (Robbe *et al.*, 1987). The phase relationship between R-R interval and SBP, due to the joint effect of vagal and sympathetic baroreflex regulation on cycle length, reflected that change occurred firstly in SBP followed by changes (in response) in R-R interval thus the calculation of the phase difference as a function of LF was negative (De Boer *et al.*, 1987; Kuusela, 2007). Due to the influence of respiration on HF and because respiration was not controlled, BRS in the spectral domain was undertaken in the LF domain only (Badra *et al.*, 2001; Lord *et al.*, 1998; Maestri *et al.*, 2009).

3.5.2(ii) Frequency: $BRS_{\alpha LF}$

The software calculated the square root of the ratio of RRI and SBP powers in LF region which was taken as $BRS_{\alpha LF}$. The basic assumption for this measure is that the ratio between RRI and SBP powers where they are coherent is a reflection of the baroreflex (Parati *et al.*, 2000) (Appendix VI; table A6).

3.5.2(iii) Frequency: BRS_{TFTG}

The software calculated the mean transfer gain in SBP and RRI signals (i.e. the strength of RRI or gain) following a specific change in SBP in LF where the coherence value is ≥ 0.5. The basic assumption of this method is that SBP signal is the input signal and RRI is the output signal (Robbe *et al.*, 1987) (Appendix VI; table A6).

The assumptions, advantages and disadvantages for the three techniques for BRS assessment have been discussed previously (see: sections 2.5.6; 2.5.10).

3.6 Missing data values

Overall, 1,296 measures were taken. Due to occasional equipment failure, 12 measures were lost and this equated to 0.93% of missing data. Due to lack of sequence identification, 2 measures were lost and this equated to 0.15% of missing data. The total amount of missing data was 14 measures, which equated to 1.08% of missing data.

To deal with the missing data, four datasets were compiled to ascertain the most prudent method to accommodate the missing values:

(i) *Dataset 1*: Missing data was in-filled with the mean individual value at that particular time point. This was undertaken by averaging the two values either side of the missing value. Where the missing value was at + 24 h, the values used for averaging purposes were baseline and + 180 min

(ii) *Dataset 2*: Missing data was in-filled by utilising the average of all participant values at that particular time period with the group mean replaced the missing value.

(iii) *Dataset 3*: Missing values were not replaced and no in-filling was undertaken. The two measures for lack of sequence identification were recorded as zero.

(iv) *Dataset 4*: Discrete missing value codes were recorded. Missing values were coded as –1.00 for the 12 equipment failures measures and -2.00 for the 2 sequence failure measures.

The datasets may be further characterised as follows:

- *Dataset 1* represented in-filling by utilising the individual participant data
- *Dataset 2* represented in-filling by utilising other participant data. Dataset 2 was analysed twice (i) compiling the mean by using a division of 9 (total participant number) and (ii) compiling the mean by using a division of 7 (for one time point

with two missing values) and a division of 8 (for time point of one missing value).

- *Dataset 3* recognized the 12 measures as missing but recorded the zero values as actual values.
- *Dataset 4* accepted all 14 values as missing

On reflection, dataset 3 was eliminated for analysis consideration because the use of 'zero' as an actual measure was clearly incorrect and dataset 2 was not utilised as the in-filled values did not relate directly to individual participant data. Interestingly, datasets 1, 2 and 4 provided very similar BRS measures although overall, dataset 1 appeared to provide the most conservative values (Appendix XVI: tables A11; A12; A13; A14). Thus, as dataset 1 utilised individual participant data together with conservative values it was decided that this dataset would be the most prudent option for use in the final analysis.

3.7 Study design for reproducibility study

The reproducibility study investigated the same day reproducibility and between day reproducibility of the measure for supine BRS and tilt BRS. A test-retest reproducibility study of the procedure for assessment of BRS was conducted. Each participant was required to visit the laboratory on 3 separate occasions. Visit one included the completion of a health questionnaire and consent form (Appendix XI; XII), attainment of resting HR and resting BP (procedure: see sections 3.3.3; 3.3.4) and familiarisation with equipment and testing procedure (procedure: see section 3.3.19). During visits two and three, data collection (procedure: see section 3.5.1) in both supine (procedure: see section 3.3.7) and tilt (procedure: see section 3.3.8) positions was undertaken at baseline, + 60 min and + 24 h respectively (figure 3.7.1). Total duration time for the testing procedure for each participant was 6 h. Participants were requested not to drink alcohol 24 h before each test, not to consume any caffeine beverages on the day of each test, nor to drink or eat anything other than water in the final 3 h before each visit. Participants were also requested not to exercise 48 h before each test beyond normal daily activities. In the final hour prior to visiting the laboratory, participants were instructed to abstain from consuming any fluid. Testing at baseline and + 24 h

was scheduled at the same time of day to avoid circadian variation. Participant clothing was consistent over the testing period. However, as it was impractical to monitor participant activities outside the laboratory environment there is a possibility of individual divergence from the control measures and this is a possible limitation of the study design.

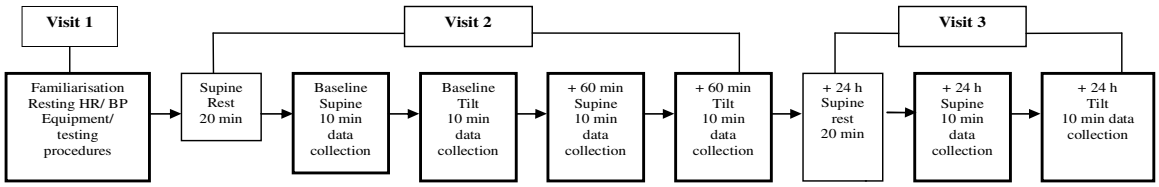

Figure 3.7.1. Order of testing procedures for determination of reproducibility of BRS assessment

3.8 Statistical analysis for the reproducibility study

The reproducibility analyses were undertaken in Microsoft Excel using a scatter plot to display agreement and limits of agreement (LOA) employing the technique of Bland and Altman (1986) to assess the extent of agreement. An alternative approach of estimating the technical error of measurement (TEM) to assess reproducibility was also undertaken.

3.9 Study design for the experimental exercise study

The experimental study explored the influence of intensity of exercise on post-exercise BRS and also compared both exercise conditions with a control condition (no exercise). The study design was within subjects repeated measures with two separate exercise conditions (procedure: see sections 3.3.14; 3.3.15) and a control condition (procedure: see section 3.3.17) in a counterbalanced order. Each participant was required to visit the laboratory on seven separate occasions for each study. Visit 1 included completion of health questionnaire and consent form (Appendix XI; XII), attainment of resting HR and BP (procedure: see sections 3.3.3; 3.3.4) and familiarisation with equipment (procedure: see section 3.3.19). Participants were also required to undertake a PET (procedure: see section 3.3.9) for VO_{2peak} assessment (procedure: see section 3.3.10) to

determine their individual fitness level, HR_{peak} (procedure: see section 3.3.11) and WR_{max} (procedure: see section 3.3.12). Visits 2, 4 and 6 were separated by 3 - 6 days but scheduled at the same time of day to avoid circadian variation. A hydration strategy was incorporated during these visits for participant welfare and consideration (procedure: see section 3.3.18). Visits 3, 5 and 7 were 24 h after the second, fourth and sixth visit respectively. The equipment familiarisation was undertaken in the cardiovascular laboratory at the University of Gloucestershire under similar conditions for the experimental trials. The determination of VO_{2peak} was undertaken with a PET in the exercise physiology laboratory at the University of Gloucestershire and was scheduled > 72 h before the first exercise condition to ensure adequate recovery (James & Doust, 1998). During visits 2, 4 and 6, data collection (procedure: see section 3.5.1) was undertaken at baseline, + 15 min, + 60 min, +120 min, + 180 min and during visits 3, 5 and 7 data collection (procedure: see section 3.5.2) was undertaken + 24 h respectively (figure 3.9.1). Total testing time for each participant was 27 h. Participants were requested not to drink alcohol 24 h before each test, not to consume any caffeine beverages on the day of each test, nor to drink or eat anything other than water in the final 3 h before each visit. Participants were also requested not to exercise 48 h before each test beyond normal daily activities. In the final hour prior to visiting the laboratory, participants were instructed to abstain from consuming any fluid. Testing at baseline and + 24 h was scheduled at the same time of day to avoid circadian variation. Participant clothing was consistent over the testing period.

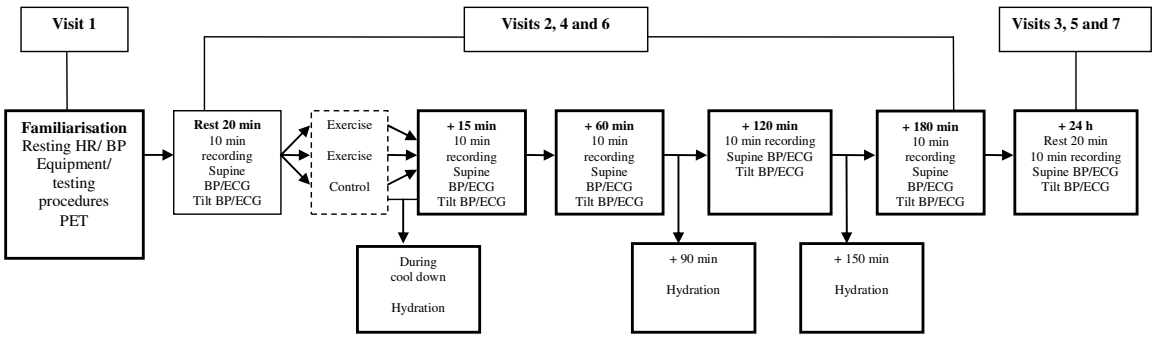

Figure 3.9.1. Order of testing procedures for determination of BRS for the experimental exercise study

3.10 Statistical analysis for the experimental study

The experimental study was statistically analysed using SPSS version 16.01. The interaction between time and condition was examined using a 3 (condition) x 6 (time) factor fully repeated measures ANOVA. The main effect of time and condition was examined with one-way repeated measures ANOVA. Significant effects ($p \leq 0.05$) were explored with post-hoc t-tests (with Bonferoni adjustment) to locate the any differences.

CHAPTER FOUR

RESULTS

CHAPTER 4: RESULTS

4.1. Reproducibility study

Data from repeat measurements were presented as a scatter plot with a line of identity to allow visual inspection of the data and to observe the degree of reproducibility (figures 4.1.1 – 4.1.16) and these figures show varying reproducibility across supine and tilt and across the within day and between day measurements. The degree of reproducibility also varies across analysis techniques (i.e. the time and frequency analyses). However in order to quantify reproducibility, agreement was assessed using Bland and Altman (1986) technique. This technique is known to be affected by heteroscedastic data, so initially the relationship between the mean of the two repeat measures and the mean absolute difference of the two repeat measures was plotted and quantified (equation of line of best fit). (Appendix XVIII (a); figures A8 – A23). Given the weak relationship (low slope), the bias and limits of agreement (LOA) were determined with the standard approach (figures 4.1.17 – 4.1.32). The bias and LOA parameters are summarised in table 4.1.1. In general, between day reproducibility was marginally better than same day reproducibility for the sequence parameters while same day reproducibility was marginally better than between day reproducibility for the spectral parameters. Overall, there was larger variability (i.e. lower reproducibility) and between subject (heterogeneity) observed between the two tests for parameters in supine position compared to tilt position with all BRS outcomes. In the supine position the sequence outcomes provided larger variability and heterogeneity (figures 4.1.17, 4.1.18, 4.1.21, 4.1.22) than the spectral outcomes (figures 4.1.19, 4.1.20, 4.1.23, 4.1.24). There was markedly improved reproducibility and reduced heterogeneity with all BRS outcomes in the tilt position (figures 4.1.25 – 4.1.32). Data for BRS outcome measures, bias (mean difference), standard deviation, 95% LOA and confidence intervals (CI) are provided in table 4.1.1. The bias was found to be small across all BRS outcomes at all time points. As an additional method for expressing reproducibility, data for technical error of measurement (TEM) are given in table 4.1.2. Precision for all spectral outcomes was good in both supine and tilt although precision was lower for the time (sequence) outcomes in both positions.

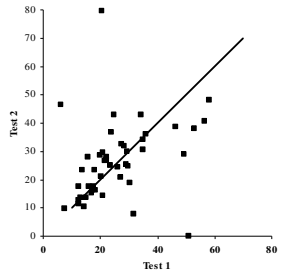

Figure 4.1.1. BRS_{UpUp} in supine at baseline (Test 1) and + 60 min (Test 2)

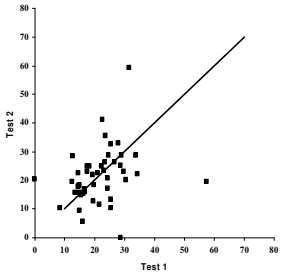

Figure 4.1.2. $BRS_{DownDown}$ in supine at baseline (Test 1) and + 60 min (Test 2)

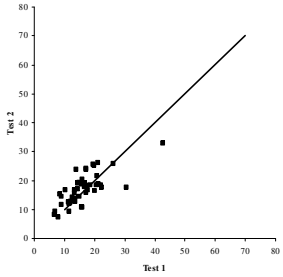

Figure 4.1.3. $BRS_{\alpha LF}$ in supine at baseline (Test 1) and + 60 min (Test 2)

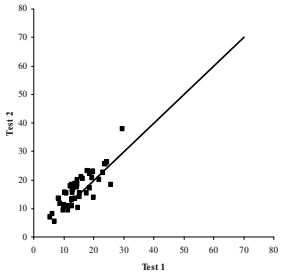

Figure 4.1.4. BRS_{TFTG} in supine at baseline (Test 1) and + 60 min (Test 2)

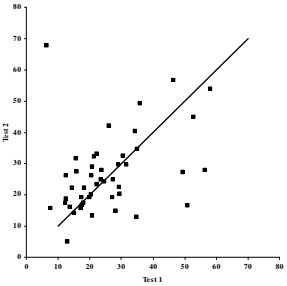

Figure 4.1.5. BRS_{UpUp} in supine at baseline (Test 1) and + 24 h (Test 2)

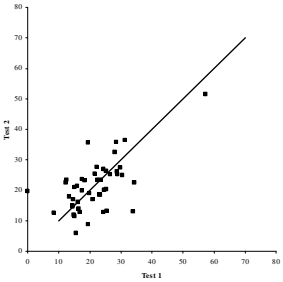

Figure 4.1.6. $BRS_{DownDown}$ in supine at baseline (Test 1) and + 24 h (Test 2)

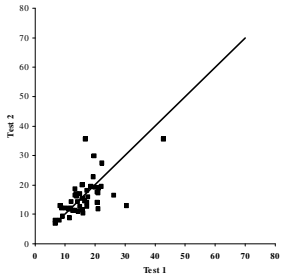

Figure 4.1.7. $BRS_{\alpha LF}$ in supine at baseline (Test 1) and + 24 h (Test 2)

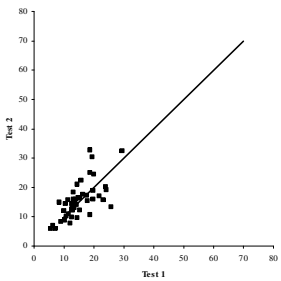

Figure 4.1.8. BRS_{TFTG} in supine at baseline (Test 1) and + 24 h (Test 2)

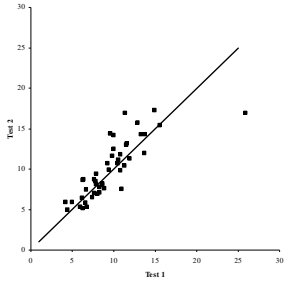

Figure 4.1.9. BRS_{UpUp} in tilt at baseline (Test 1) and + 60 min (Test 2)

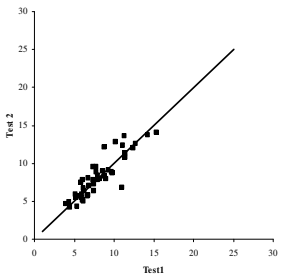

Figure 4.1.10. $BRS_{DownDowm}$ in tilt at baseline (Test 1) and + 60 min (Test 2)

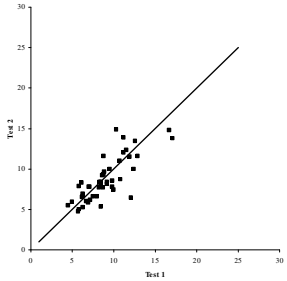

Figure 4.1.11. $BRS_{\alpha LF}$ in tilt at baseline (Test 1) and + 60 min (Test 2)

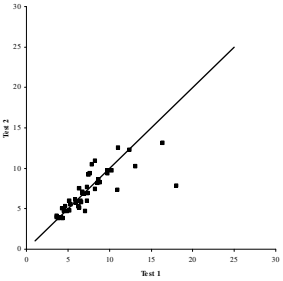

Figure 4.1.12. BRS_{TFTG} in tilt at baseline (Test 1) and + 60 min (Test 2)

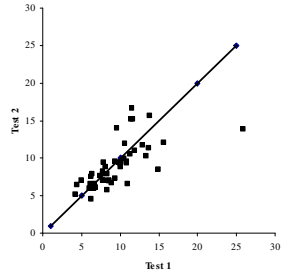

Figure 4.1.13. BRS_{UpUp} in tilt at baseline (Test 1) and + 24 h (Test 2)

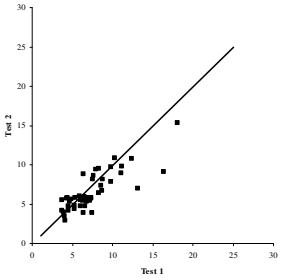

Figure 4.1.14. $BRS_{DownDowm}$ in tilt at baseline (Test 1) and + 24 h (Test 2)

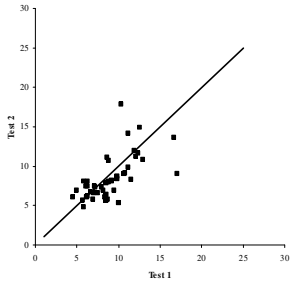

Figure 4.1.15. $BRS_{\alpha LF}$ in tilt at baseline (Test 1) and + 24 h (Test 2)

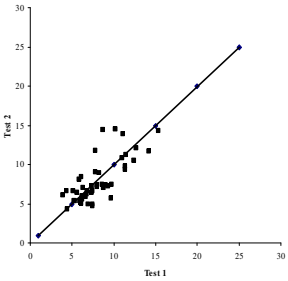

Figure 4.1.16. BRS_{TFTG} in tilt at baseline (Test 1) and + 24 h (Test 2)

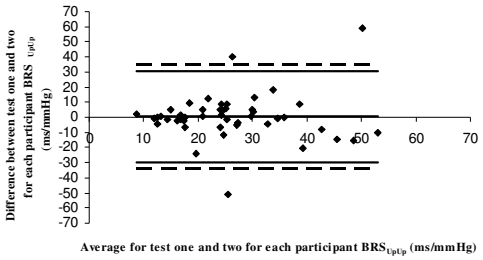

Figure 4.1.17 Bland and Altman plot in supine BRS_{UpUp} between baseline and + 60 min

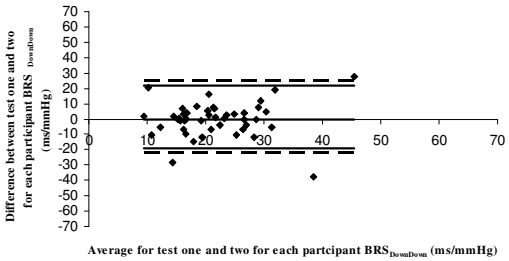

Figure 4.1.18. Bland and Altman plot in supine $BRS_{DownDown}$ between baseline and + 60 min

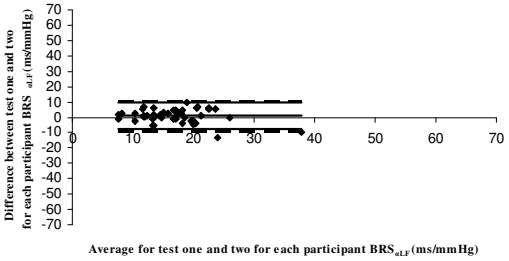

Figure 4.1.19. Bland and Altman plot in supine $BRS_{\alpha LF}$ between baseline and + 60 min

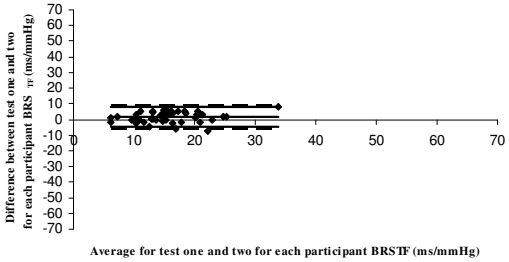

Figure 4.1.20. Bland and Altman plot in supine BRS_{TFTG} between baseline and + 60 min

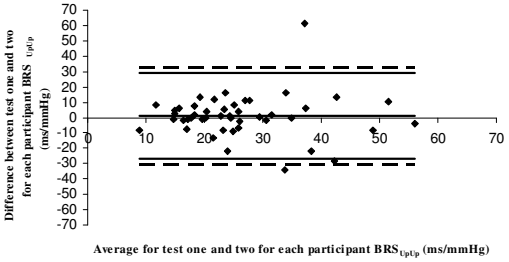

Figure 4.1.21. Bland and Altman plot in supine BRS_{UpUp} between baseline and + 24 h

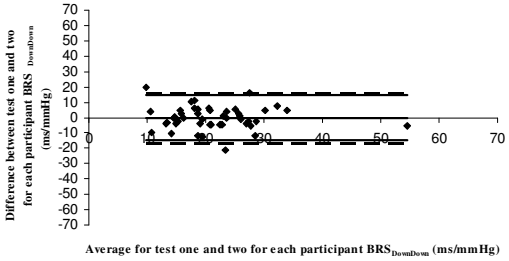

Figure 4.1.22. Bland and Altman plot in supine $BRS_{DownDown}$ between baseline and + 24 h

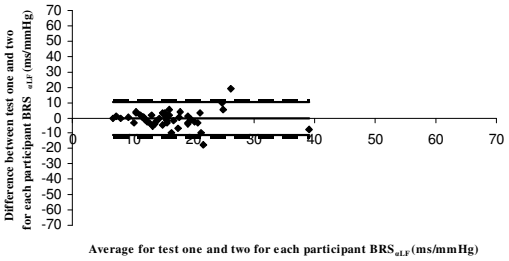

Figure 4.1.23. Bland and Altman plot in supine $BRS_{\alpha LF}$ between baseline and + 24 h

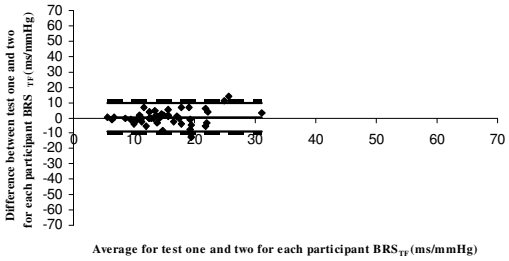

Figure 4.1.24. Bland and Altman plot in supine BRS_{TFTG} between baseline and + 24 h

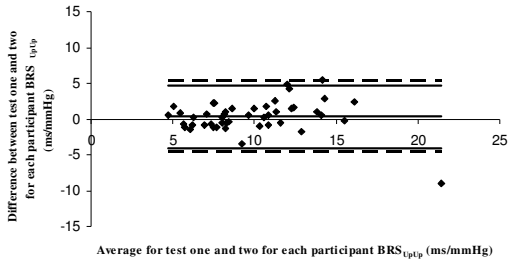

Figure 4.1.25. Bland and Altman plot in tilt BRS_{UpUp} between baseline and + 60 min

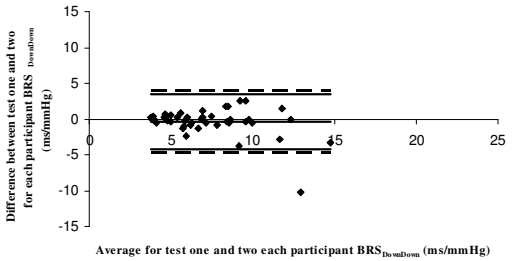

Figure 4.1.26. Bland and Altman plot in tilt $BRS_{DownDown}$ between baseline and + 60 min

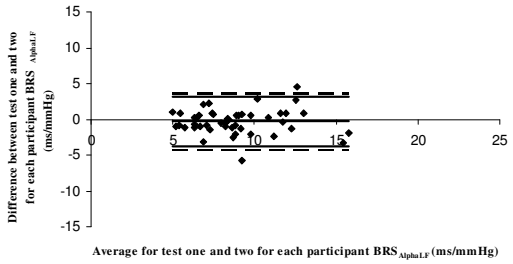

Figure 4.1.27. Bland and Altman plot in tilt $BRS_{\alpha LF}$ between baseline and + 60 min

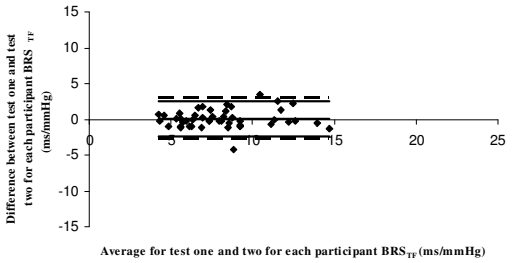

Figure 4.1.28. Bland and Altman plot in tilt BRS_{TFTG} between baseline and + 60 min

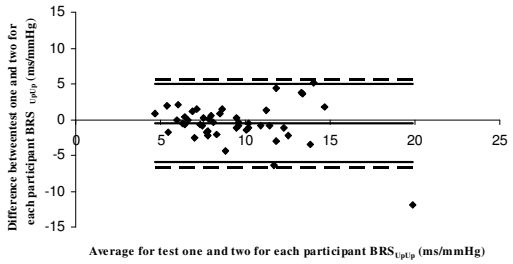

Figure 4.1.29. Bland and Altman plot in tilt BRS_{UpUp} between baseline and + 24 h

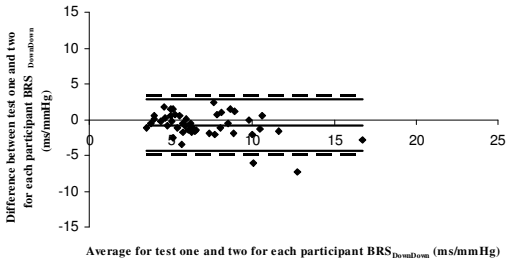

Figure 4.1.30. Bland and Altman plot in tilt $BRS_{DownDown}$ between baseline and + 24 h

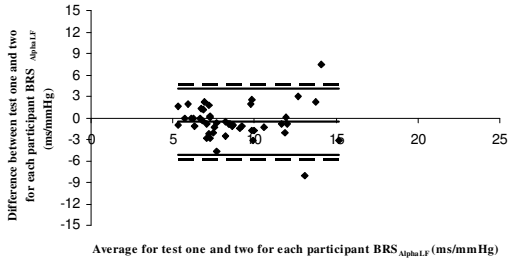

Figure 4.1.31. Bland and Altman plot in tilt $BRS_{\alpha LF}$ between baseline and + 24 h

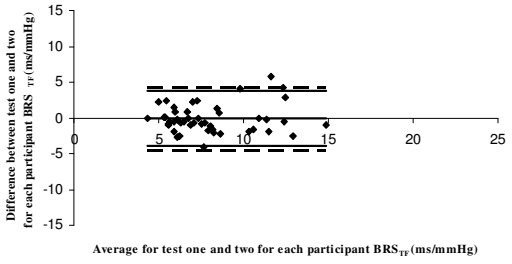

Figure 4.1.32. Bland and Altman plot in tilt BRS_{TFTG} between baseline and + 24 h

Table 4.1.1. Limits of Agreement for supine and tilt BRS measures

BRS (ms/mmHg)	Bias Mean Difference	SD Differences	95% Limits of Agreement (+) (ms/mmHg)	95% Limits of Agreement (-) (ms/mmHg)	Confidence Intervals (+) (ms/mmHg)	Confidence Intervals (-) (ms/mmHg)
Base / +60 min						
Seq UpUp (S)	0.57	15.45	30.84	-29.70	34.79	-33.65
Seq UpUp(T)	0.36	2.24	4.75	-4.04	5.33	-4.61
Seq DownDown (S)	-0.17	11.21	21.80	-22.13	24.67	-19.27
Seq DownDown (T)	-0.38	1.95	3.44	-4.20	3.94	-4.70
α LF (S)	0.85	4.42	9.50	-7.81	10.63	-8.93
α LF (T)	-0.31	1.77	3.17	-3.78	3.62	-4.23
TFTG (S)	1.69	3.34	8.24	-4.85	9.09	-5.07
TFTG (T)	0.09	1.28	2.60	-2.43	2.93	-2.76
Base / +24 h						
Seq UpUp (S)	0.99	14.17	28.76	-26.78	32.38	-30.40
Seq UpUp(T)	-0.52	2.78	4.93	-5.97	5.64	-6.68
Seq DownDown (S)	-0.23	7.45	14.36	-14.83	16.26	-16.73
Seq DownDown (T)	-0.80	1.83	2.78	-4.38	3.25	-4.84
α LF (S)	-0.62	5.45	10.06	-11.30	11.45	-12.69
α LF (T)	-0.54	2.36	4.08	-5.16	4.68	-5.76
TFTG (S)	0.34	4.75	9.65	-8.97	10.86	-10.18
TFTG (T)	-0.15	1.97	3.71	-4.00	4.21	-4.50

Note: Seq is Sequence; LF is low frequency; TFTG is Transfer Function Transfer Gain; (S) is supine (T) is tilt

Table 4.1.2. BRS parameters and Technical Error of Measurement

BRS (ms/mmHg)	TEM	% TEM
Base / +60 min		
Seq UpUp (S)	10.81	10.41
Seq UpUp(T)	1.59	4.06
Seq DownDown (S)	7.84	9.11
Seq DownDown (T)	1.39	4.83
α LF (S)	3.15	4.70
α LF (T)	1.26	3.56
TFTG (S)	2.62	4.11
TFTG (T)	0.90	2.77
Base / +24 h		
Seq UpUp (S)	9.93	9.49
Seq UpUp(T)	1.98	5.29
Seq DownDown (S)	5.21	6.06
Seq DownDown (T)	1.40	5.00
α LF (S)	3.84	6.00
α LF (T)	1.69	4.86
TFTG (S)	3.33	5.44
TFTG (T)	1.38	4.31

Note: Seq is Sequence; LF is low frequency; TFTG is Transfer Function Transfer Gain; (S) is supine (T) is tilt

4.2. Exercise study

4.2.1 Exercise bout HR response

The HR response to exercise is summarised in figure 4.2.1 and table 4.2.1. The data suggests the exercise bouts of 40% WR_{max} represented moderate intensity exercise and the 75% WR_{max} represented high intensity exercise. Heart rates (over exercise bouts) for 40% WR_{max} exercise condition increased from 113 (71 – 130) to 128 (92 - 149) and for 75% WR_{max} exercise condition increased from 135 (94 – 158) to 163 (130 – 187) bpm. The exercise HR data when compared to the HR_{peak} data elicited during the PET indicate that the 40% WR_{max} exercise condition evoked mean heart rates of 61-69% of HR_{peak} and the 75% WR_{max} exercise mean heart rates of 73-88% of HR_{peak}. A significant condition and time interaction for HR_{mean} ($p = < 0.001$) was observed over

all exercise bouts. There was a significant main effect for both the moderate and high intensity exercise conditions ($p = < 0.001$; $p = < 0.001$). Post hoc analysis indicated increases ($p = 0.05$) between successive bouts in both exercise conditions with the exception of bout 4 to 5 and bout 6 to 7 during the moderate intensity exercise. Statistical analysis output for HR_{mean} data is provided in Appendix XVIII (d).

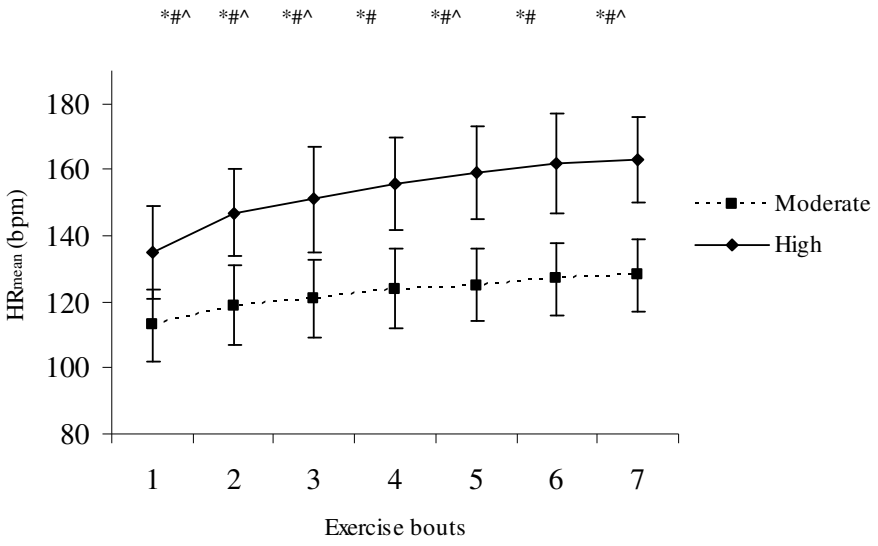

Figure 4.2.1. Mean heart rate (± SD) response to exercise bouts of moderate intensity exercise (40%WR_{max}) and high intensity exercise (75% WR_{max}). *Significant difference between the two exercise conditions. #Significant effect between successive bouts for high intensity exercise condition. ^Significant effect between successive bouts for moderate exercise condition.

4.2.2 Exercise bout RPE response

The rate of perceived exertion (RPE) response to exercise is summarised (table 4.2.2). The data suggested that the moderate exercise condition represented fairly light to somewhat hard physical exertion while high intensity exercise condition represented somewhat hard to very hard physical exertion. Rate of perceived exertion for moderate intensity exercise condition increased from level 11 to level 14 over bouts 1 – 7 and during the high intensity exercise condition increased from level 14 to level 18 over bouts 1 – 7 respectively.

Table 4.2.1. Mean heart rate (range) during moderate intensity and high intensity exercise conditions for all exercise bouts

	Interaction Condition x Time *p value*	Main Effect Condition *p value*	Main Effect Time *p value*	Condition	1	2	3	4	5	6	7
HR_{mean} (bpm)	< 0.001	< 0.001	< 0.001	40% WR_{max}	113 (71 - 130)	119 (77 - 138)	121 (81 - 144)	124 (89 - 143)	125 (91 - 143)	127 (94 - 146)	128 (92 - 149)
				75% WR_{max}	135 (94 - 158)	147 (105 - 168)	151 (105 - 176)	156 (115 - 179)	159 (118 - 183)	162 (122 - 189)	163 (130 - 187)

Note: HR_{mean} = mean heart rate; bpm = beats per minute; WR_{max} = maximal work rate

Table 4.2.2. Mean Rate of Perceived Exertion during moderate intensity and high intensity exercise conditions for all exercise bouts

	Intensity	Exercise Bouts						
		1	2	3	4	5	6	7
RPE	40% WR_{max}	11	12	12	13	13	14	14
	75% WR_{max}	14	14	15	16	17	17	18

Note: RPE = rate of perceived exertion; WR_{max} = maximal work rate

4.2.3 BRS response following exercise

The descriptive data for BRS responses following exercise are provided in Appendix XVIII (e). Following initial assessment, Kolmogorov-Smirnov tests were undertaken to test for normal distribution (Appendix XVIII (f)). All significance values ($p = > 0.05$) (Appendix XVIII (b); table A21) indicated that the data was not significantly different ($p = < 0.05$) to a normal distribution and thus the data was treated as parametric and analysed in the appropriate manner.

The findings (mean ± SE) are presented in figures 4.2.2 – 4.2.9. The findings (mean ± SD) are presented in Appendix XVIII (c); figures A24 – A31. The BRS outcomes and statistical outcomes (p values) following exercise are summarised in table 4.2.3 and table 4.2.4 respectively.

A significant interaction ($p = 0.05$) between time and condition in supine was found for spectral indices $BRS_{\alpha LF}$ ($p = 0.006$) and BRS_{TFTG} ($p = 0.004$) (table 4.2.4) (figures 4.2.4 – 4.2.5). In tilt, a significant interaction between time and condition was found for both time indices of BRS_{UpUp} ($p = 0.027$) and $BRS_{DownDown}$ ($p = 0.004$) and spectral indices of $BRS_{\alpha LF}$ ($p = 0.001$) and BRS_{TFTG} ($p < 0.001$), (table 4.2.4) (figures 4.2.6 – 4.2.9). Post-hoc analysis suggested there were significant differences between all conditions at + 15 min and between control and 75% WR_{max} and between 40% WR_{max} and 75% WR_{max} conditions at + 60 min following exercise, (tables 4.2.3 and 4.2.4). At + 15 min, BRS was lower in the 75% WR_{max} condition compared with the 40% WR_{max} and the control condition and the 40% WR_{max} condition was lower than the control condition. No differences were found between exercise conditions at baseline, + 120 min, + 180 min and + 24 h.

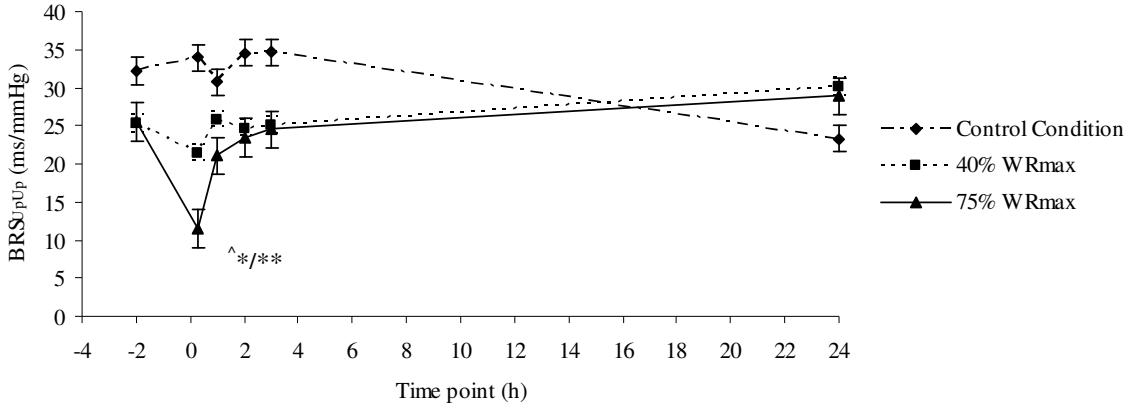

Figure 4.2.2. BRS_{UpUp} in supine (± SE) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. No significant condition x time interaction. ^Significant main effect for condition (p = 0.032). */**Significant difference for all condition comparisons at + 15 min (Control vs 40%; p = 0.025; 34 vs 21 ms/mmHg), (Control vs 75%; p = 0.006; 34 vs 11 ms/mmHg) and (40% vs 75%; p = 0.012; 21 vs 11 ms/mmHg) respectively.

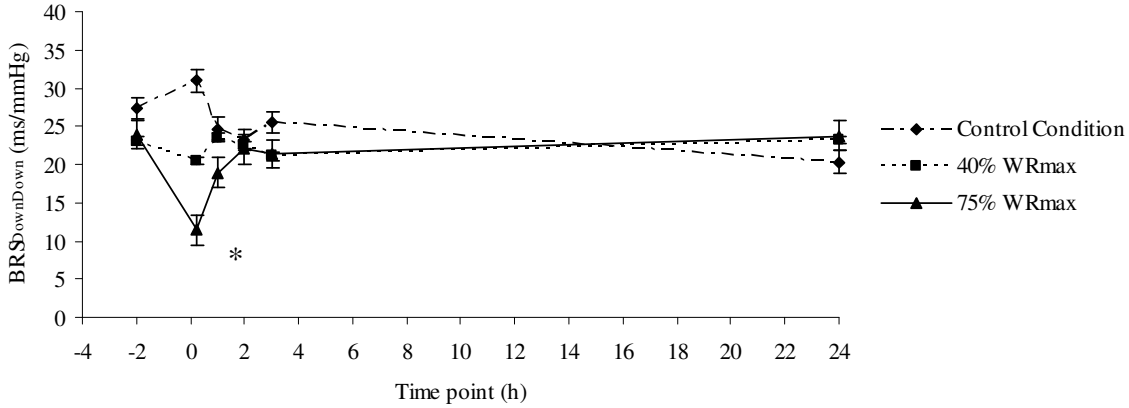

Figure 4.2.3. $BRS_{DownDown}$ in supine (± SE) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. Marginal significant condition x time interaction (p = 0.082). Marginal significant main effect for condition (p = 0.084). *Significant difference for condition comparison at + 15 min (Control vs 75%; p = 0.019, 31 vs 11 ms/mmHg) and (40% vs 75%; p = 0.025, 20 vs 11 ms/mmHg) respectively.

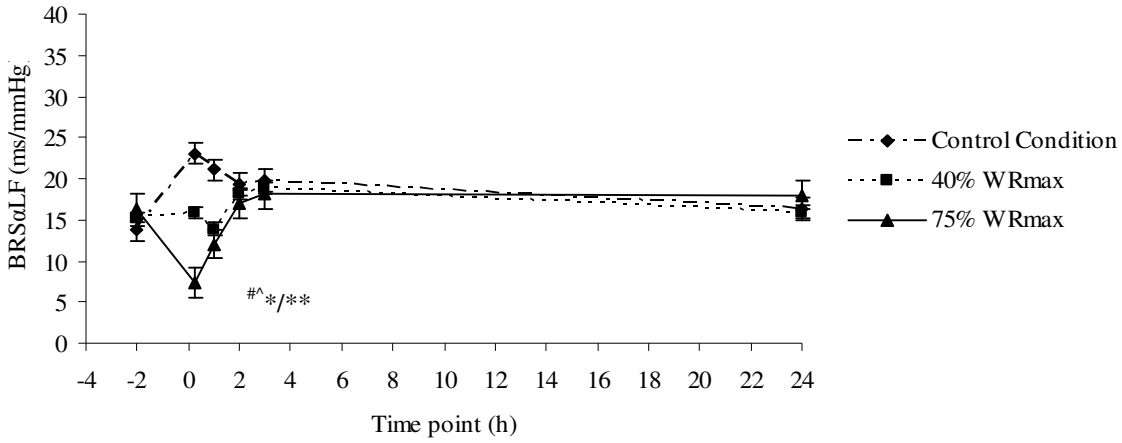

Figure 4.2.4. $BRS_{\alpha LF}$ in supine (± SE) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. #Significant condition x time interaction (p = 0.006). ^Significant main effect for condition (p = 0.032). */**Significant difference for condition comparison at + 15 min and + 60 min (Control vs 40%; p = 0.054, 23 vs 16 ms/mmHg; p = 0.013, 21 vs 14 ms/mmHg), (Control vs 75%; p = 0.007, 23 vs 7 ms/mmHg; p = 0.004, 21 vs 12 ms/mmHg) and (40% vs 75%; p = 0.023, 16 vs 7 ms/mmHg; p = 0.016, 14 vs 12 ms/mmHg) respectively.

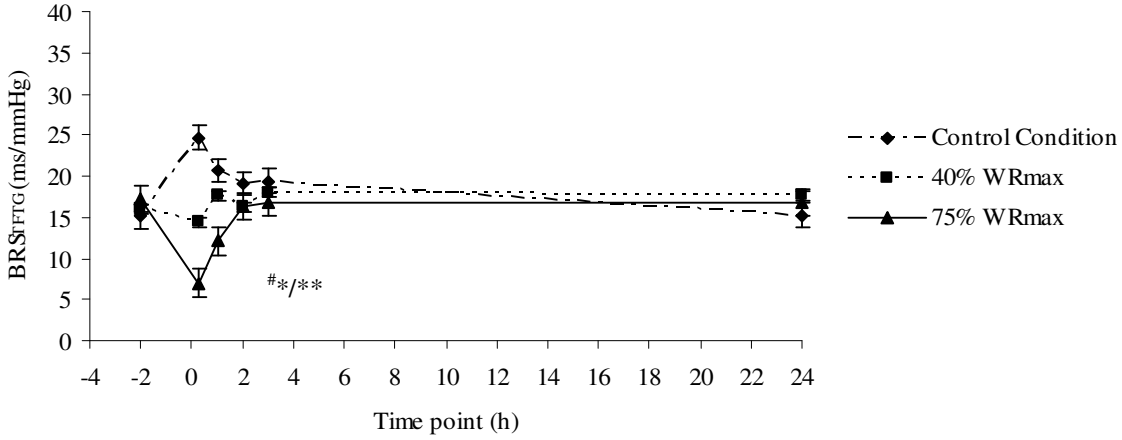

Figure 4.2.5. BRS_{TFTG} in supine (± SE) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. #Significant condition x time interaction (p = 0.004). Marginal significant main effect for condition (p = 0.078). */**Significant difference for condition comparison at + 15 min and + 60 min (Control vs 40%; p = 0.010, 25 vs 14 ms/mmHg), (Control vs 75%; p = 0.003, 25 vs 7 ms/mmHg; p = 0.066, 21 vs 12 ms/mmHg) and (40% vs 75%; p = 0.027, 14 vs 7 ms/mmHg; p = 0.015, 18 vs 12 ms/mmHg) respectively.

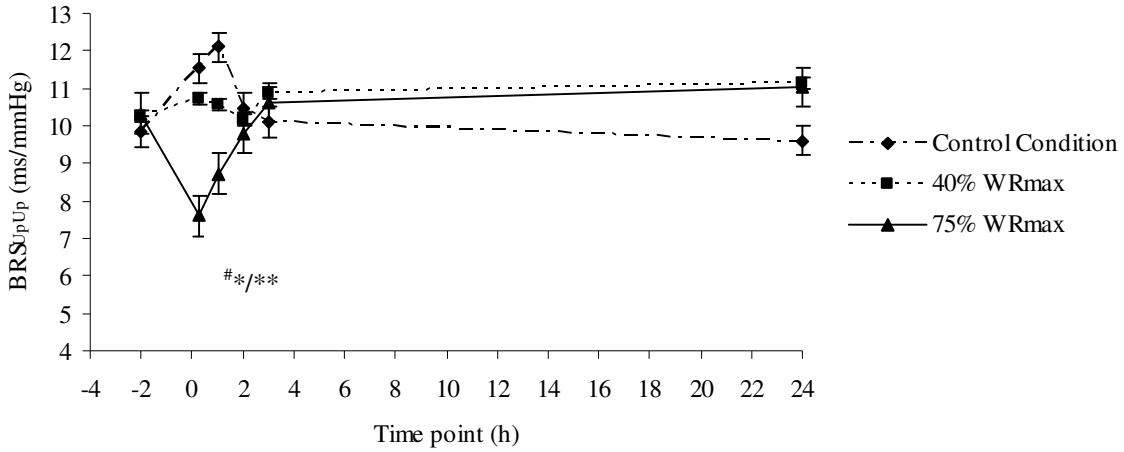

Figure 4.2.6. BRS_{UpUp} in tilt (± SE) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. #Significant condition x time interaction (p = 0.027). No significant main effect for condition. */**Significant difference for condition comparison at + 15 min and + 60 min (Control vs 75%; p = 0.031, 12 vs 8 ms/mmHg; p = 0.051, 12 vs 9 ms/mmHg) and (40% vs 75%; p = 0.006, 11 vs 8 ms/mmHg; p = 0.027, 11 vs 9 ms/mmHg) respectively.

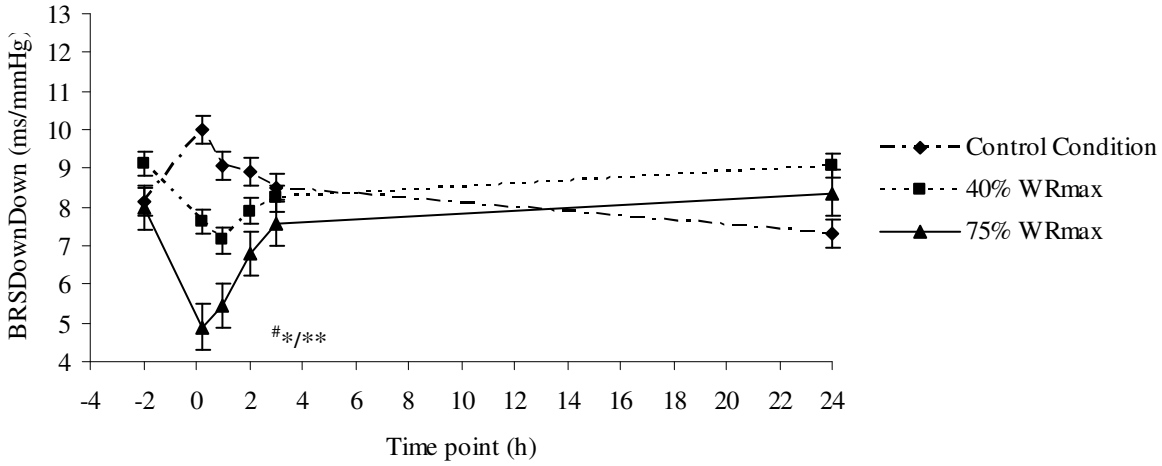

Figure 4.2.7. $BRS_{DownDown}$ in tilt (± SE) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. #Significant condition x time interaction (p = 0.004). No significant main effect for condition. */**Significant difference for condition comparison at + 15 min and + 60 min (Control vs 75%; p = 0.008, 10 vs 5 ms/mmHg; p = 0.019, 9 vs 5 ms/mmHg) and (40% vs 75%; p = 0.004, 8 vs 5 ms/mmHg; p = 0.037, 7 vs 5 ms/mmHg) respectively.

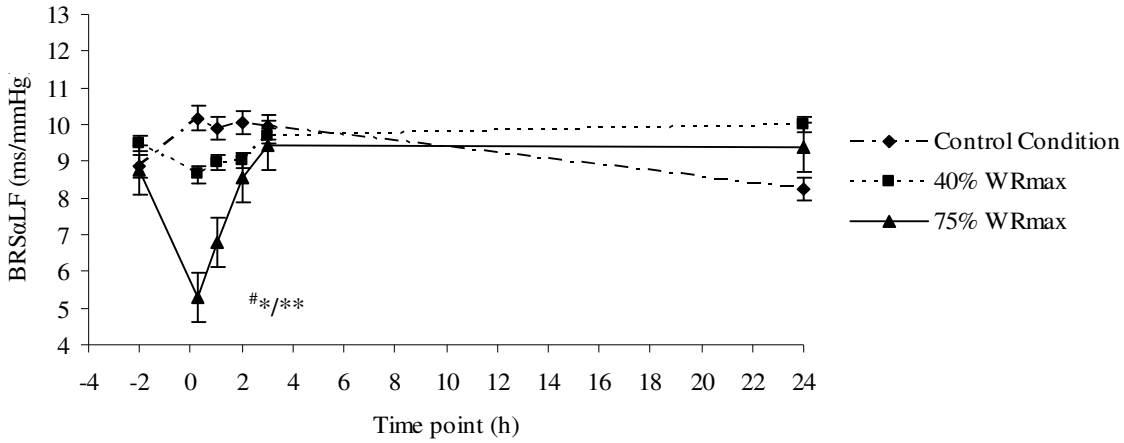

Figure 4.2.8. $BRS_{\alpha LF}$ in tilt (± SE) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. #Significant condition x time interaction (p = 0.001). Marginal significant main effect for condition (p = 0.084). */**Significant difference for condition comparison at + 15 min and + 60 min (Control vs 40%; p = 0.024, 10 vs 9 ms/mmHg), (Control vs 75%; p = 0.001, 10 vs 5 ms/mmHg; p = 0.008, 10 vs 7 ms/mmHg) and (40% vs 75%; p = 0.001, 9 vs 5 ms/mmHg; p = 0.007, 9 vs 7 ms/mmHg) respectively.

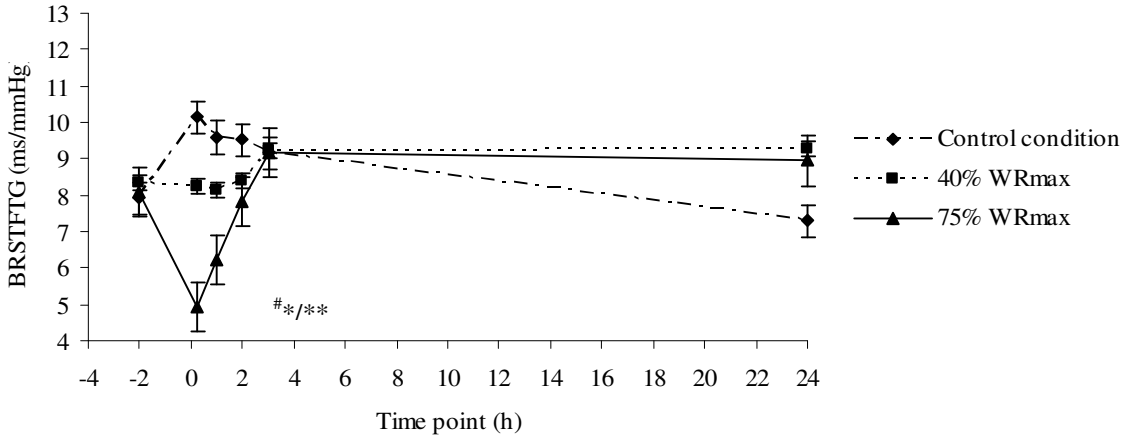

Figure 4.2.9. BRS_{TFTG} in tilt (± SE) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. #Significant condition x time interaction (p = < 0.001). Marginal significant main effect for condition (p = 0.070). */**Significant difference for condition comparison at + 15 min and + 60 min (Control vs 40%; p = 0.046, 10 vs 8 ms/mmHg), (Control vs 75%; p = < 0.001, 10 vs 5 ms/mmHg; p = 0.005, 10 vs 6 ms/mmHg) and (40% vs 75%; p = 0.001, 8 vs 5 ms/mmHg; p = 0.020, 8 vs 6 ms/mmHg) respectively.

Table 4.2.3. Baroreflex sensitivity parameters prior to and at 15, 60, 120, 180 min and 24 h following the three conditions of control (no exercise), 40% WR_{max} and 75% WR_{max}

BRS (ms/mmHg) (± SD)

	Baseline			15 min			60 min		
	C/Condition	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*
$BRS_{Up/Up}$ (S)	32.18 (14.45)	25.23 (11.44)	25.50 (10.37)	33.97 (13.35)	21.49 (7.69)	11.50 (9.74)	30.71 (20.27)	25.86 (12.42)	21.09 (14.24)
$BRS_{Up/Up}$ (T)	9.83 (2.53)	10.24 (2.05)	10.33 (3.00)	11.53 (3.90)	10.74 (4.71)	7.60 (2.69)	12.10 (3.99)	10.57 (3.53)	8.73 (2.58)
$BRS_{DownDown}$ (S)	27.30 (10.33)	23.08 (10.64)	24.01 (9.79)	30.93 (17.60)	20.41 (7.60)	11.38 (10.01)	24.64 (5.94)	23.51 (7.77)	18.91 (7.40)
$BRS_{Down/Down}$ (T)	8.13 (2.76)	9.11 (4.10)	7.97 (2.69)	10.00 (3.56)	7.62 (4.29)	4.90 (3.16)	9.08 (3.74)	7.14 (3.11)	5.44 (1.81)
$BRS_{\alpha LF}$ (S)	13.88 (6.42)	15.09 (5.96)	16.34 (8.92)	23.10 (8.49)	15.82 (6.11)	7.37 (6.42)	21.04 (4.01)	13.90 (5.51)	12.05 (5.09)
$BRS_{\alpha LF}$ (T)	8.86 (2.17)	9.49 (2.45)	8.78 (2.21)	10.17 (2.60)	8.63 (2.56)	5.28 (2.62)	9.91 (2.69)	8.97 (3.01)	6.81 (2.05)
BRS_{TFTG} (S)	15.07 (5.48)	16.00 (5.82)	17.26 (6.51)	24.65 (8.67)	14.43 (5.73)	6.96 (5.38)	20.7 (5.73)	17.66 (7.66)	12.12 (6.06)
BRS_{TFTG} (T)	7.92 (2.06)	8.36 (2.30)	8.09 (2.02)	10.14 (2.42)	8.25 (3.46)	4.92 (2.67)	9.58 (2.58)	8.15 (3.16)	6.23 (1.69)
	120 min			180 min			24 h		
	C/Condition	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*
$BRS_{Up/Up}$ (S)	34.54 (13.32)	24.71 (14.56)	23.44 (12.20)	34.66 (11.95)	25.04 (9.72)	24.50 (8.10)	23.30 (9.28)	30.17 (14.53)	28.89 (13.52)
$BRS_{Up/Up}$ (T)	10.46 (3.57)	10.16 (2.83)	9.81 (3.21)	10.12 (2.09)	10.90 (4.62)	10.62 (3.72)	9.61 (2.66)	11.14 (4.23)	11.04 (3.51)
$BRS_{DownDown}$ (S)	23.22 (7.31)	22.57 (8.04)	21.98 (14.24)	25.53 (9.34)	21.09 (7.12)	21.38 (7.92)	20.33 (6.36)	23.21 (8.14)	23.78 (6.55)
$BRS_{Down/Down}$ (T)	8.91 (2.37	7.90 (3.13)	6.80 (2.21)	8.49 (1.84)	8.22 (3.43)	7.59 (2.76)	7.30 (2.09)	9.08 (3.38)	8.37 (2.47)
$BRS_{\alpha LF}$ (S)	19.32 (7.84)	18.18 (8.70)	16.94 (6.04)	19.71 (4.76)	18.81 (7.14)	18.10 (7.99)	16.23 (6.93)	15.97 (6.11)	17.99 (8.77)
$BRS_{\alpha LF}$ (T)	10.04 (2.58)	9.04 (2.09)	8.54 (2.67)	9.93 (2.44)	9.68 (3.11)	9.43 (5.01)	8.23 (2.34)	10.01 (3.18)	9.39 (2.29)
BRS_{TFTG} (S)	19.10 (6.42)	16.30 (7.04)	16.29 (5.95)	19.36 (5.07)	17.96 (7.04)	16.88 (7.22)	15.23 (5.98)	17.67 (5.71)	16.80 (6.53)
BRS_{TFTG} (T)	9.51 (2.25)	8.41 (2.28)	7.82 (2.45)	9.15 (1.91)	9.23 (3.48)	9.19 (4.52)	7.29 (2.00)	9.26 (3.00)	8.94 (2.59)

Note: Parameters are group mean. SD is standard deviation; Seq is Sequence; LF is low frequency; TFTG is transfer function transfer gain; (S) is supine (T) is tilt

Table 4.2.4. Supine and tilt baroreflex sensitivity statistical outcomes (p values) for interaction, main effects and condition comparisons prior to and at 15, 60, 120, 180 min and 24 h following three conditions of control, 40% WR_{max} and 75% WR_{max}

Variable	Interaction	Main Effect		Condition Comparison								
	Condition x Time	Condition	Time	Contol vs 40%	Control vs 75%	40% vs 75%	Control vs 40%	Control vs 75%	40% vs 75%	Control vs 40%	Control vs 75%	40% vs 75%
SUPINE					Baseline			+ 15 min			+ 60 min	
BRS_{UpUp}	*0.082*	**0.032**	0.327	0.125	0.148	0.946	**0.025**	**0.006**	**0.012**	0.587	0.338	0.203
$BRS_{DownDown}$	*0.058*	*0.084*	0.491	0.148	0.335	0.714	0.175	**0.019**	**0.025**	0.729	0.104	0.151
$BRS\alpha_{LF}$	**0.006**	**0.032**	0.136	0.608	0.344	0.667	*0.054*	**0.007**	**0.023**	**0.013**	**0.004**	**0.016**
BRS_{TFTG}	**0.004**	*0.078*	0.291	0.671	0.373	0.619	**0.010**	**0.003**	**0.027**	0.530	*0.066*	**0.015**
					+ 120 min			+180 min			+ 24 h	
BRS_{UpUp}				0.106	*0.082*	0.667	**0.048**	**0.013**	0.791	*0.087*	0.191	0.845
$BRS_{DownDown}$				0.851	0.839	0.841	0.169	0.174	0.904	**0.027**	0.137	0.752
$BRS\alpha_{LF}$				0.675	0.258	0.492	0.622	0.493	0.601	0.879	0.562	0.420
BRS_{TFTG}				0.452	0.472	0.993	0.443	0.132	0.613	*0.060*	0.396	0.490
TILT					Baseline			+ 15 min			+ 60 min	
BRS_{UpUp}	**0.027**	0.453	0.602	0.683	0.682	0.907	0.637	**0.031**	**0.006**	0.275	*0.051*	**0.027**
$BRS_{DownDown}$	**0.004**	0.151	0.192	0.560	0.877	0.182	0.202	**0.008**	**0.004**	0.154	**0.019**	**0.037**
$BRS\alpha_{LF}$	**0.001**	*0.084*	0.119	0.537	0.912	0.299	**0.024**	**0.001**	**0.001**	0.373	**0.008**	**0.007**
BRS_{TFTG}	**< 0.001**	*0.070*	0.154	0.645	0.790	0.679	**0.046**	**< 0.001**	**0.001**	0.150	**0.005**	**0.020**
					+ 120 min			+180 min			+ 24 h	
BRS_{UpUp}				0.787	0.612	0.525	0.609	0.737	0.808	0.095	0.175	0.937
$BRS_{DownDown}$				0.370	*0.050*	*0.051*	0.828	0.396	0.173	*0.070*	0.148	0.542
$BRS\alpha_{LF}$				0.280	0.157	0.263	0.785	0.751	0.786	**0.015**	*0.084*	0.374
BRS_{TFTG}				0.187	*0.078*	*0.060*	0.933	0.981	0.944	**0.006**	**0.010**	0.710

Note: LF is low frequency; TFTG is transfer function transfer gain; WR_{max} is work rate maximum; **bold** denotes statistical significance (< 0.05); *italics* denotes marginal significance (0.05 - < 0.10)

CHAPTER FIVE

DISCUSSION

CHAPTER 5: DISCUSSION

The first main aim of this research project was to investigate the same day reproducibility and between day reproducibility of the measurement of supine BRS and tilt BRS in a healthy adult male population. The determination of BRS was undertaken utilising the modern method and employing various techniques for the assessment of spontaneous BRS. These investigations informed the following exercise study. The second main aim of this research project was to investigate the effect of intensity of exercise on supine BRS and tilt BRS following a single bout of exercise in a healthy male population, employing a comprehensive range of BRS measures together with six time points to reflect the immediate to long-term post-exercise responses to track the time course of events over various BRS measures.

5.1 Main findings: reproducibility of baroreflex sensitivity

Initial research investigated the within day and between day reproducibility of BRS during supine and tilt conditions and incorporated time and spectral techniques with four BRS outcome measures to elucidate the findings. The BRS outcome measures were BRS_{UpUp} and $BRS_{DownDown}$ via the sequence technique in the time domain and, $BRS_{\alpha LF}$ and BRS_{TFTG} in the spectral domain. Key findings included between day reproducibility was marginally better than same day reproducibility for the sequence parameters while same day reproducibility was marginally better than between day reproducibility for the spectral parameters and reproducibility was markedly improved in all BRS outcomes in the tilt position. The TEM reflected good precision for the spectral measures in supine and for all measures in tilt for both same day and between day reproducibility. The precision was lower but acceptable for the sequence measures for same day and between day reproducibility. Thus all BRS measures were found to be worthy and of interest, therefore all of the measures and the tilt procedure were incorporated into the exercise study.

Although the spontaneous non-invasive BRS techniques are now routinely employed for baroreflex testing, there are still only a few studies that have assessed the reproducibility of these techniques (Davies *et al.*, 1999; Dawson *et al.*, 1997; Herpin &

Ragot, 1997; Iellamo *et al.*, 1996; Lord *et al.*, 1998; Maestri *et al.*, 2009) and the variation between studies has resulted in conflicting findings for the reproducibility of BRS. Limitations concerning the reproducibility of BRS have included low sample size (Davies *et al.*, 1999; Herpin & Ragot, 1997; Iellamo *et al.*, 2001; Lord *et al.*, 1998), limited choice of BRS parameters (Iellamo *et al.*, 1996) and lack of protocols for between day reproducibility (Davies *et al.*, 1999; Dawson *et al.*, 1997; Herpin & Ragot, 1997; Lord *et al.*, 1998). The one study that has included a large sample size, a wide selection of BRS parameters and a protocol for between day reproducibility did not include same day reproducibility or an orthostatic manoeuvre (Maestri *et al.*, 2009). The inclusion of an orthostatic manoeuvre was deemed to be of interest because earlier studies which had included standing (Herpin & Ragot, 1997; Iellamo *et al.*, 1996) had found improved BRS reproducibility during the orthostatic manoeuvre. Indeed, the high reproducibility of spontaneous BRS in standing over the mid and long term suggested small significant changes could be detected via small sample size in both the time and spectral domains in follow-up studies (Herpin & Ragot, 1997). This is an important finding because in exercise experimental research testing it is usual to incorporate low participant numbers in testing procedures and, the previously reported significant changes in BRS from exercise training in clinical and older populations have been small i.e., ~ 3 ms/mmHg (Costes *et al.*, 2004; Galbreath *et al.*, 2011; Iellamo *et al.*, 2000; La Rovere *et al.*, 2002; Monahan *et al.*, 2000; Pagani *et al.*, 1988). Thus to date, current BRS reproducibility studies have not included a comprehensive protocol to include a large sample size, a wide BRS parameter selection, same day/ between day reproducibility and an orthostatic manoeuvre. The reproducibility study undertaken for this project has incorporated all of these aspects to assess the reproducibility for BRS.

In healthy individuals the variability in BRS determined by the sequence technique has been reported to be high (Iellamo *et al.*, 1996; Parati *et al.*, 1988) although the variability was not found to differ significantly between two consecutive days (Iellamo *et al.*, 1996; Maestri *et al.*, 2009). Mechanisms for the variability in BRS are speculated to include the complex central integration of cortical and peripheral neural inputs leading to changes in HR via vagal and sympathetic outflows to the sinus node (Iellamo *et al.*, 1996). Indeed, various influences can be brought about by imposed modifications (i.e., hand-grip, mental arithmetic, standing) which provide different BRS outcome

measures (Iellamo *et al.*, 1996). For example, hand-grip was not found to alter BRS when compared to resting measures while mental activity during mental arithmetic and the employment of both emotional and physical stimuli during standing reduced BRS (Herpin & Ragot, 1997; Iellamo *et al.*, 1996). These findings provided evidence for the complexity of baroreflex control of the sinus node and the inherent high variability of BRS which may be associated with the outcome measure (Iellamo *et al.*, 1996). In standing, the lower BRS variation despite lower average values may be linked to an orthostatic-induced stimulation of sympathetic activity, decreasing the magnitude of the BRS outcome measure and reducing the influence of internal and external stimuli on the sympathovagal balance (Herpin & Ragot, 1997). Thus, an imposed modification such as an orthostatic manoeuvre during testing procedures may be a useful tool to employ to aid in the attenuation of stimuli which influence the determination of BRS and, ultimately, could impact upon study design considerations. An important finding in the present study was the marked improvement in reproducibility in all BRS outcome measures in the tilt position. This observation supported previous findings of improved reproducibility incorporating an orthostatic manoeuvre (Herpin & Ragot, 1997; Iellamo *et al.*, 1996) and endorsed the present study's hypothesis that a tilt manoeuvre could improve the reproducibility for BRS and provide robustness for future research study findings.

Reproducibility assessed via various techniques has provided variation in the magnitude of the outcome measure. For example, in the present study the magnitude of BRS assessed via the sequence technique was markedly greater than the magnitude of BRS via the spectral techniques. Furthermore, the reproducibility of different spectral techniques has been shown to be markedly reduced in BRS measures incorporating the HF component (under spontaneous breathing) compared to those measures incorporating LF (Davies *et al.*, 1999; Lord *et al.*, 1998; Maestri *et al.*, 2009), probably due to the influence of respiration in the HF band. These findings suggested the selection of the BRS technique may be an important consideration in research testing because the magnitude of the outcome measure for BRS may be highly variable under the same condition, in the same population and under the same testing environment (Maestri *et al.*, 2009) which could ultimately obscure the detection of genuine change and provide comparability issues between studies.

The reproducibility of BRS is an important consideration for future study design in follow-up studies and in the elucidation of subsequent observations. All four BRS outcome measures were found to be worthy and of interest thus all of the measures and the tilt procedure were incorporated into the second phase of this research project. The present reproducibility study provided a context for supine and tilt same day/ between day BRS outcome measures for pre and post exercise assessment which should aid in the detection of a significant effect in BRS if such an effect is there and, may facilitate greater understanding in the interpretation of the exercise study findings.

5.2 Main findings: post-exercise response of baroreflex sensitivity

Research was undertaken to investigate the influence of intensity of exercise on post-exercise BRS by a within subjects repeated measures study design which included two counterbalanced exercise conditions and a control condition in both supine and tilt. Previous research has shown that a single bout of exercise alters BRS temporarily (Convertino & Adams, 1991; Halliwill *et al.*, 1996b; Niemelä *et al.*, 2008; Piepoli *et al.*, 1993; Ploutz *et al.*, 1993; Raczak *et al.*, 2005; Somers *et al.*, 1985; Stuckey *et al.*, 2012; Terziotti *et al.*, 2001) although the role of exercise intensity on autonomic dynamics is unclear.

Interval exercise testing has been incorporated previously in research relating to post-exercise autonomic responses (James *et al.*, 2002; James *et al.*, 2012; Stuckey *et al.*, 2012). The single bout of moderate intensity exercise was similar to previously administered exercise bouts (Halliwill *et al.*, 1996b; Niemelä *et al.*, 2008; Raczak *et al.*, 2005) (table 2.5.1) and reflects the intensity of exercise advocated in current public health recommendations for clinical and non-clinical populations for the improvement of cardiorespiratory fitness and enhanced cardiovascular health (ACSM, 2006a). A single bout of high intensity exercise has been employed less often in autonomic research exercise testing (Stuckey *et al.*, 2012; Terziotti *et al.*, 2001) (table 2.5.1) and this exercise intensity is generally undertaken in trained individuals who require exercise intensity at the higher end of the exercise intensity continuum to achieve improved cardiorespiratory fitness and in whom high intensity exercise does not impose an adverse risk (ACSM, 2006a). Although in the present study both exercise conditions

provided equal amounts of work done, the physiological response differed between the two intensities of exercise which was exemplified by the HR data (table 4.2.1) and by participant perception of work done (table 4.2.2) because both HR and RPE were lower in the moderate intensity condition compared to the high intensity exercise condition.

The determination of spontaneous BRS is a non-invasive, indirect marker to reflect changes in autonomic activity (Mancia & Mark, 1983; Parati *et al.*, 2000). The determination of BRS may be particularly useful for assessing overall cardiovascular control post-exercise. Whether BRS may be acutely manipulated following exercise is an important question. Currently, there is little research that has investigated the effect of a single bout of exercise on post-exercise BRS and in particular, the influence of intensity of exercise on cardiovascular control. The present study employed two distinct intensities of exercise (moderate and high) and a control condition of no exercise in the intervention procedure. None of the previous studies have incorporated these features. Previous studies (table 2.5.1) have incorporated either a maximal exercise test (Convertino & Adams, 1991; Piepoli *et al.*, 1993; Somers *et al.*, 1985), Wingate sprint exercise (Stuckey *et al.*, 2012), resistance exercise (Ploutz *et al.*, 1993), a mixture of aerobic and resistance exercise (Niemelä *et al.*, 2008) or a single bout of exercise of one intensity (Halliwill *et al.*, 1996b; Raczak *et al.*, 2005) and only half of these studies incorporated a control condition. The one study which did incorporate two intensities of aerobic exercise (50% and 80% AT) (and no control condition) included same duration length (20 min) (Terziotti *et al.*, 2001). Another study utilised two exercise conditions of light and heavy resistance exercise and one condition of aerobic exercise (50% WR_{max}) of same duration length (40 min) with no measure to standardise work done between the different exercise conditions (Niemelä *et al.*, 2008). The incorporation of equal duration length would not reflect a matched amount of work done between exercise conditions and this would undermine the distinction of intensity in the different exercise conditions, providing a confounding influence of volume of exercise. The two studies which incorporated a single bout of aerobic exercise of one intensity (60% $\dot{V}O2_{peak}$ and 65% HRmax respectively) (Halliwill *et al.*, 1996b; Raczak *et al.*, 2005) did not include a control condition. Thus, none of the previous studies had explicitly identified intensity of exercise in the intervention procedure. The present exercise study clearly identified two distinct intensities of exercise which was

demonstrated by the HR, RPE and significant differences found between the two exercise conditions following an equal amount of work done in each exercise condition. The present exercise study also incorporated a tilt procedure which had not been undertaken by any of the previous studies, a comprehensive range of BRS measures together with six time points to reflect the immediate to long-term post-exercise responses to track the time course of events over various BRS measures. Such procedures had not been incorporated (*en masse*) in the previous related studies.

In the present exercise study, several notable findings were observed in BRS in the time and spectral domains in the short term recovery period (+ 15 min and + 60 min) following exercise. Baroreflex sensitivity was not immediately restored following exercise in either exercise condition and was in agreement with previous findings. Divergent responses between the moderate and high intensity conditions were observed indicating a possible intensity-dependent autonomic response via exercise. A significant interaction between time and condition was found in the spectral indices in supine (table 4.2.4) (figures 4.2.4; 4.2.5) and in both time and spectral measures in tilt (table 4.2.4) (figures 4.2.6 – 4.2.9). Significant differences were found immediately following both exercise conditions with a small reduction in the magnitude of BRS values following the moderate intensity exercise condition and a marked reduction in the magnitude of BRS values following the high intensity exercise condition (tables 4.2.3; 4.2.4). These findings suggested a change in autonomic dynamics of increased vagal withdrawal and greater sympathetic outflow immediately following exercise in both exercise conditions which was notably more pronounced following the high intensity exercise condition. In the main, by + 120 min all BRS values for both exercise conditions had returned to baseline levels. There were significant differences in supine and tilt between baseline and + 15 min for all BRS outcomes and in tilt only between baseline and + 60 min following the high intensity exercise condition. There were no significant differences for the control condition.

In the immediate recovery period following exercise (< 15 min), HR decreases in a marked non-linear fashion and spectral analysis may be impeded because FFT and AR spectrum analysis require steady state HR conditions (Savin *et al.*, 1982; Terziotti *et al.*, 2001). Analysis in this immediate recovery period should be avoided due to a possible

error in the measure (Terziotti *et al.*, 2001) thus, in the present exercise study the first post-exercise time point was + 15 min to evade such impedance of the spectral analysis.

Baroreflex sensitivity was significantly reduced + 15 min in all BRS outcome measures in supine and tilt for both exercise conditions (table 4.2.4). A reduction in BRS was consistent with previous studies which have also reported reduced BRS in the early stage of the recovery period (≥ + 15 min) following exercise (Halliwill *et al.*, 1996b; Niemelä *et al.*, 2008; Piepoli *et al.*, 1993; Somers *et al.*, 1985; Terziotti *et al.*, 2001). Because BRS may be dominated by the disturbance of cardiovascular indices in the early stages following exercise, research studies which report BRS assessment at time points ≥ + 60 min to + 24 h post-exercise (Convertino & Adams, 1991; Halliwill *et al.*, 1996b; Niemelä *et al.*, 2008; Ploutz *et al.*, 1993; Stuckey *et al.*, 2012; Terziotti *et al.*, 2001) may be of greater interest because they may reflect better the short and long term changes in BRS following exercise. However, early responses (> + 15 min to ≤ 60 min) following exercise can be useful because they may demonstrate change in BRS during the early stages of recovery which may not be evident at + 60 min following exercise and these early BRS responses may help to provide a context for BRS during the later stages of the recovery period.

Following exercise and the immediate reduction in the measure, BRS gradually increases back to baseline levels. Some studies have reported a decrease lasting for only a short time period of ≤ 20 min (Halliwill *et al.*, 1996b; Somers *et al.*, 1985) while other studies have suggested the reduction may persist for > 2 h (Stuckey *et al.*, 2012), providing evidence of an altered autonomic balance which may be dependent on the intensity or volume of exercise. For example, in the present exercise study BRS recovery was markedly different between the two exercise intensity conditions. A longer recovery period (+ 60 min) with notably greater reduction in the magnitude of the BRS outcome measures following the high intensity exercise condition was observed compared to the relatively short recovery period (< 60 min) and marginal reduction in the magnitude of BRS outcome measures following the moderate intensity exercise condition. This pattern of recovery was observed across the spectral BRS outcome measures in supine and across both the time and spectral indices in tilt providing concordant evidence in the findings and robustness for BRS outcome

assessment. Time domain values provide a general overview for autonomic influence while spectral indices allow a greater discrimination for autonomic arm involvement (Terziotti *et al.*, 2001) and therefore a greater ability to discriminate between parasympathetic and sympathetic influence. These observations supported previous findings which indicated greater volumes of exercise achieved via resistance exercise and Wingate sprint testing may contribute to a longer recovery of BRS indices following exercise (Niemelä *et al.*, 2008; Stuckey *et al.*, 2012) and may be more apparent during an orthostatic manoeuvre (Stuckey *et al.*, 2012) suggesting a possible greater influence of the sympathetic nervous system in BRS recovery which may also be intensity-dependent. Interestingly, the BRS recovery period following moderate intensity exercise compared to light intensity exercise of equal exercise duration length was not significantly different (Terziotti *et al.*, 2001). However, the R-R interval HF data suggested a greater persisting vagal withdrawal following the moderate intensity exercise condition compared to the light intensity condition intimating a possible change in the autonomic balance of HR control even between lower intensities of exercise, albeit this study was confounded by volume of exercise.

The deceleration of HR during the recovery period following exercise is influenced by the dynamics of parasympathetic and sympathetic control and there is some controversy as to which limb of the ANS is more dominant during the recovery phase following exercise (Borresen & Lambert, 2008). Some research has suggested the autonomic control involves a co-ordinated interaction of parasympathetic reactivation and sympathetic withdrawal with the faster parasympathetic reactivation being the dominant feature (Javorka *et al.*, 2002; Kannankeril & Goldberger, 2002; Pierpont & Voth, 2004) while earlier research proposed the sympathetic withdrawal was the more dominant influence (Savin *et al.*, 1982). The disparity between studies regarding the dominant influence in autonomic activity may be related to the intensity of exercise. For example, HR recovery following maximal exercise is slower than the recovery following submaximal exercise in healthy individuals and has been attributed to the stronger sympathetic activity during maximal exercise thus, HR recovery following high intensity exercise may be strongly influenced by a sympathetic withdrawal in addition to the reactivation of the parasympathetic system (Borresen & Lambert, 2008; Pierpont & Voth, 2004). Conversely, HR recovery following mild/ moderate intensity exercise is

largely controlled via parasympathetic reactivation because of the lower levels of sympathetic stimulation evoked during the exercise bout (Pierpont & Voth, 2004). Thus, the relationship between sympathetic activity and the intensity of exercise may serve to alter autonomic dynamics in HR control following exercise and may provide the opportunity to manipulate BRS outcomes via different exercise conditions.

The present exercise study has provided further evidence for a strong sympathetic influence following high intensity exercise by the observed marked reduction in BRS across all BRS indices in tilt (tables 4.2.3; 4.2.4) (figures 4.2.6 – 4.2.9). In healthy individuals the active change from supine to upright during tilt increases HR and the autonomic balance changes from a parasympathetic predominance in supine to one of increased sympathetic influence when upright (Aubert *et al.*, 2003). Thus tilting may provide greater insight into the relationship between autonomic dynamics and intensity of exercise which may be exhibited in the spectral bands. For example, an increase in sympathetic activity from an orthostatic manoeuvre reflects a relative decrease in HF and relative increase in LF of R-R interval and an increase in LF spectrum of BP (Bernardi *et al.*, 1997; Pagani *et al.*, 1986; Radaelli *et al.*, 1994; Saul *et al.*, 1991). Thus an increase in LF dominance post exercise compared to baseline measures may indicate increased sympathetic activity (Bernardi *et al.*, 1997) and this may only be apparent by employing an orthostatic challenge. The assessment of the short and long term recovery (+ 1 h, + 24 h and + 48 h) in cardiac autonomic indices following a single bout of constant and interval training exercise reported a continuing cardiovascular disturbance which was only evident at + 48 h with an orthostatic manoeuvre (Mourot *et al.*, 2004). The present study also found some evidence of long term autonomic change between the moderate and high intensity exercise conditions and the control condition at + 24 h (table 4.2.4) (figures 4.2.8 – 4.2.9) which was only evident with BRS spectral indices in tilt, suggesting a change in sympathetic influence in the opposite direction. However, this finding did not provide a definitive pattern of change unlike findings at + 15 min and + 60 min.

Following the early depression of BRS and subsequent recovery, a number of studies have reported an enhancement in BRS between pre-exercise levels and following exercise (Convertino & Adams, 1991; Halliwill *et al.*, 1996b; Raczak *et al.*, 2005;

Somers *et al.*, 1985). Baroreflex sensitivity was increased at + 60 min following moderate intensity exercise (Halliwill *et al.*, 1996b; Raczak *et al.*, 2005) and maximal exercise (Somers *et al.*, 1985) with no measures taken beyond this time point (Raczak *et al.*, 2005; Somers *et al.*, 1985) or had returned to baseline by + 120 min (Halliwill *et al.*, 1996b). One study reported long term enhanced BRS change at + 24 h following maximal exercise (Convertino & Adams, 1991). Other related studies have not observed an augmentation in BRS which is consistent with the findings of the present exercise study (Niemelä *et al.*, 2008; Piepoli *et al.*, 1993; Stuckey *et al.*, 2012). Baroreflex sensitivity remained reduced at + 60 min following heavy resistance exercise which had returned to baseline by + 120 min (Niemelä *et al.*, 2008) and following single Wingate sprint testing (assessed during standing) and multiple Wingate sprint testing (assessed during supine and standing) at + 120 min with no measures taken beyond this time point (Stuckey *et al.*, 2012). In the present exercise study, BRS had returned to baseline by + 60 min following the moderate intensity exercise condition and by + 120 min following the high intensity exercise condition. It is unclear why some studies have observed a significant decrease in BRS following exercise while conversely others have reported significant increases in BRS following exercise, although one important consideration might include fitness status because BRS has been found to be significantly reduced in young very fit adults compared with moderately fit young adults (Smith *et al.*, 2000). This would support the findings of reduced BRS following exercise in the present study and one other related study (Niemelä *et al.*, 2008) because the testing participants in these investigations were very fit individuals compared to the less fit participants in the other related studies. Indeed, the finding of enhanced BRS following exercise (Convertino & Adams, 1991; Halliwill *et al.*, 1996b; Piepoli *et al.*, 1993; Raczak *et al.*, 2005; Somers *et al.*, 1985) was reported in participants with descriptive profiles of lesser fitness.

The findings in the present exercise study suggested the magnitude for change in post-exercise BRS at + 15 min and + 60 min (table 4.2.3) was greater than the measurement error observed in the present reproducibility study in supine BRS spectral measures and in tilt BRS time and spectral measures (table 4.1.1). For example, measurement error in supine BRS spectral measures was 9 ms/mmHg and 7 ms/mmHg for $BRS_{\alpha LF}$ and BRS_{TFTG} respectively and the magnitude for change compared to control post-exercise

ranged from 7 to 16 ms/mmHg and 6 to 18 ms/mmHg in $BRS_{\alpha LF}$ and BRS_{TFTG} respectively. The measurement error in tilt BRS time and spectral measures was 4 ms/mmHg for the sequence measures and 3 ms/mmHg for the spectral measures and the magnitude for change compared to control post-exercise ranged from 3 to 4 ms/mmHg, 4 to 5 ms/mmHg, 1 to 5 ms/mmHg and 2 to 5 ms/mmHg in BRS_{UpUp}, $BRS_{DownDown}$, $BRS_{\alpha LF}$ and BRS_{TFTG} respectively. The magnitude for change was greater following the high intensity exercise condition compared to the magnitude for change following the moderate intensity exercise condition. Overall, the majority of findings suggested the observed effects were greater than the measurement error and therefore such change may be due to alterations in physiological mechanisms. These mechanisms may also be responsible for the divergent findings between the related studies although other issues such as participant characteristics, exercise history, BRS assessment techniques and different exercise protocols between the related studies and the present exercise study may also have some bearing on the divergent findings.

Sympathetic stimulation during exercise causes the release of catecholamines adrenalin and noradrenalin in proportion to the exercise intensity which indirectly modulate HR (MacDonald, 2002). Following cessation of exercise, residual elevated circulating levels of catecholamines may be responsible for the attenuation of vagal and increased sympathetic outflow during recovery (Halliwill *et al.*, 1996a; Parekh & Lee, 2005). Elevated catecholamine levels activate β-adrenergic receptors and accelerate the rate of diastolic depolarisation with the result of increased HR, increased contractility and increased $\dot{Q}$ (MacDonald, 2002). Thus, changes from resting catecholamine levels may be a possible mechanism for the alterations in autonomic balance following exercise. However in two previous studies which assessed catecholamine levels following exercise, plasma catecholamines were not found to influence BRS outcome. Noradrenalin levels were found to remain above pre-exercise levels at + 60 min suggesting symptho-excitation regardless of the increase in BRS (Halliwill *et al.*, 1996b) and elevations of circulating noradrenalin returned to baseline levels shortly following maximal exercise while BRS remained enhanced for + 24 h (Convertino & Adams, 1991). Whether or not catecholamine influence can be attributed to the significant reductions in BRS reported by the present study or related to increasingly higher levels of intensity of exercise cannot be stated because catecholamine levels were

not assessed. However, it may be unlikely because the two studies which assessed catecholamine levels following exercise had undertaken moderate intensity exercise or maximal exercise thus distinguishing higher levels of intensity in the intensity continuum.

Exercise increases heat production through an increased demand for $\dot{O}_2$ consumption by the working muscles. The rate of heat production is known as the metabolic rate. Increased $\dot{O}_2$ delivery requires $\dot{Q}$ to increase and this is directly proportional to the metabolic rate required for the activity (Powers & Howley, 2004). Cardiac output is the product of HR and SV with increases in $\dot{Q}$ achieved through increases in both HR and SV. Initially SV and HR work together, but at a particular workload (~ 40% $\dot{V}O_{2max}$ in untrained and moderately trained individuals) SV plateaus while HR continues to increase (Powers & Howley, 2004). Thus, above this workload level any increase in $\dot{Q}$ would be achieved through an increase in HR alone. As the intensities of exercise in this study were moderate intensity (which evoked mean heart rates of 61 - 69% of HR_{peak}) and high intensity (which evoked mean heart rates of 73 - 88% of HR_{peak}), HR clearly increased to support the rise in the metabolic rate. During exercise, blood is diverted to the working muscles due to the increased demand for $\dot{O}_2$ with reduced blood flow to the visceral organs and skin. A reduction of blood to the peripheral areas of the body may cause a rise in body temperature through reduced thermoregulation. A rise in body temperature increases the metabolic rate and thus increases HR. The increase in the metabolic rate increases body temperature because not all heat is liberated from the body (Brooks *et al.*, 2000). This may result in loss of body fluids, primarily through sweating which may reduce plasma volume.

Water is essential for the maintenance of blood volume and cardiovascular system integrity and because the water requirements are increased with exercise, a hydration strategy should parallel sweat losses (Sawka *et al.*, 2005). Plasma volume decreases during exercise due to fluid moving out of the vascular space and this becomes increasingly acute as the intensity and/or duration of exercise increases (Brooks *et al.*, 2000). Thus plasma volume decreases due to fluid movement dynamics and loss of fluid during sweating. Changes in plasma volume have been associated to altered cardiac autonomic dynamics including mediation by baroreflex activity via arterial

deformation change (Spinelli *et al.*, 1999), suggesting a possible variance in BRS. However, following maximal resistance exercise, a reduction in plasma volume occurred in the absence of any change in BRS which implied there was no association between the control of plasma volume and the baroreflex response (Ploutz *et al.*, 1993). Acute hypovolemia from exercise should not contribute greatly to baroreflex changes because acute changes in blood volume from 16% expansion to 10% reduction were not found to alter the vagal baroreflex response (Convertino & Adams, 1991; Thompson *et al.*, 1990). Furthermore, a single bout of high intensity treadmill exercise did not induce a significant rise in whole-body core temperature (James & Doust, 1999) and moderate intensity treadmill running did not elicit changes in plasma volume (James & Doust, 1998). Thus it is unlikely that reduced plasma volume may explain the findings of the present study. However, the study by James and Doust (1998) implemented a hydration strategy of equal water consumption to change in body mass while the hydration strategy in the present study incorporated a provision of a predetermined quantity of water for all participants across all conditions at set intervals. Therefore it is possible that the hydration strategy in the present study did not completely fulfil the hydration needs of the participants which may have resulted in an increased cardiac work rate due to a reduction in plasma volume (Munson, 2008; Sawka & Coyle, 1999). Altered vascular volume may increase vasoconstriction for equal reductions in venous pressure during progressive hypovolemia which may compromise the capacity to provide adequate peripheral resistance during orthostatic stress (Thompson *et al.*, 1990). However, in the present study no problems with orthostatic stress occurred during tilting following exercise suggesting vascular volume had not been substantially altered.

During exercise when blood flow and $\dot{O}_2$ delivery to muscles is insufficient, chemically sensitive muscle afferents are stimulated to elicit a reflex response to increase sympathetic activity (exercise pressor reflex or muscle metaboreflex) (Iellamo, 2001). Experiments in animals have provided evidence that the sympathetic activation originating from the muscle metaboreflex increased HR substantially during exercise (O'Leary, 1993) and, in humans following static exercise, contributed to HR regulation during post-exercise muscle ischemia (Iellamo *et al.*, 1999b). In humans, the R-R intervals returned to baseline levels while BP remained significantly elevated above rest and corresponding spectral analysis revealed a return to resting levels in HF while LF

remained elevated (Iellamo *et al.*, 1999b). Baroreflex sensitivity was significantly reduced during exercise but restored during post-exercise muscle ischemia which was purported to explain a mechanism for a HR return to resting levels despite the maintained sympathetic activity (Iellamo, 2001; Iellamo *et al.*, 1999b). Thus the parasympathetic influence of the baroreflex may overpower the tachycardia effect of the muscle metaboreflex (Iellamo, 2001). However greater exercise strain during static exercise has been implicated in altered cardiac autonomic dynamics and reduced BRS (Iellamo *et al.*, 1999a). Therefore, it is plausible that varying levels of intensity of exercise and dynamic exercise may alter the BRS post-exercise response via the elevation of intramuscular metabolites (Iellamo, 2001; Parekh & Lee, 2005).

Respiration was not controlled in the present study. This was in accordance with the majority of previous studies (Convertino & Adams, 1991; Niemelä *et al.*, 2008; Piepoli *et al.*, 1993; Ploutz *et al.*, 1993; Raczak *et al.*, 2005; Somers *et al.*, 1985; Stuckey *et al.*, 2012) although two studies did control respiration (Halliwill *et al.*, 1996b; Terziotti *et al.*, 2001). One study employed a breathing rate of 15 brpm and controlled tidal volume (Halliwill *et al.*, 1996b) and reported an enhancement in BRS at + 60 min while the other study did not provide details of breathing rate (Terziotti *et al.*, 2001) and reported BRS was reduced at + 30 min, had returned to baseline levels by + 60 min and remained unchanged at + 180 min. Thus the employment of controlled breathing may, in part, be intimated in the different findings between studies. The modern methods of BRS assessment do not usually include respiratory control (Parati *et al.*, 2000), unlike HRV testing procedures (TFESC & TNASPE, 1996), and reproducibility studies have not found any consistency for improved reproducibility following paced breathing with the exception of the determination via $BRS_{\alpha HF}$ (Maestri *et al.*, 2009). Spectral analysis for BRS determination provides an opportunity to avoid most respiratory influence by the selection of frequency bands below the respiratory frequency (i.e., in LF) thus choice of BRS indices may influence the employment, or not, of paced breathing during data collection. A controlled breathing rate allows the HF component to be fixed across all participants (Hartikainen *et al.*, 1998) and various rates may be employed to provide an artificial control. Changes in respiration via tidal volume may influence R-R interval or HR fluctuations (Eckberg, 1983; Hirsch & Bishop, 1981) because respiratory changes can manipulate cardiovascular variability (Parati *et al.*, 1995b) providing a possible

mechanism for reduced parasympathetic influence during recovery post-exercise (Heffernan *et al.*, 2006). Tidal volume may also alter venous return via respiratory fluctuation which may affect sinus node activity (De Meersman *et al.*, 1995). However, imposed breathing patterns that perturb breathing frequency and tidal volume have been found to reduce participant comfort and significantly reduce parasympathetic tone (De Meersman *et al.*, 1995) thus, respiratory control may provide an undesired response which may limit the usefulness of the procedure in BRS determination.

Participant characteristics in related exercise studies (Appendix IX; table A10) indicated the majority of the participants were healthy, normotensive, non smoking males (age range: 19 – 40 y) which is in accordance with the present study (18 – 34 y). One study employed hypertensive individuals and did not provide gender, age or smoking status (Somers *et al.*, 1985). This study reported enhanced BRS at + 60 min following exercise. The hypertensive population may limit the interpretation and generalisation of this study because the findings may have demonstrated an enhancement in BRS that was pertinent to the disease and thus may not relate directly to similar studies employing normotensive participants (Convertino & Adams, 1991). Although the age range between study participants was relatively wide and BRS declines with age, it is unlikely that age would have impacted upon the findings between studies because the testing populations were healthy and aged $\leq$ 40 y while impairment in BRS in ageing was reported in hypertensive individuals in advancing age (> 60 y) (Parati *et al.*, 1995a).

The aerobic fitness and training status of participants may impact upon cardiac autonomic control following exercise (Tulppo *et al.*, 1998) and may partially explain the directional change between studies and the duration of the recovery following exercise. Aerobic fitness is related to increased vagal modulation of HR during exercise and shorter recovery period following cessation of exercise (Borresen & Lambert, 2008; Javorka *et al.*, 2002; Tulppo *et al.*, 1998). In the present study the fitness profile of the participants (52.5 (± 7.5) $ml \cdot kg^{-1}min^{-1}$) (mean (SD)) represented a high level of fitness and all participants were undertaking moderate and vigorous aerobic exercise of cycling, running and cross training on a regular weekly basis. In the previous related studies only three studies provided evidence of fitness profile (Halliwill *et al.*, 1996b; Niemelä *et al.*, 2008; Terziotti *et al.*, 2001) suggesting evidence of sedentary to high

fitness status. The lack of fitness evidence via $\dot{V}O_2$ participant characteristics did not allow direct comparison between studies. Reported descriptive activity levels included sedentary (Convertino & Adams, 1991; Halliwill *et al.*, 1996b); moderately active (Halliwill *et al.*, 1996b); physically fit (Terziotti *et al.*, 2001); regular resistance training or endurance training (Convertino & Adams, 1991); regular exercise of walking, running or cycling (Piepoli *et al.*, 1993); recreationally active (Stuckey *et al.*, 2012); detrained (Raczak *et al.*, 2005) or did not provide a description of activity (Ploutz *et al.*, 1993; Somers *et al.*, 1985). Thus fitness profiles suggested fitness between studies was highly variable. Interestingly, the majority of studies reporting enhanced BRS following exercise (Convertino & Adams, 1991; Halliwill *et al.*, 1996b; Piepoli *et al.*, 1993; Raczak *et al.*, 2005; Somers *et al.*, 1985) included participants with descriptive profiles of lesser fitness status. Thus the aerobic fitness of individuals may be a partial explanation for the divergent findings between studies.

The findings in the present exercise study and in one previous study (Niemelä *et al.*, 2008) of a larger reduction in the magnitude of the BRS outcome measures and a more sustained recovery period following high intensity exercise and heavy resistance exercise may, in part, be due to the high fitness level of the participants (< 55 $ml \cdot kg^{-1} min^{-1}$). Baroreflex sensitivity has been found to be significantly reduced in young very fit adults compared with moderately fit young adults (Smith *et al.*, 2000). The reduction in BRS in young very fit adults was purported to be due to a combination of alterations in autonomic balance, reductions in aortic baroreceptor density and changes in transduction characteristics (Smith *et al.*, 2000). In endurance trained individuals, increased SV may be the result of a combination of slower HR, hypervolemia and increased ventricular compliance (Levine *et al.*, 1991a; Levine *et al.*, 1991b). The increased blood volume may provide a greater impact on the site of the aortic baroreceptors (Shi *et al.*, 1993a; Shi *et al.*, 1993b) inducing a possible reduction in aortic receptors or an adaptation to the increased level of distortion or both (Smith *et al.*, 2000). These effects may result in a transduction intensity reduction in the afferent signal to the medulla providing a possible major cause in the reduction of the aortic baroreflex response in endurance trained, fit individuals (Smith *et al.*, 2000) and thus, may provide an explanation for the reduction in BRS in very fit young adults.

5.3 Implications

Current public health recommendations for exercise reflect the change from traditional exercise prescription to a broader public health perspective of regular activity of moderate intensity exercise ≥ 5 times per week (ACSM, 2006a). The change in emphasis occurred because research demonstrated PA and regular exercise training could provide improved health and fitness benefits and reduce the risk of morbidity and mortality in both clinical and non-clinical populations (see: sections 2.3; 2.4). Factors that could be assessed were those identified as risk factors for MetS which included BP, insulin sensitivity and blood cholesterol levels following exercise. A single bout of moderate intensity exercise had also been found to have an effect on these factors (Thompson *et al.*, 2001). Thus, the benefits of exercise could be measured by the change in factors that were directly or indirectly linked to cardiovascular function (Pober *et al.*, 2004). Another factor that was sensitive to these changes was BRS which represented cardiac autonomic modulation and could be employed as a non-invasive marker of change through the modulations of the parasympathetic and sympathetic limbs of the ANS.

Increased sympathetic activity has been associated with an increased risk of a cardiac event (Albert *et al.*, 2000; Maron, 2000) although this has not been investigated following exercise. This is interesting because it could be claimed that increased sympathetic activity post-exercise may be linked to an increase in cardiac risk. The present exercise study found supine and tilt BRS was reduced following both moderate and high intensity exercise with the reduction in the magnitude of the BRS outcome measure significantly greater and of longer duration following the high intensity exercise condition. These findings suggested the autonomic dynamics of vagal withdrawal and increased sympathetic outflow increased with the intensity of exercise, intimating a possible intensity-dependent relationship. Thus, it is possible a single bout of high intensity exercise may impose a greater and more sustained window of risk for an adverse cardiac event compared to a single bout of moderate intensity exercise due to the greater influence of the sympathetic nervous system post-exercise. In the present study, both prescribed intensities of exercise produced unfavourable changes in autonomic activity with no enhancement in BRS during the post-exercise period

although the unfavourable change was attenuated in the moderate intensity exercise condition. This is an important finding and has implications for exercise prescription, particularly in those provided in public health messages as these recommendations need to be of practical intensity while conferring health benefits without additional risk in clinical and non-clinical populations (ACSM, 2006b). It is widely accepted that exercise provides an element of risk in the initial post-exercise period (Maron, 2000) thus moderate intensity exercise is the recommended intensity of exercise incorporated in public health messages for exercise prescription purposes (ACSM, 2006a). Therefore, the present exercise study findings support the current public health recommendations in advocating moderate intensity exercise due to the observed attenuation of risk following the moderate intensity exercise condition compared to the greater risk imposed via the high intensity exercise condition.

In the present exercise study, the reduction in supine and tilt BRS was returned to baseline levels by + 60 min following the moderate exercise condition and by + 120 min following the high intensity exercise condition. These findings are in general accordance with those studies reporting a reduction in BRS following lower and higher sub maximal aerobic and resistance exercise which had returned to baseline by < 90 min (Niemelä *et al.*, 2008; Terziotti *et al.*, 2001). One study reported supine BRS had not returned to baseline following multiple Wingate sprint exercise bouts or standing BRS following single and multiple Wingate sprint exercise bouts by + 120 min with no measure taken beyond this time point (Stuckey *et al.*, 2012). Thus the intensity of exercise and/ or volume of exercise may be related to the duration of the recovery period following exercise. However, these findings are contrary to other studies which have reported an increase in supine BRS following moderate intensity exercise (Halliwill *et al.*, 1996b; Raczak *et al.*, 2005) and following maximal cycle exercise at + 60 min (Somers *et al.*, 1985) and following maximal exercise at + 24 h (Convertino & Adams, 1991). The findings in the present exercise study indicated an increased sympathetic contribution in cardiac autonomic control in the initial 60 min following moderate intensity exercise which was of greater magnitude and extended to + 120 min following the high intensity exercise condition. The ANS has a critical role in cardiac stability and changes in HR mediated by the baroreflex can provide a means to assess autonomic neural control of the heart (Billman *et al.*, 1982). Autonomic responses

following exercise include increased sympathetic outflow resulting in a possible increased risk of cardiac electrical instability and ventricular fibrillation or conversely, enhanced parasympathetic tone providing a protective cardiac effect (Albert *et al.*, 2000; Billman, 2002; Maron, 2000). Thus, the observation in the present exercise study of increased sympathetic outflow following a single bout of exercise suggested a possible increased cardiac risk up to 60 min following moderate intensity exercise and up to 120 min following high intensity exercise. The finding of increased risk up to 60 min following moderate intensity exercise may have further implications for exercise prescription in vulnerable individuals because current recommendations suggest post-exercise procedures lasting ≤ 30 min are sufficient in cardiac rehabilitation patients to ameliorate cardiovascular risk (BACR, 2006). Thus further studies should be undertaken in different populations to assess the post-exercise response in BRS following various intensities of exercise. In addition, the interaction of exercise intensity and other features of the dose-response of exercise should also be investigated to satisfy the effectiveness and safety of public health exercise recommendations in clinical and non-clinical populations.

In the present exercise study, BRS had returned to baseline by + 120 min post-exercise following moderate and high intensity exercise although other studies have suggested that BRS may still be altered + 24 h following maximal exercise (Convertino & Adams, 1991). These findings have implications regarding the residual effects of previous exercise with regard to baseline measurement and the length of time required to achieve full recovery resting conditions. In the research context, full recovery resting conditions are important because contamination in the outcome measures from a residual overlap between previous exercise exposure and baseline testing measures could negate research findings due to impairment in the magnitude of genuine change. The recommendation for the duration of exercise abstinence has come from previous research utilising HRV to determine the post-exercise effects of a single bout of exercise following moderate intensity exercise and high intensity exercise in similar populations (James & Doust, 1999; James & Doust, 1998). This research has suggested 72 h would be a suitable abstinence duration period. The results from the present study and previous related studies (Halliwill *et al.*, 1996b; Niemelä *et al.*, 2008; Terziotti *et al.*, 2001) suggest this abstinence period may be overly long because recorded recovery to baseline was

achieved < 180 min following lower and higher sub maximal aerobic and resistance exercise thus a shorter abstinence period may be adequate for the achievement of full recovery resting conditions. However, other studies have found autonomic disturbance beyond + 24 h following maximal exercise (Convertino & Adams, 1991). In the present study, participants were requested not to exercise for 48 h prior to testing and testing procedures may have been initiated on the day following the abstinence period. Thus a full 72 h abstinence period may not have been achieved. Therefore it is possible that there may have been some minimal influence of previous exercise exposure although this was considered to be unlikely. However, until the full time course of post-exercise BRS response to exercise has been achieved future research should exert caution concerning the extent of the exercise abstinence period for the achievement of a fully recovered resting state.

Consistent evidence has shown the benefits of exercise for health related outcomes while inactivity and a sedentary lifestyle are considered to be risk factors for disease (see: sections 2.3; 2.4). The benefits of exercise include the alteration in autonomic dynamics and the shift to enhanced vagal tone promoting cardiac electrical stability providing a cardio-protective effect (Billman, 2002). However, exercise may also provide cardiac risk in vulnerable individuals and thus has been termed the 'paradox' or 'double edged sword of exercise' because exercise can simultaneously increase the short term risk of sudden death and also provide protection from this risk in individuals undertaking regular exercise (Maron, 2000). Sudden cardiac death may occur during or immediately following vigorous exercise in young individuals (Maron *et al.*, 1996; Whyte, 2006) or more frequently in individuals of all ages undertaking recreational exercise, with the adverse events in both populations a possible feature of undiagnosed cardiac disorders (Albert *et al.*, 2000; Whyte, 2006; Maron, 2000). Vigorous exertion is considered a possible trigger for sudden cardiac death, particularly in previously sedentary or clinical individuals which is why moderate intensity exercise is recommended in public health messages to avoid exercise risk and promote exercise health benefits in clinical and non-clinical individuals (ACSM, 2006b). A potential mechanism for an adverse event may be the rapid reduction in parasympathetic tone and sympathetic activation during mild to moderate intensity exercise while aerobic fitness may exert cardio-protection by enhancing parasympathetic function during exercise

(Tulppo *et al.*, 1998). Regular aerobic exercise has been found to alter the autonomic balance by increasing parasympathetic tone and decreasing sympathetic outflow but the time course for change in autonomic dynamics from a single bout of exercise to regular exercise training (and the subsequent increase in aerobic fitness) has not been confirmed. The present study has suggested that following moderate intensity exercise there is a possible window of risk lasting up to 60 min with a greater sympathetic contribution in cardiac autonomic control implying a loss in cardiac electrical stability and in the cardio-protective effect (Billman, 2002). However, such risk was clearly attenuated with moderate intensity exercise when compared to the post-exercise autonomic response following high intensity exercise. Thus the findings from the present study may only have implications for the early stages of exercise prescription in clinical and vulnerable individuals in public health messages until the time course for autonomic change has been established.

Head-up tilt testing is a simple method to test the ability of the reflex mechanisms to maintain BP homeostasis and BRS is quantified by the reflex effects on HR because the priority of the baroreflex is to minimise BP changes during various postural alterations (Parati *et al.*, 2000). The present reproducibility study demonstrated marked improvement in reproducibility in tilt BRS which was consistent with previous research that reported improved reproducibility in standing (Herpin & Ragot, 1997; Iellamo *et al.*, 1996) suggesting an orthostatic manoeuvre may aid in reducing neural influences which cause variability in the measure (Iellamo *et al.*, 1996). The adoption of the tilting procedure in experimental intervention studies may have implications for study design and the achievement of a more sensitive outcome measure (Bernardi *et al.*, 1997; Mourot *et al.*, 2004). However, the practicality of tilt outside a laboratory setting is limited. Standing has been employed in both laboratory and field settings for the assessment of cardiac autonomic control following exercise (Mourot *et al.*, 2004; Stuckey *et al.*, 2012) but standing does not afford the same level of control as tilt. Whether tilt and standing can provide similar BRS outcome measures or similar reproducibility under parallel conditions and populations has not been established.

The finding for improved reproducibility in BRS following an orthostatic manoeuvre has implications for study design in experimental intervention studies regarding sample

size and statistical power. Previous research incorporating a standing manoeuvre reported the improvement in the reproducibility of BRS from standing provided the opportunity to substantially reduce the sample size in follow-up studies (Herpin & Ragot, 1997). Intervention research studies invariably employ small sample size due to the experimental nature of the research and the small participant number may be a consequence of the research protocol design. For example, testing procedures may require participants to attend the laboratory over extended concentrated time periods. Indeed, the present exercise study required each participant to attend the laboratory on 7 different occasions, over a successive 3 week period, at defined time intervals and in a prescribed resting exercise status, resulting in a total testing duration of 27 h. Such protocols have implications for participant control, recruitment and retainment. Thus, a testing procedure that can reduce the need for a large participant population may be particularly beneficial in experimental intervention studies.

Tilt testing may provide a more sensitive BRS outcome measure (Bernardi *et al.*, 1997) thus increasing the ability to detect genuine change over the short and long term recovery periods following exercise. In tilt the sympathetic nervous system is activated and becomes the more dominant reflection of autonomic activity (Bernardi *et al.*, 1997; Pagani *et al.*, 1986; Radaelli *et al.*, 1994; Saul *et al.*, 1991) thus providing the opportunity to investigate the magnitude and duration of sympathetic outflow following exercise which may have been obscured by the strength of the vagal dominance during supine resting conditions. In the present study, tilt BRS was found to be a more sensitive outcome measure in the short term recovery period and previous findings have suggested that the long term disturbance in autonomic recovery following exercise may only be found following an orthostatic manoeuvre (Bernardi *et al.*, 1997; Mourot *et al.*, 2004). Thus, the inclusion of a tilt manoeuvre may have implications regarding the ability to detect autonomic disturbance during the short and long term recovery periods following exercise.

The inclusion of a tilt procedure has implications regarding the time points for BRS assessment following exercise. The achievement of a tilt BRS outcome measure requires adequate time for data collection and a re-equilibration period following the tilt procedure for the return to supine resting conditions. If the body does not have enough

time to adjust back to the supine resting position, a factor to control for will be one of time rather than body position. The ACC recommendations for tilt testing re-equilibration suggest a period of ≥ 10 min (Benditt *et al.*, 1996). Clearly, this requirement will impact upon data collection time points. Thus studies which include an orthostatic manoeuvre will not be able to achieve similar multiple data collection time points compared to studies which incorporate supine resting measures alone.

Individual responses to conditions that induce a heightened sense of arousal may lead to adrenergic neurohumoral activation and increases in HR, BP and $\dot{Q}$ (Curtis & O'Keefe, 2002). The implication for these responses may include a change in the autonomic balance with reduced vagal tone and increased sympathetic outflow (Friedman & Thayer, 1998; Thayer *et al.*, 1996) which may be reflected in the outcome measure. In the present study a possible anticipatory response to testing environment, exercise testing and tilt procedure may have induced an arousal reaction. The levels at which anticipation and emotional stress may have caused a response to the testing procedures in the current study was not known although low work rates (20% maximal exercise) have been shown to induce change in the autonomic balance (Macor *et al.*, 1996). Thus, the effect of anticipatory and emotional responses may result in a confounding influence in the magnitude of BRS outcomes measures in pre-testing and post-exercise measures.

The determination of BRS may be undertaken via laboratory and modern methods employing various techniques in the time and frequency domains and different methods and techniques have been employed by the previous exercise studies (table 2.5.1) (Appendix IX; table A10). The present study employed the modern method and techniques which included BRS time parameters of BRS_{UpUp} and $BRS_{DownDown}$ (sequence technique) and spectral parameters of $BRS_{\alpha LF}$ and BRS_{TFTG} with spectral BRS measures being more robust (table 4.2.4). Each of the various techniques are characterised by distinct features (Parati *et al.*, 2000) (Appendix VI; table A6) which may provide variation in the magnitude of BRS outcome measures (table 4.2.3). The implications for the employment of various BRS outcome measures is a possible reduction or improvement in the ability to observe genuine change in BRS and the

absolute BRS measures are not super-imposable (Parati *et al.*, 2000) providing possible comparability issues between studies.

5.4 Limitations

A few limitations in the present exercise study warrant consideration with regard to the interpretation of the findings. The aim of the present exercise study was to investigate the post-exercise responses in supine BRS and tilt BRS following a single bout of moderate intensity exercise and following a single bout of high intensity exercise.

Participants were their own control and the present study was a well controlled study. Intra-participant control was important and was achieved via guidelines provided to the participants concerning food, drink and exercise before testing. The guidelines were verbally explained prior to the start of the study and discussed at each visit to the laboratory. Participants were requested to ensure they replicated personal preparation before each testing procedure. However, it was impossible to be completely sure the participants followed their own individual routine exactly for each visit to the laboratory and this may be a limitation of the present study.

The provision of equal work done for both exercise intensities in the two exercise conditions required the duration of the exercise to differ between the two exercise conditions. The duration of the moderate intensity exercise condition was 58 min while the duration of the high intensity exercise condition was 44 min. Thus it was not possible to control for duration of exercise. In the present study, the conclusions are dependent on the applied differences in intensities of exercise, based on equal work done across the two exercise conditions. The influence of duration of exercise on post-exercise BRS has not been established although training sessions of 30 min duration compared to 60 min duration elicited similar cardiac autonomic adaptations in animals (Sant'Ana *et al.*, 2011). In humans, a recent study utilising HRV indicated no significant difference in cardiac autonomic control between two bouts of moderate intensity exercise undertaken for 20 min and 60 min respectively (James *et al.*, 2010). Thus it may be unlikely that the reduction in BRS in the present study was due to the influence of duration of exercise and probably more likely to be due to the effect of

intensity of exercise. However, the lack of available research regarding the effect of duration of exercise on post-exercise BRS provides the possibility that duration of exercise may be a contributory factor in the present study findings and cannot be discounted.

Respiration influences the cardiovascular system via attenuation of the heart period component of the baroreflex by RSA resulting in smaller baroreflex responses and reduced sensitivity during inspiration and greater baroreflex responses and sensitivity during expiration (Eckberg *et al.*, 1980; Mancia & Mark, 1983). The RSA is usually reflected in HF HR oscillations (0.15 – 0.4 Hz) i.e., the typical frequency range of normal adult respiration (Song & Lehrer, 2003). The techniques of the modern methods for the determination of BRS do not control for respiration. Indeed, imposed breathing patterns that perturb breathing frequency and tidal volume have been found to reduce participant comfort and significantly reduce parasympathetic tone (De Meersman *et al.*, 1995) thus, respiratory control may provide an undesired response limiting the usefulness of the procedure in BRS determination. Spectral analysis for BRS determination provides an opportunity to avoid most respiratory influence by the selection of frequency bands below the respiratory frequency i.e., LF, although this does not exclude inspiratory attenuation (Hollow *et al.*, 2011). Inspiratory attenuation may be minimised by increasing breathing frequency and reducing tidal volumes (Hollow *et al.*, 2011). In accordance with usual modern method practice, the present study did not control breathing frequency or tidal volume. The determination of BRS in the time domain via the sequence technique may be compounded by respiration (Kuusela, 2007) whereas judicious choice in spectral analysis by employing techniques in LF may minimise respiratory influence. In the present study, the determination of spectral BRS was undertaken in the LF band only. Therefore, in the present study respiration may have influenced sequence BRS determination by a greater extent than spectral BRS_{LF} determination and because it was not possible to assess the extent of any respiratory influence this may be a limitation of the study.

Hydration should be controlled to parallel sweat losses (Sawka *et al.*, 2005) and is an important consideration for the comfort and wellbeing of participants in exercise research testing. Different hydration strategies may be employed under testing

conditions (James *et al.*, 2012; James & Doust, 1998) and in the present study a predetermined quantity of water was provided to all participants across all conditions at set intervals. Thus all participants consumed an equal amount of water under all testing conditions. It is possible that this hydration strategy did not completely fulfil the hydration needs of the participants in some or all of the testing conditions and this may have impacted upon cardiac work rate and plasma volume (Munson, 2008; Sawka & Coyle, 1999). The extent of the change in body mass to equal amount of water was not assessed in the control condition or in either of the exercise conditions. Therefore, the extent of increased body temperature and the loss of body fluids may have impacted upon BRS assessment via reduced plasma volume and as such is a limitation of the present study.

The participant population in the present study consisted of healthy young adult males who regularly participated in exercise training and had a high level of fitness (mean $\dot{V}O_{2peak}$ (SD) = 52.3 (± 7.5) $ml \cdot kg^{-1}min^{-1}$) (ACSM, 2006a). Cardiac autonomic control is affected by aerobic fitness via the recovery time of reduced vagal modulation (Tulppo *et al.*, 1998) and BRS has been shown to be significantly related to the fitness level of the individual (Smith *et al.*, 2000). Thus, the findings of the present study should be delimited to this study population of healthy young adult males with high levels of aerobic fitness.

The sympathetic nervous system largely mediates the arousal reflex via adrenergic neurohumoral activation which increases HR, BP and $\dot{Q}$ (Curtis & O'Keefe, 2002). Individual responses to conditions that induce a heightened sense of arousal may lead to a change in sympathetic and parasympathetic autonomic balance and increased respiration (Thayer *et al.*, 1996). In the present study a possible anticipatory response to testing environment, exercise testing and tilt procedure may have induced an arousal reaction. The implication for these responses may include a change in the autonomic balance with reduced parasympathetic tone and increased sympathetic outflow (Friedman & Thayer, 1998; Thayer *et al.*, 1996). The levels at which anticipation and emotional stress may cause a response to the testing procedures in the current study was not known. Thus, in the present study it is possible that anticipatory and emotional

responses may have occurred but the extent of their influence, if any, on BRS outcome measures was not known and thus may be a limitation of the study.

Small sample size may reduce the possibility of finding a significant effect, if such an effect is there, thus limiting the power of the test (Lipsey, 1990). In the present study, 9 participants completed all of the testing procedures. A clear pattern of significant change was observed in BRS outcome measures at + 15 min and + 60 min suggesting this study did have adequate statistical power to detect significant change. Statistical power may be enhanced via improved reproducibility. The present reproducibility study found BRS was markedly improved in tilt BRS outcome measures compared to supine BRS outcome measures and the tilt procedure was included in the present exercise study. A previous study incorporating a standing manoeuvre to investigate the reproducibility of BRS intimated any follow-up studies which included standing could include low participant numbers (4 to 14) to detect a change in BRS in the magnitude of 4 – 5 ms/mmHg (Herpin & Ragot, 1997). In the present exercise study the magnitude of change in tilt BRS was similar to this supposition following moderate and high intensity exercise (table 4.2.3). Statistical power may also be enhanced via separating the means further through having a more severe exercise intervention. The two exercise conditions in the present study were clearly delineated via intensity of moderate or high intensity exercise and, a control condition of no exercise was also included to support findings of change via the intervention. Significant change in BRS outcome measures was particularly evident following the high intensity exercise condition in supine spectral BRS measures and in tilt time and spectral BRS measures at + 60 min (table 4.2.4). Thus, the observation of significant change in BRS outcome measures during the short term recovery period suggested statistical power was adequate but such power may be limited to the inclusion of spectral BRS and tilt BRS outcome measures.

5.5 Future research directions

The determination of BRS is a non-invasive technique to assess change in the ANS in clinical and non clinical settings. More recently, BRS has been used in the fields of sports and exercise to examine the effect of various intensities and modes of exercise on autonomic modulation. Some research has included investigations of BRS following

chronic exercise training while other research has investigated BRS following a single bout of exercise and this research has provided information on the effects of cardiovascular and metabolic responses post-exercise. Information has also been gained regarding the role of the ANS and the parasympathetic and sympathetic influences in cardiac autonomic change following exercise. The investigation of BRS following a single bout of exercise may be particularly useful, as these studies may provide further insight into the immediate physiological change post-exercise. Previous research investigating the direction and magnitude of change in BRS following a single bout of exercise is inconclusive, particularly with regard to the recovery of BRS indices in the short and long term following exercise. The disparity in findings between studies may be the result of differences in experimental protocols and in the lack of a gold standard for the determination of BRS. This research area is still in an embryonic state and a consensus is required for the best way to move the research forward. Future investigations employing BRS would benefit from guidelines advising on issues such as BRS determination techniques, BRS assessment time points following exercise, participant position during data collection and respiratory control to improve comparability between studies. The present exercise study supports the use of BRS as a non-invasive tool to assess autonomic control in a healthy adult male population following a single bout of exercise. However, this research has also raised a number of issues and limitations that require consideration in future research studies.

Future research should be undertaken to replicate the present study findings in a similar participant population. Future research should also investigate the response of BRS following a single bout of moderate intensity exercise and high intensity of exercise in diverse healthy populations to ascertain any differences between intensity of exercise and between participant characteristics such as gender, age or training status. A particular focus on gender would be useful as only two of the few studies that have investigated the post-exercise response in BRS have included females in the participant population (Halliwill *et al.*, 1996b; Piepoli *et al.*, 1993). Such future investigations should also focus on the effect of hormones in the post-exercise BRS response in young, pre and post-menopausal women because gender difference could be exhibited in ANS activity from developmental differences between gender or in the prevailing male and female hormone levels (Dart *et al.*, 2002).

Exercise should be undertaken employing different modes of exercise and include exercise equipment that would be experienced by individuals accessing fitness facilities i.e., treadmill, cycles and resistance equipment, as this would reflect the type of exercise most commonly undertaken and available to the general population. The intensity of the exercise bout and the subsequent response of BRS following exercise should also be established. The interaction of intensity of exercise and duration of exercise should also be considered. Ultimately it would be useful to track the time course of change in BRS following exercise after a given exercise bout as this would establish the duration of such change. These findings would provide increased confidence in future research studies investigating BRS, particularly in studies employing exercising participants, that findings were free from confounding influences of previous exercise.

The influence of respiration on the determination of BRS should also be established. This should include both respiratory frequency and tidal volume. Paced breathing at 12 brpm is considered to reflect un-paced breathing frequency in young active individuals (Pober *et al.*, 2004) and allows the HF component to be fixed across all participants via synchronisation of afferent discharge from the lungs and thoracic structure (Hartikainen *et al.*, 1998; Strano *et al.*, 1998). This breathing frequency has been employed in studies investigating the post-exercise response in HRV (James *et al.*, 2002; James *et al.*, 2012; James *et al.*, 2010; Pober *et al.*, 2004) but the usefulness of such artificial control in BRS determination has not been established. Tidal volume influences HR fluctuations and R-R interval (Eckberg, 1983) and may result in reduced parasympathetic tone due to the variance in tidal volume influencing respiratory fluctuation in venous return and sinus node stretch (De Meersman *et al.*, 1995). Current practice utilising the modern methods for the determination of BRS do not usually employ paced breathing or control for tidal volume. In part, this may reflect the lack of a gold standard in BRS determination and the embryonic state for the employment of BRS in exercise and health related research.

Currently, there is no consensus regarding the choice of technique to employ in research investigating BRS following a single bout of exercise. Different assessment techniques may provide variation in the magnitude of the BRS outcome measure. Indeed, significant change in BRS may be small (i.e., ~ 3 ms/mmHg following exercise

training) (Costes *et al.*, 2004; Galbreath *et al.*, 2011; Iellamo *et al.*, 2000; La Rovere *et al.*, 2002; Monahan *et al.*, 2000; Pagani *et al.*, 1988) thus, chosen technique could influence statistical power and the ability to find a significant effect, if such an effect is there. Variation in choice of technique also instils comparability issues between similar studies and may reduce the agreement in general findings for the risk and benefits of exercise for particular health outcomes.

The determination for similar and multiple post-exercise BRS measurement time points would be beneficial to provide greater opportunity to establish BRS recovery following exercise in the short and long term following exercise. The lack of a consistent approach in the range of post-exercise time points restricts the evidence for BRS recovery and may be partly responsible for divergent findings between studies. Better consistency in post-exercise time points would also improve the comparability between studies.

Few studies have investigated the effect of an orthostatic manoeuvre on BRS measures. This is interesting because the employment of standing in previous reproducibility studies (Herpin & Ragot, 1997; Iellamo *et al.*, 1996) and the employment of tilt in the present reproducibility study have found improved reproducibility following an orthostatic manoeuvre. These findings have implications for experimental intervention exercise studies regarding sample size and statistical power. Experimental intervention exercise research is usually undertaken in small participant numbers which may impact upon statistical power and the ability to detect genuine change thus, a testing procedure that positively affects sample size and statistical power may be particularly beneficial in these studies. Therefore future research should investigate the usefulness of an orthostatic manoeuvre on BRS indices following exercise with regard to sample size and statistical power for the detection of genuine change.

The suggestion that tilt may provide a more sensitive BRS outcome measure should also be investigated. The present study found tilt BRS was a more sensitive outcome measure in the short term and previous research has reported the long term disturbance in autonomic recovery following exercise may only be found following an orthostatic manoeuvre (Bernardi *et al.*, 1997; Mourot *et al.*, 2004). Thus future research should

investigate the employment of tilt BRS as a more sensitive outcome measure to assess autonomic dynamics during the short term and long term recovery following exercise.

The employment of tilt is limited to the laboratory setting while standing can be employed in the field. Thus, future research should initially be undertaken to ascertain the reproducibility of standing BRS and tilt BRS in parallel conditions and populations and ascertain the similarity of the outcome measure between the two orthostatic manoeuvres. This research would inform future research regarding the usefulness of an orthostatic manoeuvre in BRS outcome measures in both laboratory and field settings to assess the change in autonomic dynamics in the short and long term recovery following exercise.

Anticipatory responses and emotional stress to testing environment, exercise testing and tilt procedures may induce an arousal reaction. The implication for these responses during the pre-testing period and during testing procedures on autonomic dynamics is not known but may include a reduction in vagal tone and increased sympathetic outflow (Friedman & Thayer, 1998; Thayer *et al.*, 1996) which may be reflected in a reduction in the magnitude of the outcome measure. Future studies should attempt to quantify the magnitude and extent of the arousal reaction, if any, on BRS outcome measures which may aid in the validity of the findings in future studies.

5.6 Summary

The present reproducibility study investigated the same day/ between day reproducibility in supine BRS and tilt BRS in a large healthy adult male population utilising three techniques for the assessment of spontaneous BRS. The majority of previous reproducibility studies were limited in sample size, range of BRS outcome measures and protocol for between day reproducibility and none of the studies had incorporated a tilt manoeuvre. The tilt manoeuvre was deemed of interest because previous studies had reported better reproducibility during standing compared to a supine resting position (Herpin & Ragot, 1997; Iellamo *et al.*, 1996). The variability between the previous studies had resulted in conflicting findings for the reproducibility of BRS. In contrast, the present reproducibility study incorporated a comprehensive

protocol to encapsulate previous limitations via the inclusion of a large sample size, a wide BRS parameter selection, same day/ between day reproducibility and a tilt manoeuvre. The key findings included between day reproducibility was marginally better than same day reproducibility for sequence measures while same day reproducibility was marginally better than between day reproducibility for spectral measures and reproducibility was markedly improved in all BRS outcome measures in the tilt position. Precision was good for all spectral measures in supine and tilt and lower but acceptable for sequence measures in both positions thus all BRS outcome measures and the tilt procedure were incorporated into the following exercise study.

The present exercise study investigated the effects of moderate and high intensity interval exercise of equal work done on post-exercise supine and tilt BRS over a 24 h period. Although previous studies have investigated the effects of a single bout of exercise on BRS, no previous studies had explicitly identified intensity of exercise in the intervention procedure or incorporated a tilt manoeuvre. Time and spectral BRS outcome measures in supine and tilt were utilised with six time points to reflect the immediate to long term post-exercise responses to track the time course of events over BRS measures. Thus, none of the previous studies were directly comparable with the present study. A clear disparity between previous studies was the divergent findings of either an enhancement in BRS following exercise or a reduction in BRS following exercise. Enhanced BRS is suggestive of a parasympathetic predominance which is related to improved cardiac electrical stability and a cardio-protective effect (Albert *et al.*, 2000; Billman, 2002; Maron, 2000) and this effect has been purported to last up to 24 h following exercise (Convertino & Adams, 1991). However, the present study found no enhancement in BRS following either moderate or high intensity exercise. Indeed, BRS was reduced up to + 60 min following moderate intensity exercise and up to + 120 min following high intensity exercise. A reduction in BRS is associated with increased vagal withdrawal and greater sympathetic outflow which may provide an increased risk of a cardiac event (Albert *et al.*, 2000; Billman, 2002; Maron, 2000) and may endure for over 120 min following exercise (Stuckey *et al.*, 2012). The present study also identified a greater reduction in the magnitude of the BRS measure following high intensity exercise compared to moderate intensity exercise and this was more apparent following a tilt manoeuvre which also implied a greater sympathetic influence

on BRS recovery. Indeed, because the present study had explicitly delineated intensity of exercise as the cursor for change, the alteration in autonomic dynamics intimated an intensity-dependent relationship in the BRS response following exercise. Intensity of exercise is a key feature in the acute response to exercise (Haskell, 2001) and is considered to be a possible factor for alterations in autonomic influences on the heart (Niemelä *et al.*, 2008; Parekh & Lee, 2005; Terziotti *et al.*, 2001). Thus, the findings of the present study support the notion that intensity of exercise may be a determining feature in the BRS response following a single bout of exercise.

The finding in the present exercise study of no enhancement in BRS following moderate or high intensity exercise has important implications for exercise prescriptions incorporating moderate intensity exercise in various populations because moderate intensity exercise is considered to provide health benefits with low risk in both clinical and non-clinical populations. However, although no enhancement in BRS was observed following either exercise condition, the moderate intensity exercise condition clearly attenuated the post-exercise risk compared to the high intensity exercise condition thus supporting the use of moderate intensity exercise in exercise prescriptions in public health messages. The findings of the present study may also be of benefit to inform training load and recovery following exercise in healthy individuals in chronic exercise training. The inclusion of tilt in experimental intervention studies may aid in providing a more sensitive BRS outcome measure which may aid in the elucidation of the findings and the improved reproducibility in BRS afforded by tilt may have implications for future experimental intervention study design. The observation in the present study that autonomic dynamics were altered toward greater sympathetic influence with higher intensity of exercise is supported by previous studies with similar findings employing sub-maximal aerobic, resistance and Wingate sprint exercise (Niemelä *et al.*, 2008; Stuckey *et al.*, 2012; Terziotti *et al.*, 2001). The present exercise study findings that alterations in autonomic dynamics in the BRS response following a single bout of exercise may be intensity-dependent will contribute to a wider discussion regarding intensity of exercise as a key determinant in the acute post-exercise cardiovascular response to exercise.

5.7 Conclusion

The present exercise study has compared the response of BRS following a single bout of moderate and high intensity exercise and examined the response in a healthy young adult male population. Both HR and RPE responses to exercise were greater in the high intensity exercise condition compared to the moderate intensity exercise condition regardless of equal workload. The high intensity exercise condition induced a greater reduction in the magnitude of the post-exercise BRS response which had recovered by + 120 min following exercise compared to the lesser reduction in BRS and recovery by + 60 min following the moderate intensity exercise condition. No enhancement in BRS was found following either the moderate or high intensity exercise conditions. The change in autonomic dynamics toward greater sympathetic influence following the high intensity exercise condition compared to the moderate intensity exercise condition suggested an intensity-dependent autonomic response following exercise. The observation of increased sympathetic outflow following a single bout of exercise intimated a possible increased cardiac risk up to 60 min following moderate intensity exercise and up to 120 min following high intensity exercise with such risk clearly augmented in the moderate intensity exercise condition. These findings are important because although they support public health messages which promote moderate intensity exercise for the provision of health benefits for exercise prescription purposes in clinical and non-clinical populations, the findings also extend understanding regarding the risk of exercise which may have particular relevance to vulnerable individuals. The present exercise study undertook an original approach with the assessment of BRS and included a tilt manoeuvre. The present exercise study also specifically delineated intensity of exercise as the cursor for change. Future research should be undertaken in similar studies to replicate the findings in the short to long term recovery period following exercise. Ultimately it would be beneficial to track the time course for change of BRS following exercise after a given exercise bout as this would establish the duration of such change. The inclusion of tilt to detect change over time may also be useful as tilt may indicate a sympathetic influence which may only be apparent by employing an orthostatic manoeuvre and thus provide a more sensitive outcome measure to assess the post-exercise BRS response. Future research should also be undertaken in diverse populations to ascertain differences in age, gender or training

status. The present study supports the use of BRS as a non-invasive tool to assess autonomic control in a healthy adult male population following a single bout of exercise. Both the present reproducibility study and the present exercise study have contributed to the wider body of knowledge regarding the reproducibility of BRS and the post-exercise cardiovascular responses following a single bout of exercise.

CHAPTER SIX

REFERENCES

CHAPTER 6: REFERENCES

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APPENDICES

APPENDIX I: BLOOD PRESSURE CLASSIFICATIONS

Table A1. Previous JNC 6 blood pressure classifications

JNC 6 Category	SBP/ DBP (mmHg)		JNC 7 Category
Optimal	< 120/ 80	→	NORMAL
Normal	120 - 129/ 80 - 84	→	PREHYPERTENSION
Borderline	130 - 139/ 85 - 89	→	PREHYPERTENSION
Hypertension	≥ 140/ 90	→	HYPERTENSION
Stage 1	140 - 159/ 90 - 99	→	STAGE 1
Stage 2	160 - 179/ 100 - 109	→	STAGE 2
Stage 3	≥ 180/ 100	→	STAGE 2

Note: SBP is systolic blood pressure; DBP is diastolic blood pressure; mmHg = millimetres of mercury; JNC is Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Taken from (JNCPDETHBP, 2004)

Table A2. British Hypertension Society classification for blood pressure levels (BHS-IV)

Category	SBP (mmHg)	DBP (mmHg)
Optimal	< 120	< 80
Normal	<130	< 85
High-normal	130 - 139	85 - 89
Grade 1 hypertension (mild)	140 - 159	90 - 99
Grade 2 hypertension (moderate)	160 - 179	100 - 109
Grade 3 hypertension (severe)	≥ 180	≥ 110
Isolated systolic hypertension	140 - 159	< 90

Note: SBP = systolic blood pressure; DBP = diastolic blood pressure; mmHg = millimetres of mercury. Taken from (ESH, 2003; Williams *et al.*, 2004)

APPENDIX II: CLASSIFICATION OF EVIDENCE FOR EPIDEMIOLOGIC STUDIES

Variance in study design requires different statistical techniques to explore and extrapolate findings from local and global population studies. The various statistical techniques have inherent properties that imbue a classification for evidence which is useful in interpretation of the findings. The classification code provided in the summaries of evidence (Appendices III; IV; V) has been taken from the scheme incorporated in Joint National Committee (JNC) reports and WHO report (JNCPDETHBP, 1997, 2004; WHO, 2002) as follows:

M: Meta analysis; use of statistical methods to combine the results from multiple trials

RA: Randomised controlled trials; also known as experimental studies

RE: Retrospective analyses; also known as case-controlled studies

F: Prospective studies; also known as cohort studies; including historical or prospective follow-up studies

X: Cross-sectional surveys; also known as prevalence studies

Meta-analysis

A meta-analysis is a statistical technique which combines findings from a number of independent studies providing the opportunity to find statistical significance which smaller independent studies may fail to achieve. The main purpose of a meta analysis is to summarise information, draw conclusions and produce a precise effect size having given due weight to the studies incorporated in the analysis (Crombie & Davies, 2009; Hyllegard *et al.*, 1996). In health related research this type of analysis can provide a retrospective review of relevant evidence which may identify risk factors for disease, level of risk for disease, effectiveness of healthcare intervention and treatment options across local or global populations (Crombie & Davies, 2009). A valid meta-analysis relies on the collation of all relevant evidence, the avoidance of bias (including publication, quality, selection and multiple endpoints bias), identifies heterogeneity and incorporates sensitivity analysis to explore the robustness of the main findings (Crombie & Davies, 2009; Oakes, 1993). Issues concerning the meta-analysis technique for

consideration include the identification and selection of studies (publication bias; search bias; selection bias), heterogeneity of results, availability of information and analysis of the data (Walker *et al.*, 2008).

Randomised controlled trials (experimental trials)

A randomized controlled trial incorporates the random allocation of participants to several interventions, one of which should be a control intervention. The control intervention enhances internal validity aiding in the removal of the possibility of an alternative explanation for the given intervention and the randomisation procedure alleviates bias in the study (Saunders *et al.*, 2009). Randomised controlled trials may be undertaken with small or large populations over varying time periods depending on the study design and field of research. More frequently, these trials are undertaken with small numbers of participants who undertake a specific intervention in a controlled environment (i.e., laboratory based) to provide evidence for a given effect.

Retrospective analyses (case controlled studies)

A retrospective analysis is an observational study employed to identify factors that may contribute to a given disease by comparing a diseased population with a similar population which is not diseased. A disadvantage of this type of analysis is the possibility of confounding factors which may be responsible for the outcome due to the inherent lack of control. The participants are not randomised i.e., the researcher does not determine the exposure because the participants themselves determine their own level of exposure and thus, outcome.

Prospective studies (cohort studies; historical or prospective follow-up studies)

Prospective studies are observational studies, usually undertaken over long time periods to assess the development of disease (*in situ*), from an initial healthy population and thus associate factors that may promote disease or protect against disease. This is in contrast to case controlled studies that attribute risk retrospectively. Potential disadvantages include subject attrition (bias), resource implications and length of study. An alternative to a prospective study is a cross-sectional study which may alleviate issues of time constraints and subject attrition by using methods (such as

questionnaires) to ascertain past, present and future behaviors, although this would introduce other disadvantages (Gratton & Jones, 2004).

Cross-sectional surveys (prevalence studies)

A cross-sectional study is descriptive in nature and may include an entire population or a subset of that population and employs a single time point for the data collection. The advantage of this type of research is the efficiency in time and resources, particularly compared to prospective studies which are usually undertaken over extended time periods (Hyllegard *et al.*, 1996). However, a disadvantage is the wide population characteristics such as broad age range and the frequent use of interviews/ questionnaires thus relying on participant recall to provide a 'snap-shot' of past events and behaviors which may be erroneous (Hyllegard *et al.*, 1996; Saunders *et al.*, 2009). Typically, this type of study may examine the prevalence of disease.

APPENDIX III: THE METABOLIC SYNDROME: SUMMARY OF EPIDEMIOLOGIC STUDIES

Table A3. The relationship between the metabolic syndrome and cardiovascular health outcomes: summary of studies

	Participants			Study details		
Author, Year; Study; Country; Classification	Baseline characteristics	Sample size (n)	Follow-up	Adjustment/ Risk	Aim	Main findings
Franklin *et al* (1997); FHS, USA; X	No BP medication at index; 50 - 79 y; m & f	2036	≤ 30 y	SBP, DBP, MAP, PP, sex, age	To investigate age related changes in BP and to infer haemodynamics based on longitudinal changes in BP	Age (≥ 50 y) associated fall in DBP and progressive rise in SBP.
Miller *et al* (1997); Peer reviewed journal articles in English; M	Overweight; 18 - 68 y; m & f	493 groups Group size: 3 to 2869 Median 33 ± 6 (± SEM)	25 y (1969 - 1994)	Diet, exercise, diet and exercise	To investigate the effectiveness of diet, exercise and diet and exercise for weight loss purposes	All components provided weight loss with the combination of diet and exercise the most effective programme for short term weight loss.
ESCHDCRG (1998); China/ Japan; M	18 cohort studies, 18 - 98 y; m & f	124774	7 y (mean)	Stroke incidence, sex, age, BP, cholesterol, smoking	To investigate contribution of DBP and cholesterol to stroke risk	DBP was the important determinant of stroke risk. Increasing levels of DBP provided a progressive increase in stroke risk.
Gartside *et al* (1998); NHANES I; USA; F	With/ without CHD; multi-ethnic; 56 - 90 y; m & f	5811	16 y	Sex, age, race, cholesterol, poverty index, ethnicity (Hispanic, Eur, Black, Am Indian; Asian, other), geographic and urban class, BMI, smoking, education, diet, leisure and habitual PA	To assess the roles of modifiable dietary and behavioural factors for causation and prevention of mortality and medical admission for CHD	Moderate exercise and moderate and heavy habitual PA was associated with lower CHD incidence.
Wilson *et al* (1998); FHS; USA; F	Without overt CHD; 30 - 74 y; m & f	5345	12 y	CHD, sex, age, hypertension, diabetes, anti-hypertensive medication, cholesterol, BMI, smoking	To assess the predictive qualities of BP and cholesterol for CHD incidence	Elevated SBP and DBP was predictive of CHD in a middle-aged white population with > 25% CHD incidence attributed to BP ≥ 130/ 85 mmHg.
Domanski *et al* (2001); NHANES I; USA; F	Free of overt CVD; non-black and black; 25 - 77 y; m & f	5771	16.5 y (mean)	Sex, race, diabetes, smoking, cholesterol, SBP, DBP, MAP	To assess the prognostic significance of PP for cardiovascular risk	A 10 mmHg increase in PP was associated to 10% and 26% increase in risk of cardiovascular mortality at 46 to 77 y and 25 to 45 y of age respectively.

Isomaa *et al* (2001); Botnia; Finland/ Sweden; X	With/ without MetS 35 - 70 y; m & f	4483	6.9 y (median)	MetS, sex, age, CHD, stroke, mortality	To estimate the prevalence and cardio-vascular risk associated with MetS using definition of MetS by WHO	The definition identified individuals with increased risk of cardiovascular morbidity and mortality and would be useful to employ as a tool for comparability purposes between other studies.
Jones *et al* (2002); ARIC; USA; F	Free of clinical CHD; white and black; 45 - 64 y; m & f	14062	7 - 10 y	MetS, sex, age, ethnicity, BP, cholesterol, diabetes, smoking, BMI, education level	To assess the race specific incidence rates and risk factor prediction for CHD	Hypertension was a risk factor for CHD and was a particularly strong indicator of risk in black women.
Schnohr *et al* (2002); CCH; Denmark; F	No history of CHD; White, 30 - 79 y; m & f	12077	21 y	CHD incidence & CHD mortality, sex, age	To assess the importance of individual and community risk factors for CHD	Hypertension and physical inactivity were high risk factors for CHD.
Vasan *et al* (2002); FHS; USA; F	Free of hypertension at baseline; 55 - 65 y; m & f	1298	20 - 25 y	Hypertension, sex, age, mortality, residual risk, anti-hypertensive medication	To assess the lifetime risk of developing hypertension	The residual lifetime risk for the development of hypertension in middle-aged and older adults was 90% indicating a large health burden.
Malik *et al* (2004); NHANES II; USA; F	With/ without MetS; 30 - 75 y; m & f	6255	13 ± 3.8 y (± SD)	MetS, sex, age, smoking, PA, cholesterol	To assess the impact of MetS on CHD, CVD and overall mortality	The presence of MetS provided a significantly higher incidence of CHD, CVD and total mortality. Multiple risk factors strongly predicted disease and mortality i.e., greater than sum of individual components.
Ninomiya *et al* (2004); NHANES III; USA; X	With/ without MetS; multi-ethnic; 20 - 89 y; m & f	10357		MetS; sex, age, smoking, ethnicity (Non- Hispanic white/ black, Mex Am, other)	To assess the association of MetS with MI and stroke	The presence of MetS provided a strong and consistent relationship with MI and stroke.
Girman *et al* (2004); 4S and AFCAPS/ TexCAPS; Scandinavia/ USA; F	Patients with CHD (4S) and participants with mild or normal cholesterol (AFCAPS/TexCAPS); 35 - 70; m & f (4S) 45 - 73; m & 55 - 73; f	Placebo groups only. Total: 5524 (2223 and 3301)	5.4 y (median)	Sex, cholesterol, triglycerides, glucose, age, BMI, SBP, DBP,	To assess longterm cardiovascular risk with MetS and with risk determinants of MetS	Elevated BP was the most common component in MetS and those with MetS had a higher risk of MI and stroke.
Greenlund *et al* (2004); NHANES; USA; X	With/ without hypertension ≥ 20 y; m & f	3488		BP status, sex, age, ethnicity (white, Af Am, Mex Am), cholesterol, BMI, Diabetes, smoking	To assess prevalence of risk factors for cardiac disease and stroke in normotensive, prehypertensive and hypertensive individuals	Prehyptension and hypertension was indicative of other risk factors for cardiac disease and stroke. Prehypertension compared to normal BP provided more adverse risk factors suggesting preventive strategies were essential in this BP state. Variance in hypertension with age were found with different ethnicity.
Yusuf *et al* (2004); INTERHEART; Global; RE	MI patients; any age; m & f	27098		MI, hypertension, diabetes, abdominal obesity, cholesterol, geographical region, ethnicity, diet, exercise, smoking, psychosocial index	To assess the risk factors for MI in global populations	Hypertension and physical inactivity were two of the main risk factors for MI acrosss all ages, sex and global regions.

Thomas *et al* (2005); NCEP ATP III; China (Hong Kong); X	With/ without MetS; 25 - 74 y; m & f	2843		MetS; sex, age, smoking, alcohol	To assess the prevalence of MetS in Chinese (Hong Kong) population	MetS was highly prevalent in this Asian population and was age related with high levels of MetS in the elderly.
Wang *et al* (2006); Strong Heart; USA; F	Thirteen Am Indian tribes; 45 - 74 y; m & f	4549	< 12 y	Hypertension, sex, age, centre, diabetes, cholesterol, obesity, parental history, alcohol, PA, smoking, education	To assess hypertension incidence and hypention risk factors and the association with CVD	Rising risk of hypertension in American Indians. Prehypertension provided > 3 times greater risk of developing hypertension and CVD than normal BP.
Mancia *et al* (2007); PAMELA; Italy; X	With/ without MetS 25 - 74 y; m & f	2013	12 y (mean)	MetS; sex, age, SBP, DBP, cardiac, mortality, smoking, alcohol	To assess prevalence of MetS and its relationship with BP, cardiac damage and prognosis with mortality	MetS was a common feature of this population and was associated to increased risk of cardiovascular and all-cause mortality and cardiac abnormalities. Elevated BP was the most common feature of MetS.
Pischon *et al* (2008); EPIC; 10 European countries; F	Predomominantly general population in given area; 25 - 70 y (mean 51.5 ± 10.4 y) (± SD); m & f	359387	9.7 ± 2 y (mean: ± SD)	Mortality; sex, age, follow-up, weight distribution, smoking, educational level, alcohol, PA, height	To investigate the association between body fat distribution and mortality	General adiposity and abdominal adiposity were associated with the risk of mortality.
Yang *et al* (2008); CRIYF; Finland; X	Without Type 1 diabetes; 24 - 39 y; m & f	2060	9 y	MetS, PA, sex, age, education, smoking	To assess the relationship of PA and its changes with the prevalence of MetS	Regular PA was associated with a lower prevalence of MetS in both men and women.
Mente *et al* (2010); INTERHEART; Global; RE	MI patients; any age; m & f	26903		MetS, MI, sex, age, geographical region, ethnicity	To assesss the risk of MI conferred by MetS and its individual risk factors in global regions and ethnicities	MetS was a risk factor for MI across sex, global populations and ethnicities with hypertension identified as a major risk factor for MI. The risk associated with MetS was not greater than the sum of its parts suggesting risk factors should be treated individually.
Loucks *et al* (2011); Framingham Offspring: USA; F	All with required educational data; ≥ 28 y; m& f	3890	30 y	Educational status, sex, age, SBP, DBP, anti hypertensive medication, alcohol, BMI, smoking	To assess the association between educational status and related factors on BP	Education was inversely associated to SBP and may stronger in women than men.

Note: n = number; y = year; m = male; f = female; < = less than; ≤; > = greater than; USA = United States of America; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure; BMI = body mass index; PA = physical activity; CVD = cardiovascular disease; MI = myocardial infarction; CHD = coronary heart disease; MetS = metabolic syndrome; FHS = Framingham Heart Study; ARIC = Atherosclerosis Risk in Communities Study; CCH = Copenhagen City Heart Study; CRIYF = Cardiovascular Risk in Young Finns Study; X = cross-sectional survey; F = prospective study; RE = Retrospective analyses; SD = standard deviation; SEM = standard error of measure; Eur = European; Am = American; Af = African; Mex = Mexican

APPENDIX IV: BLOOD PRESSURE: SUMMARY OF EPIDEMIOLOGIC STUDIES

Table A4. The relationship between blood pressure and interrelated factors which relate to cardiovascular health outcomes: summary of studies

	Participants			Study details		
Author, Year; Study; Country; Classification	Baseline characteristics	Sample size (n)	Follow-up	Adjustment/ Risk	Aim	Main findings
Rosenman *et al* (1976); WCGS; USA; F	Healthy; 39 - 59 y; m	3154	8.5 y	SBP, DBP, MAP, CHD, age, cholesterol, smoking	To investigate the strength of BP components for the prediction of risk for CHD	The risk for CHD was more strongly associated to SBP than DBP and thus is a BP component of primary importance.
Munatunga *et al* (1993); USA; F	No history of renal, CVD, diabetes or medication affecting BP; mean 9 y; m & f	509	< 6 y	Sex, ethnicity, age, SBP, DBP, BMI	To assess the longitudinal change in BP in black and white children	Increase in BP over time was significantly greater in black children than white suggesting mechanisms that predispose blacks to hypertension may be functioning in childhood.
Burt *et al* (1995); NHANES III; USA; X	General population of racial groups; ≥ 18 y; m & f	9901		Age, SBP, DBP, hypertension, sex, ethnicity	To estimate the prevalence and distribution of hypertension in USA adult population	Hypertension a common finding (24%) in USA population. The prevalence, awareness and treatement of hypertension varied between ethnic populations.
Mahoney *et al* (1996); Muscatine; USA; F	Previous participation in school survey; 8 - 37 y; m & f	384	18 y (mean)	Sex, age, coronary risk factors, CAC	To estimate the prevalence of CAC in young adults and the association between CAC and coronary risk factors measured in childhood and young adult life.	Coronary risk factors measured in children and young adults are associated with early development of CAC suggesting risk factors for cardiac disease may abide in childhood.
Franklin *et al* (1997); FHS; USA; F	No BP medication at index; 50 - 79 y; m & f	2036	≤ 30 y	SBP, DBP, MAP, PP, sex, age	To assess age related changes in BP in normotensive and untreated hypertensives	Progressive rise in SBP with age with reduced DBP ≥ 50 y.
Gillum *et al* (1998); NHANES I; USA; F	No history of CHD, 25 - 74 y; m & f	11301	≤ 22 y	Sex, age, SBP, cholesterol, education, income, ethnicity	To assess CHD risk factors in Af Am	Elevated SBP was predictive for CHD in Af Am.
van den Hoogen et al (2000); USA/ Europe/ Japan; F	16 cohorts; 40 - 59 y; m	12761	25 y	SBP, DBP, mortality, global area	To assess the relationship between BP and mortality in 6 different global populations	Relative increase in BP similar across populations whereas absolute risk at same BP level substrantially varies between populations.
Franklin *et al* (2001); NHANES III; USA; X	Hypertensives; ≥ 18 y; m & f	19661		Age, uncontrolled hypertension (untreated/ inadequately treated); hypertensive sub-type	To assess patterns of systolic and diastolic hypertension by age	Systolic hypertension most prevalent ≥ 50 y with diastolic hypertension < 50 y which consisted of systolic and diastolic hypertension.

Isomaa *et al* (2001); Botnia;Finland/ Sweden; F	With/ without MetS 35 - 70 y; m & f	4483	6.9 y (median)	MetS, sex, age, CHD, stroke, mortality	To assess the prevalence of and cardio-vascular risk associated with MetS with WHO definition	WHO definition for MetS identified individuals with increased cardiovascular morbidity and mortality.
Psaty *et al* (2001) CHS; USA; F	Community populations with no MI, stroke or HF at baseline; ≥ 65 y; m & f	5888	6.7 y (mean)	SBP, DBP, PP, MI, Stroke, mortality	To assess the association between BP components with cardiovascular events and mortality	Only SBP associated with total mortality. All BP components were strongly related to coronary and cerebrovascular events with SBP the best predictor for a cardiovascular event.
Vasan *et al* (2001); FHS; USA; F	Free of hypertension, no antihypertensive medication, no CVD; < 50 y, 50 - 59 y, 60 - 69 y ≥ 70 y; m & f	6859	12 y	SBP, DBP, CVD, sex, age, BMI, cholesterol, diabetes, smoking	To assess the risk of CVD in individuals with high-normal BP (130-139/ 85-89 mmHg)	Individuals with high-normal BP have a greater risk of developing CVD regardless of age or sex and after adjustment for cardiovascular risk factors.
Ezzati *et al* (2002); Global; M	14 global regions; 0 - ≥ 80 y; m & f	6045017		26 risk factors including high BP and physical inactivity	To assess the contribution of risk factors to global and regional burden of disease	High BP and physical inactivity were two of the main risk factors for mortality and burden of disease in the developed and developing regions across the world.
Jones *et al* (2002); ARIC; USA; F	Free of CHD; 45 - 64 y; m & f	14062	7 - 10 y	Sex, ethnicity; CHD incidence, hypertension, cholesterol, diabetes, smoking, weight, education	To assess the race specific and incident rates and risk factor prediction in CHD in black and white individuals	CHD incidence was similar between black and whites. Hypertension was a risk factor for CHD in all populations and was particularly strong in black individuals, especially women.
Lewington *et al* (2002); Europe/ N America/ Asia; M	61 studies; 40 - 89 y; m & f	958074		BP, sex, age, mortality	To assess the age-specific relevance of BP to cause-specific mortality	Risk of vascular and over-all mortality is strongly related to BP level ≥ 115/ 75 mmHg in middle-aged and older individuals in men and women.
Schnohr *et al* (2002); CCHS; Denmark; F	Random population sample; No history of CHD; > 20 y; m & f	12077	21 y	Sex, age, hypertension, diabetes, smoking, physical inactivity, alcohol, cholesterol, obesity, triglycerides; education, economic status	To assess the difference between individual and community CHD risk factors	In both men and women, hypertension and physical inactivity were major risk factors for CHD for the individuals and across populations.
Vasan *et al* (2002); FHS; USA; F	Free of hypertension at baseline; 55 - 65 y; m & f	1298	20 - 25 y	Hypertension, sex, age, mortality, residual risk, anti-hypertensive medication	To assess the lifetime risk of hypertension in older adults	The residual lifetime risk of hypertension in older adults is 90% indicating a major public health burden.
APCSC (2003); Asia Pacific; F	16 cohort studies; < 50 to ≥ 70 y; m & f	94147	8.5 y (mean)	BP components, stroke, IHD, sex, age, cholesterol, smoking	To compare the importance of BP components as risk factors for stroke and IHD	In individuals > 50 y, SBP was the most important BP component as a risk factor for stroke and IHD while both SBP and DBP were important < 50 y.
Raitakari *et al* (2003); CRIYFS; Finland; F	Random selection; 3 - 39 y; m & f	2229	21 y	Common carotid artery IMT, sex, age, SBP, DBP, cholesterol, triglycerides, BMI, smoking	To assess the exposure to cardiovascular risk factors in childhood and adolescence with the development of atherosclerosis in later life	Risk factor profile at 12 - 18 y adolescents was predictive for adult carotid artery IMT and independent of other risk factors suggesting a possible early life influence for disease in later life.

Greenlund *et al* (2004); NHANES; USA; X	White, Af Am or Mex Am; > 20 y; m & f	3488		BP status, sex, age, ethnicity	To compare differences in the prevalence of cardiac disease and stroke risk factors in normal, prehypertension and hypertension	Individuals with prehypertension or hypertension had ≥ 1 risk factor for cardiac disease or stroke. Af Am were more likely to have hypertension at an earlier age than other ethnicities.
Muntner *et al* (2004); NHANES III/ NHANES; USA; X	Children and adolescents 8 - 17 y; m & f	5582	12 y	Sex, age, SBP, DBP, ethnicity, BMI	To assess the trends in BP and the role of overweight in childhood and adolescence	Over 10 y both SBP and DBP had increased in childhood and adolescence and was partially attributed to an increased prevalence of overweight.
Yusuf *et al* (2004); INTERHEART; Global; RE	MI patients; any age; m & f	27098		MI, hypertension, diabetes, abdominal obesity, cholesterol, geographical region, ethnicity, diet, exercise, smoking, psychosocial index	To assess the risk factors for MI in global populations	Hypertension and physical inactivity were two of the main risk factors for MI in global populations.
Kearney *et al* (2005); Global; M	30 studies; 20 - 95 y; m & f	706641 (range 665 - 484185)		Hypertension, sex, age, global areas	To assess the global prevalence and burden of hypertension and estimate the global burden of hypertension in 2025	In 2000 the estimated number of individuals with hypertension was 972 million (mean) and predicted to increase by 60% to > 1.5 billion by 2025.
Sarnak *et al* (2005); MDRD; USA; RA	Renal disease; 18 - 70 y; m & f	840	10 y	SBP, DBP, MAP, kidney failure, mortality	To assess the effects of low BP on kidney failure and all-cause mortality	Lower BP targets slowed the progression of non-diabetic kidney disease and delayed all-cause mortality.
Zureik *et al* (2005); SUVIMAX Vascular; France; X	Healthy; > 50 y; m & f	< 1000	7 y	Sex, age, Parental data, SBP, DBP, PP, MAP, MetS risk factors, smoking	To assess BP changes in adult offspring according to parental longevity	Paternal premature death was associated to accelerated progression of SBP and higher rates of hypertension in adult offspring. No association was found with maternal longevity.
Srinivasan *et al* (2006); BHS; USA; Linking of cross-sectional surveys	City children; 5 - 42 y; m & f	3255		Age, SBP, DBP, hypertensive status, MetS risk factors,	The longitudinal trend in BP in normotensive, prehypertensive and hypertensive individuals during childhood to adulthood	On attaining adulthood, prehypertensive and hypertensive individuals had a greater prevalence of risk factors for MetS compared to normotensive individuals and early elevations of BP were indicative for progression to clinical hypertension.
Zhang *et al* (2006); Strong Heart; USA; F	Am Ind; free of hypertension, CVD; 45 - 74 y; m & f	2629	12.6 y (mean)	Prehypertension, CVD, diabetes, age	To assess impact of prehypertension on the risk for CVD	Prevalence of prehypertension was ~ 50% in Am Ind population and provided a greater risk of CVD compared to normotensive indivduals.
Mancia *et al* (2007); PAMELA; Italy; X	Random selection; 25 - 74 y; m & f	2013	> 12 y	SBP, DBP, Met S components, sex, age, smoking, alcohol, medical history	To assess the prevalence of MetS and its relationship with daily BP and cardiac damage	Cardiac damage and increased daily life BP were common features of MetS. The contribution of MetS to mortality risk was unbalanced and mainly related to BP and glucose abnormalities.

Tu *et al* (2008a); Canada; X	Hypertensives; ≥ 20 y; m & f	≤ 2311042		Hypertension, mortality, sex, age	To assess whether the increase in diagnosed hypertension could be explained by a reduction in mortality	The increased incidence of hypertension may be associated to the reduction in mortality rate.
Tu *et al* (2008b); Canada; X	Hypertensives; ≥ 20 y; m & f	≤ 2311042		Hypertension, sex, age, diabetes, socioeconomic status, primary care	To assess whether the future estimates for hypertension have been underestimated	The continuing rise in prevalence of hypertension suggested current estimates for hypertension incidence in 2025 were markedly underestimated.
Franklin *et al* (2009); FHS; USA; F	No CVD events or BP medication; 42 ± 11 y at first index; m & f	9657	≤ 49 y	SBP, DBP, MAP, PP, sex, age, cholesterol, smoking, BMI, diabetes, CVD events/ risk	To assess the single vs combined BP components for prediction of risk for CVD	The combination of SBP and DBP was superior for predicting risk for CVD compared to PP and MAP and better than SBP alone.
Mente *et al* (2010); INTERHEART; Global; RE	MI patients; any age; m & f	26903		MetS, MI, sex, age, geographical region, ethnicity	To assess the risk of MI conferred by MetS and individual risk factors across regions and in different ethnic populations	MetS was a risk factor across sex, global region and ethnicities with hypertension identified as a major risk factor for MI. The risk associated with MetS was not greater than the sum of its parts suggesting risk factors should be treated indivdiually.
Chen *et al* (2011); BHS; USA; Linking of cross-sectional surveys	City children; 4 - 48 y; m & f	1797		Sex, age, ethnicity, SBP, DBP, BMI	To assess whether hildhood BP variability was predictive of adult hypertension	Increased BP variability in childhood was predictive of adult hypertension suggesting the risk of hypertension may abide in childhood.
Powell *et al* (2011); Women's Health; USA; X	No history of CVD or cancer; ≥ 45 y; f	39260	13.3 y (median)	SPB, DBP, PAD, age, BMI, ethnicity, cholesterol,diabetes, smoking, family history, HRT, medication	To assess the relative contribution of SBP and DBP control for PAD	Uncontrolled BP had a prognostic role for the development of PAD which was particularly evident with uncontrolled SBP.

Note: n = number; y = year; m = male; f = female; < = less than; ≤; > = greater than; USA = United States of America; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure; BMI = body mass index; PA = physical activity; HRT = hormone replacement therapy; CVD = cardiovascular disease; MI = myocardial infarction; CHD = coronary heart disease; IHD = ischaemic heart disease; MetS = metabolic syndrome; CAC = coronary artery calcification; IMT = intima-media thickness; WCGS = Western Collaborative Group Study; FHS = Framingham Heart Study; CHS = Cardiovascular Health Study; ARIC = Atherosclerosis Risk in Communities Study; CCHS = Copenhagen City Heart Study; CRIYFS = Cardiovascular Risk in Young Finns Study; MDRD = Modification of Diet in Renal Disease Study; BHS = Bogalusa Heart Study; F = prospective study; X = cross-sectional survey; M = Meta-analysis; RE = Retrospective analyses; RA = randomised controlled trial

APPENDIX V: PHYSICAL ACTIVITY, CARDIOVASCULAR RISK AND BLOOD PRESSURE: SUMMARY OF EPIDEMIOLOGIC STUDIES

Table A5. The relationship between physical activity and cardiovascular health outcomes: summary of studies

	Participants			Study details		
Author, Year; Study; Country; Classification	Baseline characteristics	Sample size (n)	Follow-up	Adjustment/ Risk	Aim	Main findings
Morris *et al* (1953); Transport and postal; UK; F	35 - 64 y, m	31,000/ 110,000		None	To assess an association between CHD mortality and occupational work effort	Greater work effort reduced CHD mortality.
Paffenbarger *et al* (1970); Longshoremen; USA; F	35 - 74 y; m	3,263	16 y	Age; SBP, smoking	To assess an association between CHD mortality and occupational work effort	Greater work effort reduced CHD mortality. Linked smoking and higher SBP to CHD mortality.
Paffenbarger *et al* (1978); HCAS; USA; F	No heart attack; 35 - 74 y; m	16,936	6 - 10 y	Age, follow-up period, SBP, sport play (h/ wk), smoking, hypertension, body mass, parental history	To assess an association between CHD mortality and PA	< 2000 kcal/ wk increased risk of CHD. Inverse relationship between CHD risk and PA. Need for habitual PA for retention of lower risk.
Paffenbarger *et al* (1983); HCAS; USA; F	No hypertension; 35 - 74 y; m	14,998	6 - 10 y	Age, follow-up interval, BMI, parental history of hypertension; vigorous sport PA	To assess the association between PA and hypertension	Vigorous PA reduced risk of hypertension. Increased BMI (obesity), parental history and lack of vigorous PA increased risk of hypertension
Blair *et al* (1984); Cooper Clinic; USA; X	No CVD, normotensive; 20 - 65 y; m & f	6,039: 4,820 (m) 1,219 (f)	1 - 12 y	Age, sex, baseline BP, BMI, length of follow-up	To assess the association of baseline fitness with development of hypertension	Low fitness associated to increased risk of hypertension. Increased baseline BP increased risk for development of hypertension.
Morris *et al* (1990); Civil servants; UK; F	No CHD; 45 - 64 y; m	9,376	9 y (mean)	Age, family history, stature, smoking, BMI, sublinical CVD,	To assess the association between CHD and mortality rates with PA behaviour	Vigorous aerobic PA reduced CHD and mortality from other causes.
Shaper and Wannamethee (1991); BRHS; UK; F	Regional clinical random selection; 40 - 59 y; m	7,735	8 y	Age, smoking, BMI, social class, smoking, SBP, HDL , cholesterol, FEV_1, breathlessness, HR	To assess the association between IHD and PA	Moderate PA reduced risk of IHD and increased survival rate following cardiac event. Vigorous (sport) PA reduced incidence of coronary event.
Wannamethee and Shaper (1992); BRHS; UK; F	Regional clinical random selection; 40 - 59 y; m	7,735	9.5 y	Stroke, heart attack, age, social class, smoking, BMI, alcohol	To assess the association between PA and stroke	Moderate PA reduced risk for stroke and cardiac event.

Paffenbarger *et al* (1993); HCAS; USA; F	No CHD, CORD, diabetes, cancer; 45 - 84 y; m	10,269	≤ 23 y	Age, physical activity, energy expenditure (kcal/wk) smoking, BP, BMI, parental death	The association between changes in PA and lifestyle behaviours with mortality	Moderate vigorous (sport) PA, smoking cessation and maintaining BP and body weight reduced risk of mortality. Long term hypertension linked to increased risk of mortality.
Folsom *et al* (1997); ARIC; USA; F	No CHD; 45 - 64 y; m & f	14,040: 6,188 (m) 7,852 (f)	4 - 7 y	Age, sex, race, field centre, education, smoking, alcohol, HRT, diabetes, W/H ratio, cholesterol, SBP, fibrinogen anti-hypertensive medication	To assess the association between PA and CHD incidence	Regular PA reduced risk of CHD and vigorous (sport) PA inversely associated to CHD in non-black men and women. No association in black individuals.
Franklin *et al* (1997); FHS; USA; F	No CHD or anti-hypertensive medication; 50 - 79 y; m & f	2,036: 890 (m) 1,146 (f)	< 30 y	Age, sex	To assess age-related change in BP in normotensives and untreated hypertensives	Reduced DBP ≥ 50 y while SBP continues to rise with age.
Haapanen *et al* (1997); Census population; Finland; F	19 63 y; m & f	2,840: 1,340 (m) 1,500 (f)	10 y	Age, smoking, BMI, hypertension, diabetes, total PA, alcohol	To assess the association between PA and risk of CHD, hypertension and diabetes	Leisure PA reduced hypertension and risk of CHD in men but not in women.
Rosengren and Wilhelmsen (1997); Primary Prev'tion; Sweden; F	No CHD; 47 - 55 (in 1970 - 1973); m	7,142	20 y (mean)	Age, DBP, cholesterol, smoking, alcohol, BMI, diabetes, occupational class	To assess occupational and leisure PA on CHD and all cause mortality	Leisure PA reduces CHD mortality and all cause mortality. Moderate activity (walking) ≥ 4 h/ wk was as beneficial as more strenuous acitivity.
Lee and Paffenbarger (1998); HAHS; USA; F	No CVD or cancer; 43 - 88 y; m	11,130	13 y	Age, smoking, alcohol, early parental death, PA	To assess the association between PA and stroke risk	Moderate PA ≥ 1000 - 2999 kcal/ wk reduced stroke risk.
Hayashi *et al* (1999); Osaka Health; Japan; F	No hypertension or diabetes; 35 - 60 y; m	6,017	16 y	Age, BMI, alcohol,PA, smoking, plasma glucose, SBP, DBP, PA duration;	To assess the association between PA duration with hypertension	Duration of PA (walking) associated to decreased risk of hypertension.
Lee *et al* (1999); Physicians' Health; USA; F	No MI, stroke, TIA or cancer; 40 - 84 y; m	21,823	11.1 y (mean)	Age, treatment assignment, smoking, alcohol, history of angina, parental history of MI, BMI, history of diabetes, hypertension or HChl	To assess the association between PA and stroke risk	Vigorous PA once/ wk inversely associated to stroke risk (with no further benefit with increased frequency). Benefit obtained from PA effects on hypertension, cholesterol and glucose control.
Manson *et al* (1999); Nurses' Health; USA; F	No CVD or cancer; 40 - 65 y; f	72,488	8 y	Age, study period, smoking, BMI, menopausal therapy, HRT, parental history for MI, vitamin supplementation, alcohol, history of diabetes, hypertension and HChl, aspirin	To assess the association of total PA, walking and vigorous PA on incidence	Brisk walking and vigorous PA associated with substantial and similar reduction in coronary event incidence (5 MET-h/ wk: 1.5 h brisk walking equalled 45 min vigorous activity. Brisk walking ≥ 3 h/ wk provided greatest benefit with similar benefit from vigorous PA ≥ 6 MET/ wk (30-40% reduction).

Pereira *et al* (1999); ARIC; USA; F	No angina, MI, coronary angioplasty or cardiovascular sugery	7,441: 3,389 (m) 4,052 (f)	6 y	Age, baseline BP, study centre, education, BMI, W/H ratio, parental history of hypertension, smoking, alcohol, diet, menopausal status, HRT	To assess the association between PA and hypertension	Regular PA associated with reduced incidence of hypertension in white men with greater reductions from greater activity with no association found in white women or black individuals.
Sesso *et al* (1999); CAHS; USA; F	No CVD; 37-69 y; f	1,564	31 y	Age, BMI, hypertension, diabetes, smoking, family history for CHD, alcohol, HRT, total PA (kcal/ wk)	To assess the association between PA and CVD risk	No overall association between walking and total PA for CVD risk although walking 6 miles/ wk decreased CVD risk.
Albert *et al* (2000); Physicians' Health; USA; F	No CVD; 40 - 84 y; m	21,481	12 y	Age, aspirin and beta carotene treatment, BMI, smoking, history of diabetes, hypertension or HChl, alcohol, vitamin supplement-ation, fish consumption	To assess risk from sudden death during and following PA	Evidence of sudden cardiac death during and following vigorous PA although habitual vigorous PA attenuated relative risk of sudden cardiac death.
Andersen *et al* (2000); Denmark; F	20 - 93 y; m & f	30,640: 17,265 (m) 13,375 (f)	14.5 y	Age, sex, study entry, SBP, cholesterol, triglyceride, BMI, smoking, education, lipids, leisure physical activity,	To assess the association between PA and all-cause mortality	Moderate PA reduced all-cause mortality in men and women in all age groups. Sporting activity and cycling (transportation) increased benefit from PA.
Hu *et al* (2000); Nurses' Health; USA; F	No CVD or cancer; 40 - 65 y; f	72,488	8 y	Age, smoking, BMI, menopausal status, HRT, parental history of MI, alcohol, history of diabetes, hypertension or HChl, aspirin, vigorous PA, walking	To assess the association between PA and total stroke and stroke subtypes	Brisk walking (moderate intensity) reduced risk of total stroke and ischemic stroke.
Sesso *et al* (2000); HCAS; USA; F	No CVD or cancer or coronary risk factors 39 - 88 y; m	12,516	16 y	Age, BMI, alcohol, diabetes, hypertension, smoking, early parental death (< 65 y)	To assess the association between PA volume and intensity with risk for CHD and coronary risk factors	Total PA and vigorous PA reduced CHD risk with no inverse association between CHD risk and moderate/ light PA.
Smith *et al* (2000); Whitehall; UK; F	40 - 64 y; m	6,702	25 y	Age, work grade, BMI, smoking, SBP, cholesterol, glucose intolerance, diabetes, FEV, ischaemia	To assess the association between PA and mortality	Leisure PA and walking pace was inversely associated to reduced risk from CVD, CHD and all-cause mortality.
Wannamethee et al (2000); BRHS; UK; F	No CHD, diabetes or stroke; 40 - 59 y; m	5,159	16.8 y (mean)	Age, BMI, social class, smoking, alcohol, pre-existing CHD, other	To assess the role of serum glucose and insulin resistance syndrome in the associ-ation between PA, CHD and diabetes	PA inversely related to CHD incidence with lowest incidence from moderate PA with no further benefit thereafter.

Lee *et al* (2001); Women's Health; USA; F	No CHD, cerebrovascular disease or cancer; ≥ 45 y; f	39,372	< 7 y	Age, randomised treatment assignment, smoking, alcohol, diet, menopausal status, HRT, parental history of MI	To assess the association between PA (walking) with CHD	Light to moderate PA from walking was associated with reduced CHD incidence. ≥ 1 h / wk predicted lower CHD risk.
Laaksonen *et al* (2002); KIHD; Finland; F	No MetS; 42 - 60 y; m	612	4 y	Age, BMI, socioeconomic status, CVD, smoking, alcohol, W/H ratio, anti-hypertensive medication, SBP, DBP, HDL, insulin, glucose, family history of diabetes	To assess the association between PA and cardiorespiratory fitness with the development of MetS	Cardiorespiratory fitness protected against MetS and was related to mediating factors. Low fitness and sedentary behaviour provided a high risk for the development of MetS while low levels of PA attenuated such risk and compliance with current PA recommendations substantially reduced the risk.
Manson *et al* (2002); WHIO; USA; F	Predicted survival < 3 y, alcholism, mental illness, dementia, CHD, stroke or cancer; 50 - 70 y; f	73,743	≤ 5.9 y	Age, walking duration, smoking, race, education, income, BMI, W/H ratio, alcohol, parental history of premature MI, age at menopause, HRT, diet	To assess the association between PA and physical inactivity with coronary and cardiovascular events	Walking and vigorous PA reduced incidence of cardiovascular events among post-menopausal women irrespective of age, race, ethnicity and BMI. Physical inactivity (prolonged sitting) was predictive for increased cardiovascular risk.
Vasan *et al* (2002); FHS; USA; F	No CVD or hypertension; 55 - 65 y (1976 - 1998); m & f	1,298	20 - 25 y	Age, competing cause of mortality, BMI	To estimate the lifetime risk and trends for hypertension	Residual lifetime risk for the development of hypertension in middle-aged/ elderly was 90% thus primary prevention of hypertension was required.
Carnethon *et al* (2003); CARDIA; USA; F	No anti-hypertensive medication; 18 - 30 y; m & f	4,487: 2029 (m) 2,458 (f)	15 y	Age, race, sex, smoking, family history of diabetes, MetS, hypertension or premature MI (HChl), BMI, weight change	To assess the association between cardiorespiratory fitness and CVD	Low fitness in young individuals is associated with CVD risk factors and the development of hypertension and MetS in middle-age.
Lakka *et al* (2003); KIHD; Finland; X	No CVD, diabetes or cancer; 42 - 60 y; m	1,069		Age, smoking, alcohol, socioeconomic status,	To assess the association between cardiorespiratory fitness and PA with MetS	Sedentary lifestyle and low fitness was related to MetS incidence. Moderate intensity PA ≥ 3 h/ wk substantially reduced MetS incidence.
Hu *et al* (2004); Finland; F	No hypertensive medication, CHD, stroke, heart failure; physical impairment; 25 - 64 y; m & f	17,441: 8,302 (m) 9,139 (f)	11 y (mean)	Age, area, study year, education, smoking, alcohol, diabetes, BMI, SBP, PA	To assess the association between PA and hypertension	Reduction in hypertention risk from PA in men and women of normal weight and with increased BMI. Greater benefit achieved from high level PA in those of normal weight.
Lee *et al* (2004); HAHS; USA; F	No prevalent CVD, cancer or diabetes; mean 66 y; m	8,421	9 y	Age, smoking, alcohol, diet, early parental mortality (< 65y)	To assess the association between PA pattern with all-cause mortality	Regular PA ≥ 1000 kcal/ wk reduced mortality risk.

LaMonte *et al* (2005): ACLS; USA; F	No prevalent MetS, CHD, stroke or cancer; 20 - 80 y; m & f	10,498: 9,007 (m) 1,491 (f)	5.7 y (mean)	Age, smoking, alcohol, family history of disease, year of baseline examination, number of baseline MetS risk factors, low fitness, BP, glucose, HDL, triglycerides, abdominal obesity	To assess the association between cardiorespiratory fitness and MetS	Low fitness was predictive of MetS in men and women.
Sundquist *et al* (2005); Sweden; F	35 - 74 y; m & f	5,196: 2,645 (m) 2,551 (f)	12 y	Age, sex, physical activity, income, smoking, BMI	To assess long-term PA on CHD incidence	Leisure PA related to reduced risk of CHD in men and women with 2 sessions/ wk providing 40% reduction in risk.
Barlow *et al* (2006); F ACLS; USA; F	No hypertension, CVD, diabetes, cancer, low fitness (< 85% HR_{max}): 20 - 79 y: f	4,884	5 y (mean)	Age, examination year, survey response pattern, smoking, alcohol, family history of hypertension, SBP, DBP, waist girth, glucose, triglyceride concentration, baseline BP, BMI	To assess the association between physical fitness with hypertension	Inverse dose-response relationship between cardiorespiratory fitness and hypertension in women. Low fitness was predictive of hypertension incidence.
Hu *et al* (2007); Finland; F	No CHD or stroke; 25 - 64 y; m & f	47,840: 22,877 (m) 24,963 (f)	18.9 y (mean)	Age, study year, education, alcohol, smoking, BMI, SBP, cholesterol, diabetes, commuting, leisure, occupational physical activity	To assess the association of occupational, commuting and leisure PA with CHD risk	Moderate and high levels of PA associated with reduced CHD risk in men and women. Walking and cycling commuting decreased risk of CHD in women only.

Note: n = number; y = year; m = male; f = female; < = less than; ≤; > = greater than; UK = United Kingdom; USA = United States of America; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; PA = physical activity; HDL = high density lipoproteins; FEV = forced expiratory volume; FEV_1 = forced expiratory volume in one second; HR = heart rate; kcal/ wk = kilocalorie per week; HRT = hormone replacement therapy; W/H ratio = waist to hip ratio; HChl = hypercholesterolemia; CVD = cardiovascular disease; IHD = ischaemic heart disease; MI = myocardial infarction; CHD = coronary heart disease; MetS = metabolic syndrome; HCAS = Harvard College Alumni Study; BRHS = British Regional Heart Study; ARIC = Atherosclerosis Risk in Communities Study; FHS = Framingham Heart Study; HAHS = Harvard Alumni Health Study; CAHS = College Alumni Health Study; KIHD = Kuopio Ischemic Heart Disease Risk Factor Study; WHIO = Women's Health Initiative Observational Study; CARDIA = Coronary Artery Risk Development in Young Adults Study; ACLS = Aerobics Center Longitudinal Study; F = prospective study; X = cross-sectional survey

APPENDIX VI: SUMMARY OF FEATURES REGARDING THE MODERN METHOD FOR BRS ASSESSMENT

Table A6: Assumptions, advantages and limitations regarding the modern BRS assessment techniques

BRS technique	Assumptions	Advantages	Limitations
Time Sequence		Non invasive	Does not provide 'full range' analysis
		Ease of computation	Influenced by respiratory activity
		No external intervention required	Lesser reproducibility: sequences occur unevenly over time thus short intervals may not adequately characterise BRS; low SBP variability would produce few sequences thus longer periods of recordings may be required
		Spontaneous baroreceptor stimulation and deactivation can be assessed	
		Specificity	
		Global measure	Indirect assessment
		Provides information on a 'minute by minute' basis	Does not consider closed loop nature of BP/ HR interactions
Spectral α co-efficient	Ratio between RRI and SBP in frequency where regions are coherent is a reflection of baroreflex function	Non invasive	Coupling between RRI and SBP in HF may have a non-baroreflex origin (respiration, central influences, hormones)
		No external intervention required	
	Stationarity	If measured in LF region then respiratory influence is attenuated	Narrow frequency regions thus reflection of baroreflex modulation of of sinus node only at specific frequencies i.e. selective estimate of BRS thus fails to reflect wide frequency content
		Provides opportunity to assess both sympathetic and parasympathetic contribution to reflex heart modulation	Indirect assessment
		In the frequency regions SBP oscillations occur regularly even during short recordings	Cannot separately quantify stimulation or deactivation of baroreceptors
			Requires a time window of 128 or 256 beats
			Does not consider closed loop nature of BP/ HR interactions
Transfer function transfer gain	Linear model in that SBP is the input and RRI is the output	Non invasive	Narrow frequency regions thus reflection of baroreflex modulation of of sinus node only at specific frequencies i.e. selective estimate of BRS thus fails to reflect wide frequency content
		No external intervention required	
	Stationarity	If measured in LF region then respiratory influence is attenuated	Indirect assessment
			Cannot separately quantify stimulation or deactivation of baroreceptors
			Requires a time window of ≥ 5 min
			Does not consider closed loop nature of BP/ HR interactions

Note: BRS = baroreflex sensitivity; BP = blood pressure; SBP = systolic blood pressure; HR = heart rate; RRI = RR interval; LF = low frequency. Taken from (Parati *et al.*, 1995a; Parati *et al.*, 1997; Parati *et al.*, 2000; Parati *et al.*, 1992; Persson *et al.*, 2001; Robbe *et al.*, 1987)

APPENDIX VII: REPRODUCIBILITY OF BRS TECHNIQUES IN HEALTHY INDIVIDUALS AND CARDIAC PATIENTS

Table A7(a). Reproducibility of BRS techniques in healthy individuals

Author, date	Time period	Participant characteristics (n; gender; age)	BRS techniques	Analysis	Orthostatic manoeuvre	Healthy individuals			
						Highest reproducibility		Lowest reproducibily	
						Spontaneous	*Paced*	*Spontaneous*	*Paced*
Maestri *et al* ., 2009	24 h	44; m & f; 38 ± 8 y	BRS_{Seq} $BRS_{\alpha HF}$ $BRS_{\alpha LF}$ BRS_{TFTG} $BRS_{TFTGmod}$	LOA/ SEM	No	BRS_{Seq}/ $BRS_{TFTGmod}$	BRS_{Seq}	$BRS_{\alpha HF}$	BRS_{TFTG}/ $BRS\alpha LF$
Davies *et al* ., 1999	Same day	18; m & f; 20 - 69 y	BRS_{Phen} BRS_{Seq} $BRS_{\alpha HF}$ $BRS_{\alpha LF}$ BRS_{Cbr}	CV/ LOA	No	$BRS_{\alpha LF}$	BRS_{Cbr}	$BRS_{\alpha HF}$/ BRS_{Phen}	N/A
Lord *et al* ., 1998	Same day	26; m & f; 22 - 63 y	BRS_{HF} BRS_{LF} BRS_{Val}	CV	HUT	BRS_{LF}		BRS_{Val}	
	Wk		BRS_{HF} BRS_{LF} BRS_{Val}			BRS_{LF}		BRS_{Val}	
Dawson *et al* ., 1997	6 mth	39; m & f; 22 - 82 y	BRS_{Seq} BRS_{FFT} BRS_{Val}	CV	No		BRS_{Val}		BRS_{Seq}
Herpin and Ragot, 1997	Wk	14 healthy; m & f; 23 - 51 y	BRS_{Seq} BRS_{TFTG}	LOA	Supine	BRS_{TFTG}		BRS_{UpUp}	
			BRS_{Seq} BRS_{TFTG}	LOA	Standing	BRS_{TFTG}		BRS_{UpUp}	
	1 y		BRS_{Seq} BRS_{TFTG}	LOA	Supine	BRS_{TFTG}		BRS_{UpUp}	
			BRS_{Seq} BRS_{TFTG}	LOA	Standing	$BRS_{DownDown}$		BRS_{TFTG}	
Iellamo et al., 1996	24 h	20 healthy; m; 20 - 32 y	BRS_{Seq}	CV	Standing	N/A		N/A	

Note: n = number; m = male; f = female; y = year; mth = month; wk = week; h = hour; BRS = baroreflex sensitivity; Seq = sequence; αHF = alpha high frequency; αLF = alpha low frequency; TFTG = transfer function transfer gain; TFTGmod = transfer function transfer gain modified; Phen = phenylephrine; Cbr = controlled breathing; Val = Valsalva; FFT = mean of α coefficient in HF and LF; LOA = limits of agreement; SEM = standard error of measurement; CV = coefficient of variation; ICC = intra-class coefficient; HUT = head-up tilt; *Spontaneous* = spontaneous breathing; *Paced* = paced breathing; N/A = not applicable

Table A7(b). Reproducibility of BRS techniques in cardiac patients

Author, date	Time period	Participant characteristics (n; gender; age)	BRS techniques	Analysis	Orthostatic manoeuvre	Cardiac patients			
						Highest reproducibility		Lowest reproducibility	
						Spontaneous	*Paced*	*Spontaneous*	*Paced*
Maestri *et al* ., 2009	24 h	57 patients; m & f; 59 ± 8 y	BRS_{Seq} $BRS_{\alpha HF}$ $BRS_{\alpha LF}$ BRS_{TFTG} $BRS_{TFTGmod}$	LOA/ SEM	No	BRS_{TFTG}/ $BRS_{TFTGmod}$	BRS_{Seq}	$BRS_{\alpha HF}$	$BRS_{\alpha HF}$
Davies *et al* ., 1999	Same day	31 patients; m & f; 25 - 83 y	BRS_{Phen} BRS_{Seq} $BRS_{\alpha HF}$ $BRS_{\alpha LF}$ BRS_{Cbr}	CV/ LOA	No	BRS_{Seq}	BRS_{Cbr}	$BRS_{\alpha HF}$/ BRS_{Phen}	N/A

Note: n = number; m = male; f = female; y = year; h = hour BRS = baroreflex sensitivity; Seq = sequence; αHF = alpha high frequency; αLF = alpha low frequency; TFTG = transfer function transfer gain; TFTGmod = transfer function transfer gain modified; Phen = phenylephrine; Cbr = controlled breathing; LOA = limits of agreement; SEM = standard error of measurement; CV = coefficient of variation; *Spontaneous* = spontaneous breathing; *Paced* = paced breathing; N/A = not applicable

Table A8(a): Summary of findings for reproducibility of BRS in healthy individuals

Author and date	Time period	BRS technique	CV (%)	95% Limits of agreement (ms/mmHg)	95% Limits of random variation of the ratio between two measurements	
					Spontaneous	*Paced*
Maestri *et al* ., 2009	24 h	BRS_{Seq}		Log transformed	0.49 to 2.01	0.51 to 1.96
		$BRS_{\alpha LF}$			0.48 to 2.11	0.44 to 2.27
		$BRS_{\alpha HF}$			0.42 to 2.35	0.46 to 2.17
		BRS_{TFTG}			0.46 to 2.16	0.40 to 2.48
		$BRS_{TFTGmod}$			0.50 to 2.01	0.50 to 2.00
Davies *et al* . 1999	Same day	BRS_{Phen}	52.2	(-) 21.7 to (+) 19.7		
		BRS_{Seq}	40.4	(-) 21.2 to (+) 15.2		
		$BRS_{\alpha HF}$	52.1	(-) 31.5 to (+) 20.9		
		$BRS_{\alpha LF}$	33.7	(-) 10.9 to (+) 9.8		
		BRS_{Cbr}	19.6	(-) 9.3 to (+) 8.6		
Lord *et al* ., 1998	Same day	BRS_{HF}	17.8			
		BRS_{LF}	13.5			
		BRS_{Val}	26.4			
	Wk	BRS_{LF}	25.0			
		BRS_{HF}	25.5			
		BRS_{Val}	29.5			
Dawson *et al* ., 1997	6 mth	BRS_{UpUp}	25.3			
		$BRS_{DownDown}$	26.1			
		BRS_{Seq}	23.9			
		BRS_{FFT}	18.9			
		BRS_{Val}	16.8			
		(All under paced breathing)				
Herpin and Ragot, 1997	Wk	BRS_{UpUp} (S)		± 20.42		
		$BRS_{DownDown}$ (S)		± 14.44		
		BRS_{TF} (S)		± 8.17		
		BRS_{UpUp} (Stand)		± 4.19		
		$BRS_{DownDown}$ (Stand)		± 3.65		
		BRS_{TF} (Stand)		± 3.38		
	1 y	BRS_{UpUp} (S)		± 25.94		
		$BRS_{DownDown}$ (S)		± 14.28		
		BRS_{TF} (S)		± 10.25		
		BRS_{UpUp} (Stand)		± 3.98		
		$BRS_{DownDown}$ (Stand)		± 3.61		
		BRS_{TF} (Stand)		± 4.37		
Iellamo *et al* ., 1996	24 h	BRS_{Seq}				
		Rest (S)	15.0			
		Standing	13.9			
		Mental arithmetic	15.3			
		Static hand-grip	19.7			

Note: y = year; mth = month; wk = week; h = hour; BRS = baroreflex sensitivity; Seq = sequence; αHF = alpha high frequency; αLF = alpha low frequency; TFTG = transfer function transfer gain; TFTGmod = transfer function transfer gain modified; Phen = phenylephrine; Cbr = controlled breathing; Val = Valsalva; FFT = mean of α coefficient in HF and LF; CV = coefficient of variation; (S) = supine; *Spontaneous* = spontaneous breathing; *Paced* = paced breathing.

Table 8(b): Summary of findings for reproducibility of BRS in cardiac patients

Author and date	Time period	BRS technique	CV (%)	95% Limits of agreement (ms/mmHg)	95% Limits of random variation of the ratio between two measurements	
					Spontaneous	*Paced*
Maestri *et al* ., 2009	24 h	BRSSeq		Log transformed	0.45 to 2.21	0.50 to 1.99
		BRSαLF			0.46 to 2.16	0.45 to 2.21
		BRSαHF			0.37 to 2.68	0.43 to 2.33
		BRSTFTG			0.47 to 2.13	0.47 to 2.14
		BRSTFTGmod			0.47 to 2.11	0.48 to 2.07
Davies *et al* . 1999	Same day	BRSPhen	85.6	(-) 6.0 to (+) 9.1		
		BRSSeq	30.7	(-) 5.1 to (+) 4.4		
		BRSαHF	99.7	(-) 14.4 to (+) 14.9		
		BRSαLF	65.9	(-) 6.7 to (+) 8.1		
		BRSCbr	30.7	(-) 3.8 to (+) 4.4		

Note: h = hour; BRS = baroreflex sensitivity; Seq = sequence; αHF = alpha high frequency; αLF = alpha low frequency; TFTG = transfer function transfer gain; TFTGmod = transfer function transfer gain modified; Phen = phenylephrine; Cbr = controlled breathing; CV = coefficient of variation; *Spontaneous* = spontaneous breathing; *Paced* = paced breathing.

APPENDIX VIII: BRS IN PATIENTS FOLLOWING CHRONIC EXERCISE TRAINING: SUMMARY OF STUDIES

Table A9. BRS in patients following chronic exercise training: summary of studies

Author (Year)	Patient characterisitics	Exercise intervention	BRS technique	Results
Galbreath *et al* (2011)	n = 17; 1 m & 16 f; 27 ± 9 y; POTS	75% HR_{max}; 30-45 min 2-4/ wk over 3 months	Cross spectral BRS_{TFTG}	↑ BRS 2.9 ms/mmHg Relative ↑ 16%
Hua *et al* (2009)	n = 40; m & f; ≥ 35 y; Hypertension	35-40% HRR; 4 days/ wk Initial: 0.8 km/ day and increasing until 4.8 km/ day by wk 12	BRS_{Seq}	↑ BRS ~ 1.15 ms/mmHg Relative ↑ 14%
Laterza *et al* (2007)	n = 20; 13 m & 7 f; 44 ± 1 y; Hypertension	70% $V0_{2peak}$; 60 min 3 days/ wk; over 4 months	BRS_{Phen}	Not provided
Costes *et al* (2004)	n = 21; 62 ± 9 y; COPD	60-75% maximal exercise capacity; 3 days/ wk over 8 wk	BRS_{Seq}	↑ BRS 0.7 ms/mmHg Relative ↑ 26%
Loimaala *et al* (2003)	n = 24; m; 54 ± 5 y; Diabetes	65-75% VO_{2max}; 2 days/ wk and strength training 2 days/ wk over 12 months	BRS_{Phen}	↑ BRS 1.8 ms/mmHg Relative ↑ 26%
Iellamo *et al* (2000)	n = 86; m; 58 ± 7 y; CAD	85% HR_{max} < 65 y; 75% HR_{max} > 65 y; 30 min twice daily 6 days/ wk over 2 wk	BRS_{Seq}	↑ BRS 2.3 ms/mmHg Relative ↑ 76%
Pagani *et al* (1988)	n = 11; 8 m & 3 f; 32 ± 2 y; Hypertension	20 min jogging/ 5 days/ wk over 6 months (Cross-over design: trained/ detrained)	BRS_{Phen} $BRS_{\alpha LF}$ $BRS_{\alpha HF}$	↑ BRS 4.8 ms/mmHg Relative ↑ 33% ↑ BRS 5.0 ms/mmHg Relative ↑ 48% ↑ BRS 9.3 ms/mmHg Relative ↑ 76%

Note: n = number; m = male; f = female; y = year; min = minute; wk = week; HR_{max} = maximal heart rate; HRR = heart rate reserve; $\dot{V}O_{2peak}$ = peak oxygen consumption; $\dot{V}O_{2max}$ = maximal oxygen consumption; BRS = baroreflex sensitivity; TFTG = transfer function transfer gain; Seq = sequence; Phen = phenylephrine; α = alpha index; LF = low frequency; HF = high frequency; POTS = postural orthostatic tachycardia syndrome; COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease

APPENDIX IX: BRS FOLLOWING A SINGLE BOUT OF EXERCISE: SUMMARY OF STUDIES

Table A10. BRS following a single bout of exercise: summary of studies

Author (year)	Participant characteristics	Fitness level	Exercise intervention	Time points	BRS (ms/mmHg)	Measurement posture
Stuckey *et al* (2012)	n = 9; m; 19 ± 0.4 y; healthy		Single Wingate sprint Multiple Wingate interval sprints	Baseline, + 60, 120 min	BRS_{Seq}	Supine and standing
Niemelä *et al* (2008)	n = 12; m; 31 ± 3 y; healthy	VO_{2max} ($ml \cdot kg^{-1}min^{-1}$) 54 ± 7	40 min cycle 50% WL 40 min resistance light/ heavy 40 min control: sitting, no exercise	Baseline, + 30, 60, 90, 120, 150, 180 min	BRS_{Seq} BRS_{TFTG}	Semi-recumbant
Raczac *et al* (2005)	n = 16; m; 20 ± 2 y; healthy		30 min 65% HR_{max} (220 - age)	Baseline, + 60 min	BRS_{TFTG} BRS_{Phen}	Supine
Terziotti *et al* (2001)	n = 12; m; 28 ± 4 y; healthy	AT ($W \cdot min^{-1}$): 248 ± 29W 171 ± 5 $beats \cdot min^{-1}$	20 min cycle 50% WL 20 min cycle 80% WL	Baseline, + 15, 60, 180 min	BRS_{TFTG}	Sitting
Halliwill *et al* (1996)	n = 12, 7 m & 5 f; 24 ± 4 y; healthy	VO_{2peak} ($ml \cdot kg^{-1}min^{-1}$) Within normal range: 25.2 - 42.0	60 min cycle 60% VO_{2peak}	Basline, + 10, 55, 100, 145 min	BRS_{NP}	Supine
Piepoli *et al* (1993)	n = 10, 9 m & 1 f; 31 ± 3 y; healthy		Cycle: maximal exercise bout Control: standing for 30 min	Baseline, + 5, 20, 30, 45, 55 min (spectral) Baseline, +10, 30, 60 min	$BRS_{\alpha LF}$ $BRS_{\alpha HF}$ BRS_{Phen}	Supine
Ploutz et al (1993)	n = 8; m; 32 ± 2 y; healthy		Resistance supine exercise: 6 sets of 10 reps Control: supine, no exercise	Baseline, + 3, 6, 9, 12, 24 h	BRS_{NP}	Supine
Convertino and Adams (1991)	n = 8; m; 32 ± 6 y; healthy		Cycle: maximal supine exercise bout Control: no exercise	Baseline, + 3, 6, 12, 18, 24 h	BRS_{NP}	Supine
Somers *et al* (1985)	n = 12; borderline hypertensive		Cycle: maximal exercise bout	Baseline, + 10, 20, 40, 60 min	BRS_{Phen}	Supine

Note: n = number; m = male; f = female; y = year; h = hour; min = minute; VO_{2max} = maximal oxygen consumption; VO_{2peak} = peak oxygen consumption; ml = millilitre; kg = kilogram; W = watts; reps = repetitions; BRS = baroreflex sensitivity; Seq = sequence; TFLF = transfer function transfer gain; PE = phenylephrine; NP = neck pressure; α = alpha index; LF = low frequency; HF = high frequency; WL = work load

APPENDIX X: PARTICIPANT RECRUITMENT AND RETAINMENT

Appendix X(a): Participant recruitment and retainment for the reproducibility study

Over 14 months 130 participants provided initial interest in taking part in the study. Following meetings with all participants and discussing the testing procedures 75 participants were booked in for testing. Of those participants:

- 47 participants completed the testing
- 3 participants were required to retest due to equipment failure but did not retest
- 3 participants experienced an adverse response to the tilt procedure and did not continue testing
- 5 participants completed familiarisation and then did not want to continue testing
- 1 participant left the university before testing
- 9 participants failed to turn up for testing and became unavailable to contact
- 5 participants cancelled their testing commitment
- 2 participants were unsuitable for testing

Appendix X(b): Participant recruitment/ retainment for the exercise study

Over 14 months 26 participants showed initial interest in taking part in the study. Following meeting with all participants and discussing the testing procedures 18 participants were booked in for testing. Of those participants:

- 9 participants completed the testing
- 2 participants experienced an adverse response to the tilt procedure and did not continue testing
- 2 participants completed familiarisation and then did not want to continue testing
- 1 participant left the university
- 1 participant failed to turn up for testing and became unavailable to contact
- 2 participants cancelled their testing commitment

- 1 participant was unsuitable for testing

Note: Although a few participants experienced adverse responses to the testing procedure no serious incidents occurred with all of the participants recovering quickly and able to leave the cardiovascular laboratory without assistance.

APPENDIX XI: HEALTH QUESTIONNAIRE

UNIVERSITY OF
GLOUCESTERSHIRE

SPORT & EXERCISE LABORATORIES

Health Questionnaire

About this questionnaire:

The purpose of this questionnaire is to gather information about your health and lifestyle. We will use this information to decide whether you are eligible to take part in the testing for which you have volunteered. It is important that you answer the questions truthfully. The information you give will be treated in confidence. Your completed form will be stored securely for 5 years and then destroyed.

Section 1, which has been completed by the tester, provides basic information about the testing for which you have volunteered. Sections 2 to 7 are for you to complete: please circle the appropriate response or write your answer in the space provided. Please also complete section 8. Sections 9 and 10 will be completed by the tester, after you have completed sections 2 to 8.

Section 1: The testing (completed by tester)

To complete the testing for which you have volunteered you will be required to undertake:

Moderate exercise (i.e. exercise that makes you breathe more heavily than you do at rest but not so heavily that you are unable to maintain a conversation)

Vigorous exercise (i.e. exercise that makes you breathe so heavily that you are unable to maintain a conversation)

The testing involves:

Walking	Generating or absorbing high forces through your arms
Running	Generating or absorbing high forces through your shoulders
Cycling	Generating or absorbing high forces through your trunk
Rowing	Generating or absorbing high forces through your hips
Swimming	Generating or absorbing high forces through your legs
Jumping	

Section 2: General information

Name: .....…..…...…….. Sex: M F Age:

Height (approx.): .....……..…….. Weight (approx.):

Section 3: Initial considerations

1. Do any of the following apply to you? N/Y

   a) I have HIV, Hepatitis A, Hepatitis B or Hepatitis C
   b) I am pregnant
   c) I have a muscle or joint problem that could be aggravated by the testing described in section 1
   d) I am feeling unwell today
   e) I have had a fever in the last 7 days

(If you have answered "Yes" to question 1, go straight to section 8)

Section 4: Habitual physical activity

2a. Do you typically perform moderate exercise (as defined in section 1) N/Y

for 20 minutes or longer at least twice a week?

2b. Have you performed this type of exercise within the last 10 days? N/Y

3a. Do you typically perform vigorous exercise (as defined in section 1) N/Y

at least once a week?

3b. Have you performed this type of exercise within the last 10 days? N/Y

Section 5: Known medical conditions

4. Do **any** of the following apply to you? N/Y

   a) I have had insulin-dependent diabetes for more than 15 years
   b) I have insulin-dependent diabetes and am over 30 years old
   c) I have non-insulin-dependent diabetes and am over 35 years old

5. Have you ever had a stroke? N/Y

6. Has your doctor ever said you have heart trouble? N/Y

7. Do **both** of the following apply to you? N/Y
   a) I take asthma medication
   b) I have experienced shortness of breath or difficulty with breathing in the last 4 weeks?
8. Do you have any of the following: cancer, COPD, cystic fibrosis, other lung disease, liver disease, kidney disease, mental illness, osteoporosis, severe arthritis, a thyroid problem? N/Y

(If you have answered "Yes" to any questions in section 5, go straight to section 8.)

Section 6: Signs and symptoms

9. Do you often have pains in your heart, chest, or the surrounding areas? N/Y

10. Do you experience shortness of breath, either at rest or with mild exertion? N/Y

11. Do you often feel faint or have spells of severe dizziness? N/Y

12. Have you, in the last 12 months, experienced difficulty with breathing when lying down or been awakened at night by shortness of breath? N/Y

13. Do you experience swelling or a build up of fluid in or around your ankles? N/Y

14. Do you often get the feeling that your heart is racing or skipping beats, either at rest or during exercise? N/Y

15. Do you regularly get pains in your calves and lower legs during exercise that is not due to soreness or stiffness? N/Y

16. Has your doctor ever told you that you have a heart murmur? N/Y

17. Do you experience unusual fatigue or shortness of breath during everyday activities? N/Y

(If you have answered "Yes" to any questions in section 6, go straight to section 8.)

Section 7: Risk factors

18. Does **either** of the following apply to you? N/Y

    a) I smoke cigarettes on a daily basis
    b) I stopped smoking cigarettes on a daily basis less than 6 months ago

19. Has your doctor ever told you that you have high blood pressure? N/Y

20. Has your doctor ever told you that you have high cholesterol? N/Y

21. Has your father or any of your brothers had a heart attack, heart surgery, or a stroke before the age of 55? N/Y

22. Has your mother or any of your sisters had a heart attack, heart surgery, or a stroke before the age of 65? N/Y

23. Do **any** of the following apply to you? N/Y

    a) I have had insulin-dependent diabetes for less than 15 years
    b) I have insulin-dependent diabetes and am 30 or younger
    c) I have non-insulin-dependent diabetes and am 35 or younger

Section 8: Signatures

Participant: ……..Date: ..…….…….....

Guardian*: .....…….……..... Date: ..…….…….....
(*Required only if the participant is under 18 years of age.)

Section 9: Additional risk factors (to be completed by the tester if relevant)

24. Is the participant's body mass index >30 kg/m^2? No Yes

25. Has the participant answered no to questions 2a **and** 3a? No Yes

Section 10: Eligibility (to be completed by the tester)

26. Is the participant eligible for the testing? No Yes

Name (of tester): .....…….....……

Signature: ……

Date: ……...….……...

APPENDIX XII: INFORMED CONSENT FORM

UNIVERSITY OF GLOUCESTERSHIRE

SPORT & EXERCISE LABORATORIES

Informed Consent Form

Description of study:

I have had full details of the tests I am about to complete explained to me. I understand the risks and benefits involved, and that I am free to withdraw from the tests at any point. I confirm that I have completed a health questionnaire, and I am in a fit condition to undertake the required exercise.

Name: .....

Signed: .....… Date: .....……

Name of Guardian*: .....…….

Signed*: .....…… Date* .....…….

Tester: .....……

Signed: .....….. Date: .....…….

*to be completed only if the participant is under 18 years of age

APPENDIX XIII: LETTER TO PARTICIPANTS FOR THE REPRODUCIBILITY STUDY

From: Linda Reynolds (sXXXXXXX)
University of Gloucestershire

Date:

Dear

Re: **Familiarisation and Reproducibility Study**

Thank you for taking part in my post graduate research project. I have enclosed an explanation of participation.

Your dates and times for your visits to the cardiovascular laboratory (TC236a) at the Oxstalls Campus, School of Sport & Exercise, University of Gloucestershire are as follows:

	Date	Time
Familiarisation (TC236a)		
Reliability Study Visit 1 (TC236a)		
Reliability Study Visit 2 (TC236a)		

Please note the reproducibility study visit 2 must be undertaken 24 h following the reproducibility study visit 1 at the time specified. If you need to change the time(s) and date(s) of your visits please contact me immediately.

My contact numbers are as follows:

Home telephone number: XXXXXXXXXX
Mobile telephone number: XXXXXXXXXX
Email address: XXXXXXXXXXXXXXXX

My thanks again for your proposed participation and please do not hesitate to contact me should you require any further information.

Linda Reynolds
Enc.

Research title

Acute post-exercise cardiovascular responses in healthy participants

Explanation

This research project will investigate the influence of intensity, duration and mode of exercise on baroreflex sensitivity (BRS) post-exercise. The first study undertaken is a reproducibility study of the BRS assessment.

Familiarisation with the equipment and collection of baseline anthropometric measurements and characteristics will be undertaken prior to the reproducibility study. This will involve one visit to the cardiovascular laboratory (TC236a). Participants should wear loose comfortable clothing i.e. tracksuit bottoms or shorts, t-shirt and appropriate footwear during the visit. The completion of a health questionnaire and consent form is required and body mass, body stature, baseline heart rate (HR) and baseline blood pressure (BP) measurements will be taken.

Following familiarisation, the reproducibility study will be undertaken. Two visits to the cardiovascular laboratory (TC236a) are required. Both visits will require measurement of BP at the finger by the use of the Portapres which is a non-invasive automated system using servo-plethysmomanometry and R-R interval (RRI) data collection by use of an ECG which employs three chest pads. The collection of data will be undertaken in a supine position (lying down) and in a 60º upward tilt position. Participants should wear loose comfortable clothing i.e. tracksuit bottoms or shorts, t-shirt and appropriate footwear during the visit. A more comprehensive guideline for each visit is given below.

All testing has been cleared with the University of Gloucestershire Research Ethics Committee.

Please adhere to the pre-testing condition guidelines that are provided below for each laboratory visit:

BEFORE ALL TESTS

Please ensure that eating, drinking and exercise conditions are the same for ALL tests.

- **Do not drink alcohol 24 hours before each test**
- **Do not drink caffeine on day of each test**
- **Do not eat anything 3 hours before each test**
- **Do not drink anything 1 hour before each test**
- **Do not exercise 48 hours before each test**
- **Ensure you are adequately hydrated before each test**

Familiarisation visit

Completion of full health questionnaire and consent form
Body mass and body stature taken
Baseline BP will be undertaken three times (two minute intervals) via automated Dynapulse BP monitoring equipment
Baseline HR will be taken while sitting quietly for 20 min with Polar watch and chest strap.
Familiarisation with measurement equipment and tilt table in supine and tilt positions
(Approximate length of visit 2 h)

Reliability study
(Please see attached schematic)

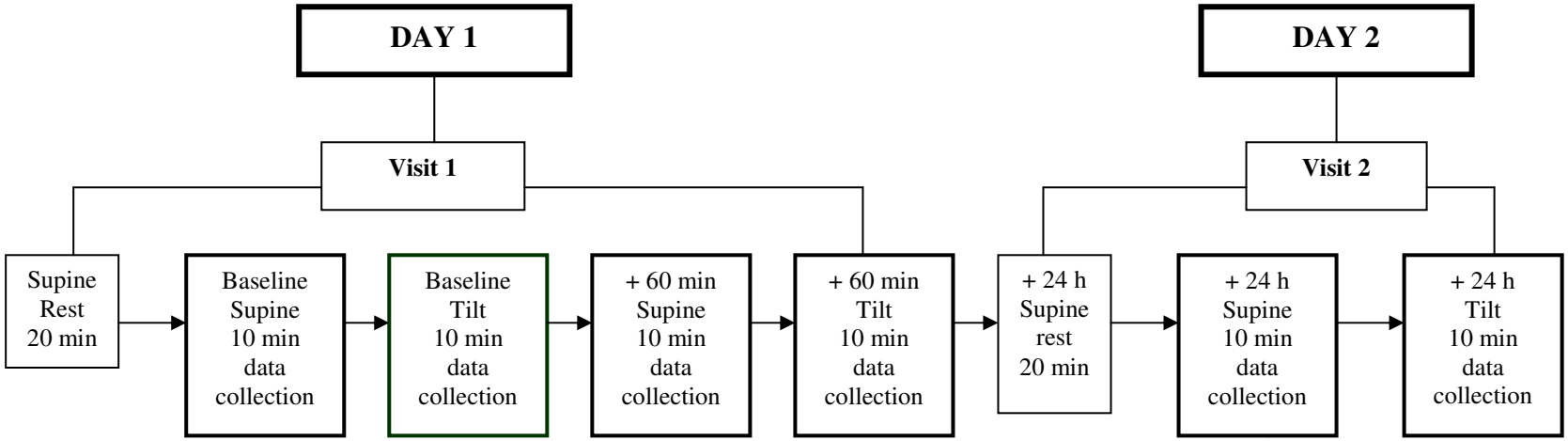
Visit 1

Attachment of Portapres equipment and ECG equipment to participant
20 min lying quietly to achieve baseline conditions
Collection of BP and RRI data in supine position and following 60º upward tilt
One hour later, collection of BP and RRI data in supine position and following 60º upward tilt
(Approximate length of visit 2.5 h)

Visit 2

Attachment of Portapres equipment and ECG equipment to participant
20 min lying quietly to achieve baseline conditions
Collection of BP and RRI data in supine position and following 60º upward tilt
(Approximate length of visit 1.5 h)

Please note: Participants may stop the tests at any time should they feel uncomfortable and/ or unwilling to proceed further



Supine and tilt testing procedures for BRS assessment for the reproducibility study

APPENDIX XIV: LETTER TO PARTICIPANTS FOR THE EXERCISE STUDY

From: Linda Reynolds (sXXXXXXX)
University of Gloucestershire
Date:
Dear

Re: **Familiarisation and Exercise Study**

Thank you for taking part in my post graduate research project. I have enclosed an explanation of participation.

Your dates and times for your visits to the main physiology laboratory (SC126) and the cardiovascular laboratory (TC236a) at the Oxstalls Campus, School of Sport & Exercise, University of Gloucestershire are as follows:

	Date	Time
Familiarisation (SC126 & TC236a)		
Exercise Study Visit 1 (TC236a)		
Exercise Study Visit 2 (TC236a)		
Exercise Study Visit 3 (TC236a)		
Exercise Study Visit 4 (TC236a)		
Exercise Study Visit 5 (TC236a)		
Exercise Study Visit 6 (TC236a)		

Please note that visits 2, 4 and 6 must be undertaken 24 h following visits 1, 3 and 5. If you need to change the time(s) and date(s) of your visits please contact me immediately.

My contact numbers are as follows:

Home telephone number: XXXXXXXXXXX
Mobile telephone number: XXXXXXXXXXX
Email address: XXXXXXXXXXXXXXXXXX

My thanks again for your proposed participation and please do not hesitate to contact me should you require any further information.

Linda Reynolds (Enc)

Research title

Acute post-exercise cardiovascular responses in healthy participants

Explanation

This research project will investigate the influence of intensity of exercise on baroreflex sensitivity (BRS) post-exercise.

Familiarisation with testing equipment and collection of baseline anthropometric measurements and characteristics will be undertaken prior to the exercise study. This will involve one visit to the main physiology laboratory (SC126) and to the cardiovascular laboratory (TC236a). Participants should wear loose comfortable clothing i.e. tracksuit bottoms or shorts, t-shirt and appropriate footwear during the visit. The completion of a health questionnaire and consent form is required and body mass, body stature, baseline heart rate (HR) and baseline blood pressure (BP) measurements will be taken.

Following the familiarisation procedure, a further six visits to the cardiovascular laboratory (TC236a) are required. Three visits will require an exercise condition to be undertaken. All visits will require measurement of BP at the finger by the use of the Portapres which is a non-invasive automated system using servo-plethysmomanometry and R-R interval (RRI) data collection by use of an ECG which employs three chest pads. The collection of data will be undertaken in a supine position (lying down) and in a 60º upward tilt position. Participants should wear loose comfortable clothing i.e. tracksuit bottoms or shorts, t-shirt and appropriate footwear during the visit. A more comprehensive guideline for each visit is given below.

All testing has been cleared with the University of Gloucestershire Research Ethics Committee.

Please adhere to the pre-testing condition guidelines that are provided below for each laboratory visit:

BEFORE ALL TESTS

Please ensure that eating, drinking and exercise conditions are the same for ALL tests:

- **Do not drink alcohol 24 hours before each test**
- **Do not drink caffeine on day of each test**
- **Do not eat anything 3 hours before each test**
- **Do not drink anything 1 hour before each test**
- **Do not exercise 48 hours before each test**
- **Ensure you are adequately hydrated before each test**

Familiarisation visit

Completion of full health questionnaire and consent form
Body mass and body stature taken
Baseline BP will be undertaken three times (two minute intervals) via automated Dynapulse BP monitoring equipment
Baseline HR will be taken while sitting quietly for 20 min with Polar watch/ chest strap
Familiarisation with measurement equipment and tilt table in supine and tilt positions
Familiarisation with cycle ergometer (Lode)
Familiarisation with gas collection equipment i.e. mouthpiece and nose clip
VO_{2peak} test: the VO_{2peak} test is a ramp protocol undertaken on a cycle ergometer starting at 25 W and increasing 25 W/ min until exhaustion. Participants will be required to wear a heart rate monitor throughout in addition to the gas collection equipment
(Approximate length of visit 3 h)

Intensity Study (Please see attached schematic)

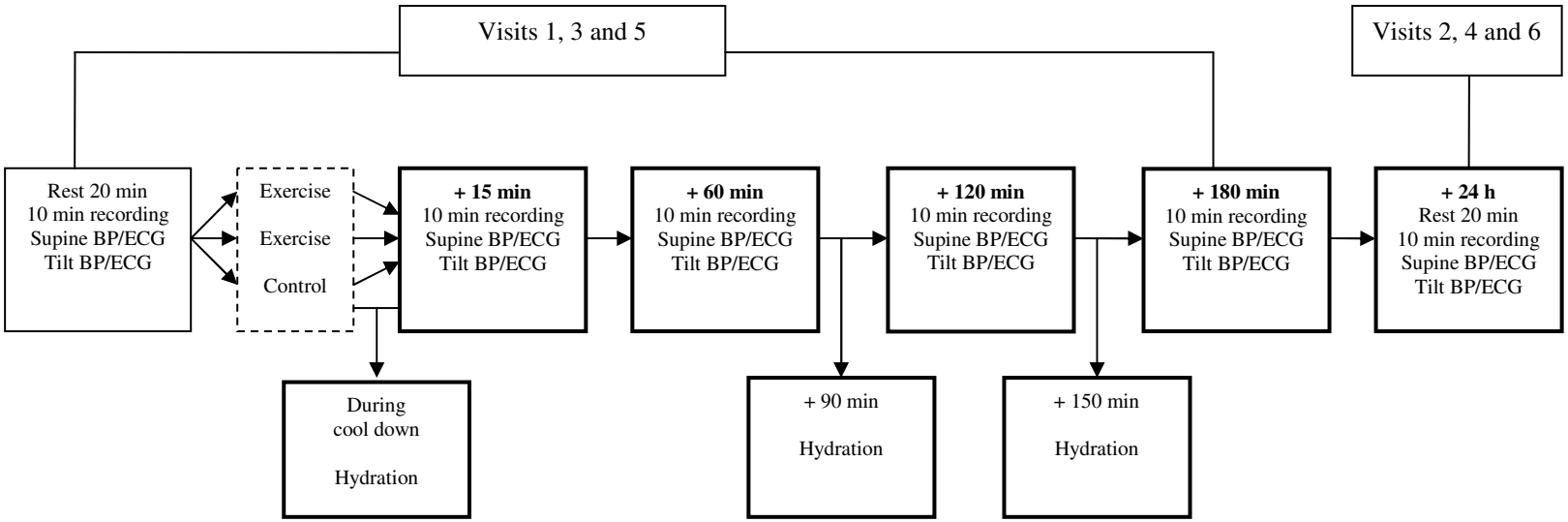
Visits 1, 3 and 5
Completion of full health questionnaire and consent form. Body mass and stature taken
Attachment of Portapres equipment and ECG equipment to participant
20 min lying quietly to achieve baseline conditions
Collection of BP and RRI data in supine position and following 60º upward tilt
Randomised exercise condition of either:

- 75% of maximal work rate
- 40% of maximal work rate
- No exercise condition (sitting quietly)

+ 15 min post exercise: collection of BP and RRI data in supine position and following 60º upward tilt
+ 60 min post exercise: collection of BP and RRI data in supine position and following 60º upward tilt
+ 120 min post exercise: collection of BP and RRI data in supine position and following 60º upward tilt
+ 180 min post exercise: collection of BP and RRI data in supine position and following 60º upward tilt
(Approximate length of visit 6 h)

Visits 2, 4, and 6
Attachment of Portapres equipment and ECG equipment to participant
20 min lying quietly to achieve baseline conditions
+ 24 h post exercise: collection of BP and RRI data in supine position and following 60º upward tilt
(Approximate length of visit 1.5 h)

Participants may stop the tests at any time should they feel uncomfortable and/ or unwilling to proceed further



The above procedure would be undertaken three times in a randomised exercise order of: (i) exercise condition 40% maximum work rate; (ii) exercise condition 75% maximum work rate; (iii) no exercise control condition

APPENDIX XV: SCALE FOR RATE OF PERCEIVED EXERTION

Borg's 15 point Scale of Rate of Perceived Exertion (RPE)

- 6 - 20% effort
- 7 - 30% effort - Very, very light (Rest)
- 8 - 40% effort
- 9 - 50% effort - Very light - gentle walking
- 10 - 55% effort
- 11 - 60% effort - Fairly light
- 12 - 65% effort
- 13 - 70% effort - Somewhat hard - steady pace
- 14 - 75% effort
- 15 - 80% effort - Hard
- 16 - 85% effort
- 17 - 90% effort - Very hard
- 18 - 95% effort
- 19 - 100% effort - Very, very hard
- 20 - Exhaustion

Borg, G. (1998). Borg's Perceived Exertion and Pain Scales. Champaign: Human Kinetics

APPENDIX XVI: DATASETS OF BRS PARAMETERS

Dataset 1: the bold denotes the values which have been compiled from taking the average of the two measures either side of the missing value.

Table A11. Dataset 1: BRS parameters prior to and + 15, 60, 120, 180 min and 24 h following three conditions of control condition (no exercise), 40% WR_{max} and 75% WR_{max}

BRS (ms/mmHg) (± SD)

	Baseline			15 min			60 min		
	C/Condition	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*
BRS_{UpUp} (S)	32.18 (14.45)	25.23 (11.44)	25.50 (10.37)	**33.97 (13.35)**	21.49 (7.69)	11.50 (9.74)	30.71 (20.27)	25.86 (12.42)	**21.09 (14.24)**
BRS_{UpUp} (T)	9.83 (2.53)	10.24 (2.05)	10.33 (3.00)	11.53 (3.90)	10.74 (4.71)	7.60 (2.69)	12.10 (3.99)	10.57 (3.53)	8.73 (2.58)
$BRS_{DownDown}$ (S)	27.30 (10.33)	23.08 (10.64)	24.01 (9.79)	**30.93 (17.60)**	20.41 (7.60)	11.38 (10.01)	24.64 (5.94)	23.51 (7.77)	**18.91 (7.40)**
$BRS_{DownDown}$ (T)	8.13 (2.76)	9.11 (4.10)	7.97 (2.69)	10.00 (3.56)	7.62 (4.29)	4.90 (3.16)	9.08 (3.74)	7.14 (3.11)	5.44 (1.81)
$BRS_{\alpha LF}$ (S)	13.88 (6.42)	15.09 (5.96)	16.34 (8.92)	**23.10 (8.49)**	15.82 (6.11)	7.37 (6.42)	21.04 (4.01)	13.90 (5.51)	**12.05 (5.09)**
$BRS_{\alpha LF}$ (T)	8.86 (2.17)	9.49 (2.45)	8.78 (2.21)	10.17 (2.60)	8.63 (2.56)	5.28 (2.62)	9.91 (2.69)	8.97 (3.01)	6.81 (2.05)
BRS_{TFTG} (S)	15.07 (5.48)	16.00 (5.82)	17.26 (6.51)	**24.65 (8.67)**	14.43 (5.73)	6.96 (5.38)	20.7 (5.73)	17.66 (7.66)	**12.12 (6.06)**
BRS_{TFTG} (T)	7.92 (2.06)	8.36 (2.30)	8.09 (2.02)	10.14 (2.42)	8.25 (3.46)	4.92 (2.67)	9.58 (2.58)	8.15 (3.16)	6.23 (1.69)
	120 min			180 min			24 h		
	C/Condition	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*
BRS_{UpUp} (S)	**34.54 (13.32)**	24.71 (14.56)	23.44 (12.20)	34.66 (11.95)	25.04 (9.72)	24.50 (8.10)	23.30 (9.28)	30.17 (14.53)	28.89 (13.52)
BRS_{UpUp} (T)	10.46 (3.57)	10.16 (2.83)	9.81 (3.21)	10.12 (2.09)	10.90 (4.62)	10.62 (3.72)	9.61 (2.66)	**11.14 (4.23)**	11.04 (3.51)
$BRS_{DownDown}$ (S)	23.22 (7.31)	22.57 (8.04)	21.98 (14.24)	25.53 (9.34)	21.09 (7.12)	21.38 (7.92)	20.33 (6.36)	23.21 (8.14)	23.78 (6.55)
$BRS_{DownDown}$ (T)	8.91 (2.37	7.90 (3.13)	6.80 (2.21)	8.49 (1.84)	8.22 (3.43)	7.59 (2.76)	7.30 (2.09)	**9.08 (3.38)**	8.37 (2.47)
$BRS_{\alpha LF}$ (S)	19.32 (7.84)	18.18 (8.70)	16.94 (6.04)	19.71 (4.76)	18.81 (7.14)	18.10 (7.99)	16.23 (6.93)	15.97 (6.11)	17.99 (8.77)
$BRS_{\alpha LF}$ (T)	10.04 (2.58)	9.04 (2.09)	8.54 (2.67)	9.93 (2.44)	9.68 (3.11)	9.43 (5.01)	8.23 (2.34)	**10.01 (3.18)**	9.39 (2.29)
BRS_{TFTG} (S)	19.10 (6.42)	16.30 (7.04)	16.29 (5.95)	19.36 (5.07)	17.96 (7.04)	16.88 (7.22)	15.23 (5.98)	17.67 (5.71)	16.80 (6.53)
BRS_{TFTG} (T)	9.51 (2.25)	8.41 (2.28)	7.82 (2.45)	9.15 (1.91)	9.23 (3.48)	9.19 (4.52)	7.29 (2.00)	**9.26 (3.00)**	8.94 (2.59)

Note: Parameters are group mean. SD is standard deviation; LF is low frequency; TFTG is Transfer Function; (S) is supine (T) is tilt

Dataset 2(i): the bold denotes the values which have been compiled from taking the average using a division of 9.

Table A12. Dataset 2(i): BRS parameters prior to and + 15, 60, 120, 180 min and 24 h following three conditions of control condition (no exercise), 40% WR_{max} and 75% WR_{max}

BRS (ms/mmHg) (± SD)

	Baseline			15 min			60 min		
	C/Condition	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*
BRS_{UpUp} (S)	32.18 (14.45)	25.23 (11.44)	25.50 (10.37)	**34.71 (12.94)**	21.49 (7.69)	11.50 (9.74)	30.71 (20.27)	25.86 (12.42)	**22.36 (13.49)**
BRS_{UpUp} (T)	9.83 (2.53)	10.24 (2.05)	10.33 (3.00)	11.53 (3.90)	10.74 (4.71)	7.60 (2.69)	12.10 (3.99)	10.57 (3.53)	8.73 (2.58)
$BRS_{DownDown}$ (S)	27.30 (10.33)	23.08 (10.64)	24.01 (9.79)	**31.25 (17.47)**	20.41 (7.60)	11.38 (10.01)	24.64 (5.94)	23.51 (7.77)	**19.99 (6.28)**
$BRS_{DownDown}$ (T)	8.13 (2.76)	9.11 (4.10)	7.97 (2.69)	10.00 (3.56)	7.62 (4.29)	4.90 (3.16)	9.08 (3.74)	7.14 (3.11)	5.44 (1.81)
$BRS_{\alpha LF}$ (S)	13.88 (6.42)	15.09 (5.96)	16.34 (8.92)	**24.33 (7.19)**	15.82 (6.11)	7.37 (6.42)	21.04 (4.01)	13.90 (5.51)	**12.40 (4.89)**
$BRS_{\alpha LF}$ (T)	8.86 (2.17)	9.49 (2.45)	8.78 (2.21)	10.17 (2.60)	8.63 (2.56)	5.28 (2.62)	9.91 (2.69)	8.97 (3.01)	6.81 (2.05)
BRS_{TFTG} (S)	15.07 (5.48)	16.00 (5.82)	17.26 (6.51)	**25.81 (7.50)**	14.43 (5.73)	6.96 (5.38)	20.7 (5.73)	17.66 (7.66)	**12.33 (5.97)**
BRS_{TFTG} (T)	7.92 (2.06)	8.36 (2.30)	8.09 (2.02)	10.14 (2.42)	8.25 (3.46)	4.92 (2.67)	9.58 (2.58)	8.15 (3.16)	6.23 (1.69)
	120 min			180 min			24 h		
	C/Condition	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*
BRS_{UpUp} (S)	**34.53 (13.33)**	24.71 (14.56)	23.44 (12.20)	34.66 (11.95)	25.04 (9.72)	24.50 (8.10)	23.30 (9.28)	30.17 (14.53)	28.89 (13.52)
BRS_{UpUp} (T)	10.46 (3.57)	10.16 (2.83)	9.81 (3.21)	10.12 (2.09)	10.90 (4.62)	10.62 (3.72)	9.61 (2.66)	**10.96 (4.25)**	11.04 (3.51)
$BRS_{DownDown}$ (S)	23.22 (7.31)	22.57 (8.04)	21.98 (14.24)	25.53 (9.34)	21.09 (7.12)	21.38 (7.92)	20.33 (6.36)	23.21 (8.14)	23.78 (6.55)
$BRS_{DownDown}$ (T)	8.91 (2.37	7.90 (3.13)	6.80 (2.21)	8.49 (1.84)	8.22 (3.43)	7.59 (2.76)	7.30 (2.09)	**8.30 (2.72)**	8.37 (2.47)
$BRS_{\alpha LF}$ (S)	19.32 (7.84)	18.18 (8.70)	16.94 (6.04)	19.71 (4.76)	18.81 (7.14)	18.10 (7.99)	16.23 (6.93)	15.97 (6.11)	17.99 (8.77)
$BRS_{\alpha LF}$ (T)	10.04 (2.58)	9.04 (2.09)	8.54 (2.67)	9.93 (2.44)	9.68 (3.11)	9.43 (5.01)	8.23 (2.34)	**9.42 (2.87)**	9.39 (2.29)
BRS_{TFTG} (S)	19.10 (6.42)	16.30 (7.04)	16.29 (5.95)	19.36 (5.07)	17.96 (7.04)	16.88 (7.22)	15.23 (5.98)	17.67 (5.71)	16.80 (6.53)
BRS_{TFTG} (T)	9.51 (2.25)	8.41 (2.28)	7.82 (2.45)	9.15 (1.91)	9.23 (3.48)	9.19 (4.52)	7.29 (2.00)	**8.63(2.58)**	8.94 (2.59)

Note: Parameters are group mean. SD is standard deviation; LF is low frequency; TF is Transfer Function; (S) is supine (T) is tilt

Dataset 2(ii): the bold denotes the values which have been compiled from taking the average using a division of 7 (for one time point with two 'missing' values) and a division of 8 (for time points with one 'missing value').

Table A13. Dataset 2(ii): BRS parameters prior to and + 15, 60, 120, 180 min and 24 h following three conditions of control condition (no exercise), 40% WR_{max} and 75% WR_{max}

BRS (ms/mmHg) (± SD)

	Baseline			15 min			60 min		
	C/Condition	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*
BRS_{UpUp} (S)	32.18 (14.45)	25.23 (11.44)	25.50 (10.37)	**35.14 (12.44)**	21.49 (7.69)	11.50 (9.74)	30.71 (20.27)	25.86 (12.42)	**22.64 (13.47)**
BRS_{UpUp} (T)	9.83 (2.53)	10.24 (2.05)	10.33 (3.00)	11.53 (3.90)	10.74 (4.71)	7.60 (2.69)	12.10 (3.99)	10.57 (3.53)	8.73 (2.58)
$BRS_{DownDown}$ (S)	27.30 (10.33)	23.08 (10.64)	24.01 (9.79)	**32.87 (17.17)**	20.41 (7.60)	11.38 (10.01)	24.64 (5.94)	23.51 (7.77)	**20.24 (6.23)**
$BRS_{DownDown}$ (T)	8.13 (2.76)	9.11 (4.10)	7.97 (2.69)	10.00 (3.56)	7.62 (4.29)	4.90 (3.16)	9.08 (3.74)	7.14 (3.11)	5.44 (1.81)
$BRS_{\alpha LF}$ (S)	13.88 (6.42)	15.09 (5.96)	16.34 (8.92)	**24.63 (7.13)**	15.82 (6.11)	7.37 (6.42)	21.04 (4.01)	13.90 (5.51)	**12.55 (4.87)**
$BRS_{\alpha LF}$ (T)	8.86 (2.17)	9.49 (2.45)	8.78 (2.21)	10.17 (2.60)	8.63 (2.56)	5.28 (2.62)	9.91 (2.69)	8.97 (3.01)	6.81 (2.05)
BRS_{TFTG} (S)	15.07 (5.48)	16.00 (5.82)	17.26 (6.51)	**26.14 (7.44)**	14.43 (5.73)	6.96 (5.38)	20.7 (5.73)	17.66 (7.66)	**12.49 (5.95)**
BRS_{TFTG} (T)	7.92 (2.06)	8.36 (2.30)	8.09 (2.02)	10.14 (2.42)	8.25 (3.46)	4.92 (2.67)	9.58 (2.58)	8.15 (3.16)	6.23 (1.69)
	120 min			180 min			24 h		
	C/Condition	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*
BRS_{UpUp} (S)	**34.96(13.26)**	24.71 (14.56)	23.44 (12.20)	34.66 (11.95)	25.04 (9.72)	24.50 (8.10)	23.30 (9.28)	30.17 (14.53)	28.89 (13.52)
BRS_{UpUp} (T)	10.46 (3.57)	10.16 (2.83)	9.81 (3.21)	10.12 (2.09)	10.90 (4.62)	10.62 (3.72)	9.61 (2.66)	**11.10 (4.23)**	11.04 (3.51)
$BRS_{DownDown}$ (S)	23.22 (7.31)	22.57 (8.04)	21.98 (14.24)	25.53 (9.34)	21.09 (7.12)	21.38 (7.92)	20.33 (6.36)	23.21 (8.14)	23.78 (6.55)
$BRS_{DownDown}$ (T)	8.91 (2.37	7.90 (3.13)	6.80 (2.21)	8.49 (1.84)	8.22 (3.43)	7.59 (2.76)	7.30 (2.09)	**8.40 (2.70)**	8.37 (2.47)
$BRS_{\alpha LF}$ (S)	19.32 (7.84)	18.18 (8.70)	16.94 (6.04)	19.71 (4.76)	18.81 (7.14)	18.10 (7.99)	16.23 (6.93)	15.97 (6.11)	17.99 (8.77)
$BRS_{\alpha LF}$ (T)	10.04 (2.58)	9.04 (2.09)	8.54 (2.67)	9.93 (2.44)	9.68 (3.11)	9.43 (5.01)	8.23 (2.34)	**9.54 (2.85)**	9.39 (2.29)
BRS_{TFTG} (S)	19.10 (6.42)	16.30 (7.04)	16.29 (5.95)	19.36 (5.07)	17.96 (7.04)	16.88 (7.22)	15.23 (5.98)	17.67 (5.71)	16.80 (6.53)
BRS_{TFTG} (T)	9.51 (2.25)	8.41 (2.28)	7.82 (2.45)	9.15 (1.91)	9.23 (3.48)	9.19 (4.52)	7.29 (2.00)	**8.74 (2.56)**	8.94 (2.59)

Note: Parameters are group mean. SD is standard deviation; LF is low frequency; TF is Transfer Function; (S) is supine (T) is tilt

Dataset 4: the bold denotes the values which have been compiled from taking the average of available data. These values are virtually identical to table A13 dataset 2(ii) except the SD's are slightly higher in this table.

Table A14. Dataset 4: BRS parameters prior to and at + 15, 60, 120, 180 min and 24 h following three conditions of control condition (no exercise), 40% WR_{max} and 75% WR_{max}

BRS (ms/mmHg) (± SD)

	Baseline			15 min			60 min		
	C/Condition	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*
BRS_{UpUp} (S)	32.18 (14.45)	25.23 (11.44)	25.50 (10.37)	**35.14 (13.77)**	21.49 (7.69)	11.50 (9.74)	30.71 (20.27)	25.86 (12.42)	**22.64 (14.40)**
BRS_{UpUp} (T)	9.83 (2.53)	10.24 (2.05)	10.33 (3.00)	11.53 (3.90)	10.74 (4.71)	7.60 (2.69)	12.10 (3.99)	10.57 (3.53)	8.73 (2.58)
$BRS_{DownDown}$ (S)	27.30 (10.33)	23.08 (10.64)	24.01 (9.79)	**32.87 (19.83)**	20.41 (7.60)	11.38 (10.01)	24.64 (5.94)	23.51 (7.77)	**20.24 (6.66)**
$BRS_{DownDown}$ (T)	8.13 (2.76)	9.11 (4.10)	7.97 (2.69)	10.00 (3.56)	7.62 (4.29)	4.90 (3.16)	9.08 (3.74)	7.14 (3.11)	5.44 (1.81)
$BRS_{\alpha LF}$ (S)	13.88 (6.42)	15.09 (5.96)	16.34 (8.92)	**24.63 (7.63)**	15.82 (6.11)	7.37 (6.42)	21.04 (4.01)	13.90 (5.51)	**12.55 (5.20)**
$BRS_{\alpha LF}$ (T)	8.86 (2.17)	9.49 (2.45)	8.78 (2.21)	10.17 (2.60)	8.63 (2.56)	5.28 (2.62)	9.91 (2.69)	8.97 (3.01)	6.81 (2.05)
BRS_{TFTG} (S)	15.07 (5.48)	16.00 (5.82)	17.26 (6.51)	**26.14 (7.95)**	14.43 (5.73)	6.96 (5.38)	20.7 (5.73)	17.66 (7.66)	**12.49 (6.37)**
BRS_{TFTG} (T)	7.92 (2.06)	8.36 (2.30)	8.09 (2.02)	10.14 (2.42)	8.25 (3.46)	4.92 (2.67)	9.58 (2.58)	8.15 (3.16)	6.23 (1.69)
	120 min			180 min			24 h		
	C/Condition	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*	*C/Condition*	*40% WR max*	*75% WR max*
BRS_{UpUp} (S)	**34.96 (14.18)**	24.71 (14.56)	23.44 (12.20)	34.66 (11.95)	25.04 (9.72)	24.50 (8.10)	23.30 (9.28)	30.17 (14.53)	28.89 (13.52)
BRS_{UpUp} (T)	10.46 (3.57)	10.16 (2.83)	9.81 (3.21)	10.12 (2.09)	10.90 (4.62)	10.62 (3.72)	9.61 (2.66)	**11.10 (4.52)**	11.04 (3.51)
$BRS_{DownDown}$ (S)	23.22 (7.31)	22.57 (8.04)	21.98 (14.24)	25.53 (9.34)	21.09 (7.12)	21.38 (7.92)	20.33 (6.36)	23.21 (8.14)	23.78 (6.55)
$BRS_{DownDown}$ (T)	8.91 (2.37	7.90 (3.13)	6.80 (2.21)	8.49 (1.84)	8.22 (3.43)	7.59 (2.76)	7.30 (2.09)	**8.40 (2.89)**	8.37 (2.47)
$BRS_{\alpha LF}$ (S)	19.32 (7.84)	18.18 (8.70)	16.94 (6.04)	19.71 (4.76)	18.81 (7.14)	18.10 (7.99)	16.23 (6.93)	15.97 (6.11)	17.99 (8.77)
$BRS_{\alpha LF}$ (T)	10.04 (2.58)	9.04 (2.09)	8.54 (2.67)	9.93 (2.44)	9.68 (3.11)	9.43 (5.01)	8.23 (2.34)	**9.54 (3.04)**	9.39 (2.29)
BRS_{TFTG} (S)	19.10 (6.42)	16.30 (7.04)	16.29 (5.95)	19.36 (5.07)	17.96 (7.04)	16.88 (7.22)	15.23 (5.98)	17.67 (5.71)	16.80 (6.53)
BRS_{TFTG} (T)	9.51 (2.25)	8.41 (2.28)	7.82 (2.45)	9.15 (1.91)	9.23 (3.48)	9.19 (4.52)	7.29 (2.00)	**8.74 (2.74)**	8.94 (2.59)

Note: Parameters are group mean. SD is standard deviation; LF is low frequency; TF is Transfer Function; (S) is supine (T) is tilt

APPENDIX XVII: PRELIMINARY TESTING

Preliminary testing was undertaken to inform the present reproducibility and exercise studies. The preliminary testing included assessment for:

Appendix XVII (a): Sampling rate
Appendix XVII (b): Blood pressure drift over time and physiocal servo-adjustment
Appendix XVII (c): Hand-warming devices for successful Portapres operation
Appendix XVII (d) Work load for intensity criteria for exercise conditions

Appendix XVII (a) Assessment of sampling rate

A continuing equipment failure problem during data collection at a sampling rate of 800 Hz impacted upon the research process. It was considered possible that the equipment failure could have been due to the collection of data at 800 Hz and there would be very little difference in the final BRS outcome measures if the data was collected at a lower sampling rate. Thus a procedure was undertaken to evaluate the variance in BRS outcome measures from the same data which was sampled at different rates (800, 400 and 200 Hz) at dedicated time intervals to provide greater insight into the impact of sampling rate differences.

The optimal range for sampling of resting HR data has been reported to be 250 – 500 Hz (TFESC & TNASPE, 1996) or higher (Pinna *et al.*, 1994) and the employment of low sampling rates ($\geq$ 100 Hz to $<$ 200 Hz) may only be used satisfactorily with the interpolation of data to refine the R-wave fiducial point (Merri *et al.*, 1990; TFESC & TNASPE, 1996). This is because the use of an inappropriate sampling rate may cause aliasing i.e., the discrete sampling may change the apparent frequency, thus a sampling rate which is too low may produce inaccuracy in the determination of the R-wave fiducial point resulting in an altered power spectrum (Priestly, 2001; TFESC & TNASPE, 1996).

Graphical representation of sampling rate was obtained from ECG data recorded during preliminary testing (figure A1). The sampling rate was reduced from the original 800

Hz to 400 Hz and 200 Hz respectively. The higher sampling rate produced a better reconstruction of the sine wave and thus a more defined tip for the QRS complex fiducial point suggesting a higher sampling rate may provide more accurate R-R interval data.

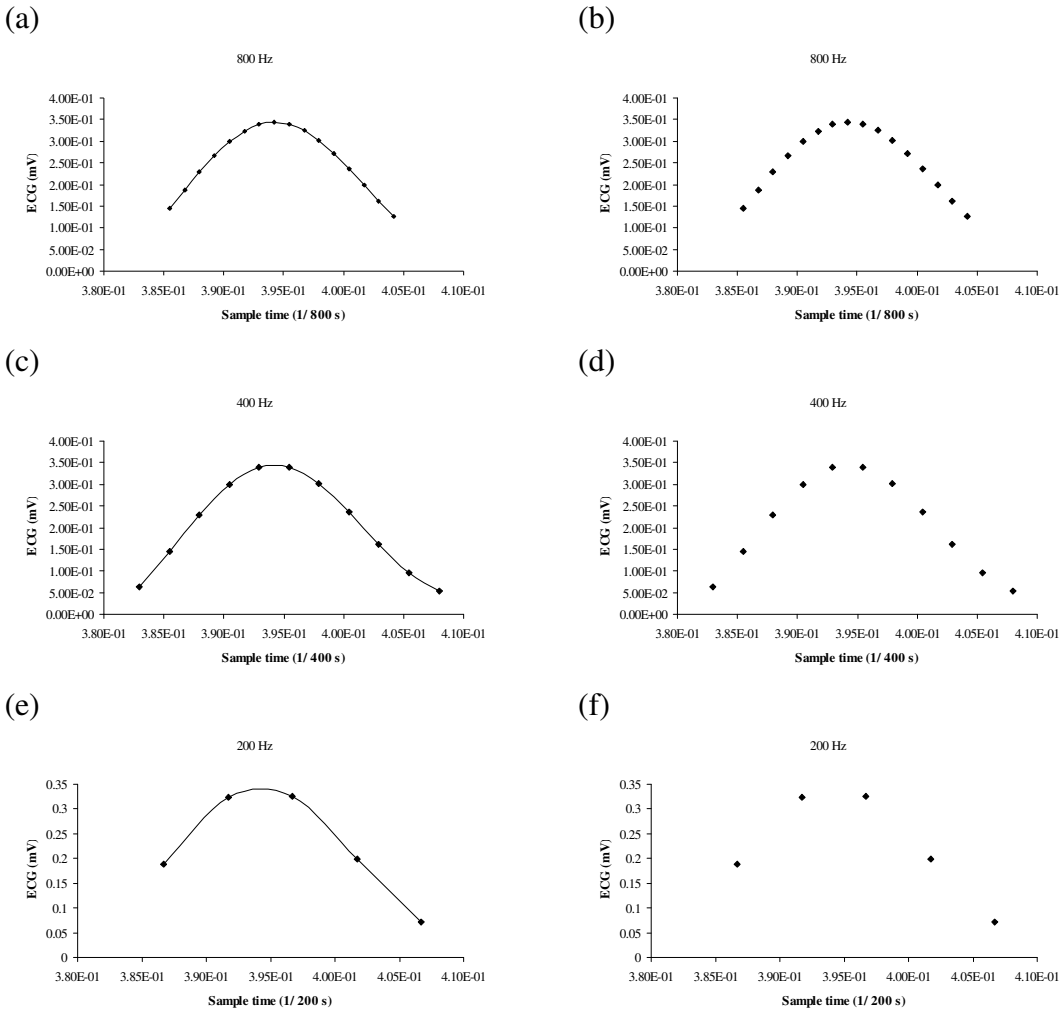


Figure A1. (a), (c) and (e) Sine wave at sampling rates of 800, 400 and 200 Hz with trendline and (b), (d) and (f) without trendline respectively for detection of QRS complex fiducial point

Beat-by-beat BP and HR data was collected over a 10 min period in resting supine conditions. Following data collection, the data was stored for later analysis. Dedicated software provided spectral ($BRS_{\alpha LF}$ and BRS_{TFTG}) and time (sequence: BRS_{UpUp}; $BRS_{DownDown}$) BRS outcome measures obtained from the same data sampled at 800 Hz

and then reduced to 400 Hz and 200 Hz over a 10 min interval, the first 5 min interval, the second 5 min interval and at each 1 min interval.

The spectral BRS measures provide small variances (-0.99 to 0.3 ms/mmHg) at the different sampling rates (tables A15; A16) which suggested there would be negligible impact when comparing like with like at different sampling rates.

The time BRS measures provided greater variances (-5.9 to 2.8 ms/mmHg) at the different sampling rates (tables A17; A18) and occasional very large variance was observed of 14.6 ms/mmHg (table A17: 10 min interval) and - 42.4 ms/mmHg (table A18: 6 min interval). These findings suggested a possible large impact when comparing like with like at different sampling rates with sequence BRS measures. However in practice, BRS measures would not be reported at individual 1 min intervals due to the lack of significance over such a short time period. A 3 min time period is the shortest collection period considered for an acceptable BRS measure (Parati *et al.*, 1995b) with sequence analysis reproducibility improved over longer duration periods (Parati *et al.*, 2000). Thus, the largest variance over a 5 min time period was - 5.9 ms/mmHg (table A18: second 5 min) and over a 10 min time period was – 2.9 ms/mmHg (table A18). Clearly, this is a greater BRS variance than that found with the spectral BRS measures over a 5 min interval (0.3 ms/mmHg) (table A15: first 5 min) and over a 10 min interval (0.29 ms/mmHg) (table A16).

Table A15. $BRS_{\alpha LF}$ (ms/mmHg) using same data with reduced sampling rates of 800, 400 and 200 (Hz)

Time	Sampling Rate			Differences		
	800	400	200	800/400	800/200	400/200
10 min	18.7	18.7	18.9	0.0	0.2	0.2
First 5 min	15.6	15.7	15.9	0.1	0.3	0.2
Second 5 min	19.4	19.5	19.6	0.1	0.2	0.1
1 min	18.0	18.0	18.1	0.0	0.1	0.1
2 min	13.2	13.2	13.2	0.0	0.0	0.0
3 min	21.3	21.4	21.5	0.1	0.2	0.1
4 min	20.5	20.5	20.2	0.0	-0.3	-0.3
5 min	15.0	15.1	15.2	0.1	0.2	0.1
6 min	11.7	11.8	11.8	0.1	0.1	0.0
7 min	9.2	9.3	9.4	0.1	0.2	0.1
8 min	17.3	17.3	17.3	0.0	0.0	0.0
9 min	14.8	14.9	15.0	0.1	0.2	0.1
10 min	20.1	20.2	20.2	0.1	0.1	0.0

Table A16. BRS_{TFTG} (ms/mmHg) using same data with reduced sampling rates of 800, 400 and 200 (Hz)

Time	Sampling Rate			Differences		
	800	400	200	800/400	800/200	400/200
10 min	20.36	20.47	20.65	0.11	0.29	0.18
First 5 min	21.03	21.13	20.96	0.10	-0.07	-0.17
Second 5 min	22.55	22.62	22.74	0.07	0.19	0.12
1 min	15.39	15.53	15.54	0.14	0.15	0.01
2 min	26.14	26.05	26.31	-0.09	0.17	0.26
3 min	22.93	23.10	23.14	0.17	0.21	0.04
4 min	25.32	25.41	24.42	0.09	-0.90	-0.99
5 min	27.84	27.77	27.61	-0.07	-0.23	-0.16
6 min	20.37	20.45	20.49	0.08	0.12	0.04
7 min	8.77	8.81	9.06	0.04	0.29	0.25
8 min	20.86	20.84	20.86	-0.02	0.00	0.02
9 min	17.79	17.87	18.04	0.08	0.25	0.17
10 min	26.02	26.11	26.16	0.09	0.14	0.05

Table A17. BRS_{UpUp} (ms/mmHg) using same data with reduced sampling rates of 800, 400 and 200 (Hz)

Time	Sampling Rate			Differences		
	800	400	200	800/400	800/200	400/200
10 min	38.1	38.3	40.1	0.2	2.0	1.8
First 5 min	36.4	36.9	37.2	0.5	0.8	0.3
Second 5 min	39.2	39.4	42.0	0.2	2.8	2.6
1 min	0.0	0.0	0.0	0.0	0.0	0.0
2 min	19.9	20.0	19.7	0.1	-0.2	-0.3
3 min	0.0	0.0	0.0	0.0	0.0	0.0
4 min	45.8	46.6	47.1	0.8	1.3	0.5
5 min	37.5	37.8	38.3	0.3	0.8	0.5
6 min	38.8	38.9	38.0	0.1	-0.8	-0.9
7 min	39.0	39.3	40.5	0.3	1.5	1.2
8 min	15.8	15.9	15.6	0.1	-0.2	-0.3
9 min	80.6	80.5	79.1	-0.1	-1.5	-1.4
10 min	29.4	29.6	44.0	0.2	14.6	14.4

Table A18. $BRS_{DownDown}$ (ms/mmHg) using same data with reduced sampling rates of 800, 400 and 200 (Hz)

Time	Sampling Rate			Differences		
	800	400	200	800/400	800/200	400/200
10 min	36.1	33.2	33.3	-2.9	-2.8	0.1
First 5 min	40.0	40.4	41.0	0.4	1.0	0.6
Second 5 min	32.9	27.0	27.2	-5.9	-5.7	0.2
1 min	44.6	44.9	45.0	0.3	0.4	0.1
2 min	22.6	22.8	23.1	0.2	0.5	0.3
3 min	66.4	66.4	64.7	0.0	-1.7	-1.7
4 min	28.3	28.9	30.0	0.6	1.7	1.1
5 min	40.5	41.1	40.3	0.6	-0.2	-0.8
6 min	62.3	19.9	19.9	-42.4	-42.4	0.0
7 min	20.5	16.4	16.9	-4.1	-3.6	0.5
8 min	35.2	35.4	35.7	0.2	0.5	0.3
9 min	25.8	25.9	26.4	0.1	0.6	0.5
10 min	31.4	31.7	31.8	0.3	0.4	0.1

Conclusion

An equipment failure problem impacted upon the research testing process during data collection and it was considered possible that the sampling rate (800 Hz) could have been responsible for the continuing problem. This was because larger sampling rates generate greater amounts of data imposing increasing demands on computer technical abilities. Therefore, a procedure was undertaken to evaluate the variance in BRS outcome measures from the same data which was sampled at different rates (800, 400 and 200 Hz) at dedicated time intervals to afford greater insight into the impact of sampling rate differences. Although the dedicated software provided the opportunity to reduce the sampling rate post hoc i.e., data could be collected at 800 Hz and reduced to 400 and 200 Hz, it was not possible to upgrade lower sampling rates to higher sampling rates post hoc i.e., data collected at 200 Hz could not be increased to 400 and 800 Hz. Thus, because the same data could not be re-sampled at a higher sample rate post hoc it was important to evaluate the extent of the variance in the outcome measures obtained via different sampling rates to ascertain whether data obtained via different sampling rates could be combined for later analysis.

The variance in BRS outcome measures observed over a 10 min period were of particular interest because this time period equated with the data collection time period in the present reproducibility and exercise studies. The findings suggested a reduction in sampling rate from 800 Hz to 400 or 200 Hz over a 10 min time period would have a negligible effect in spectral BRS outcome measures (change of 0 to 0.29 ms/mmHg) and a minimal effect in sequence BRS outcome measures (change of - 2.9 to 0.2 ms/mmHg). Therefore, reductions in sampling rate were not found to markedly affect the magnitude of BRS outcome measures and although sequence BRS outcome measures had greater variance than spectral BRS outcome measures it was considered acceptable that data obtained from sampling rates of 800 and 400 Hz could be combined for later analysis. Indeed, due to the necessity to continue with data collection as quickly and smoothly as possible, testing was continued at a sampling rate of 400 Hz in anticipation for a reduction in equipment failure issues.

Appendix XVII (b): Blood pressure drift over time and physiocal servo-adjustment

Blood pressure drift is a transient shift in BP away from resting baseline levels which may affect the Portapres to accurately track BP over time and may be caused by constant finger cuff pressure producing artifactual elevations of resting BP after prolonged measurement (Ristuccia *et al.*, 1997). The modern BRS techniques such as sequence analysis require exacting demands on the ability of the Portapres to faithfully reproduce beat by beat BP accurately (Panerai *et al.*, 2007) which can be achieved, in part, via the 'Physiocal' servo-adjustment (see below) (FMS, 2005a). However due to the properties of the physiocal and the interruption of BP measurement during the data collection period, the physiocal is switched off during testing which could lead to BP drift because over time there may be a gradual deterioration of the optimal setting leading to possible erroneous results (Panerai *et al.*, 2007). In the present studies, continuous 10 min BP measurements were required thus preliminary testing was undertaken to assess the extent, if any, of BP drift during the utilisation of the Portapres (without physiocal servo-adjustment) over 5 min and 10 min periods. Blood pressure drift can be assessed by visually inspecting the BP trace over various measurement durations which have been interspersed with physiocal verification and, if no marked change in physiocal shape pattern occurs with a shift in BP observed following the physiocal servo-adjustment, it is reasonable to assume that very little BP drift has occurred.

The Portapres uses a variable volume clamp method to measure beat-by-beat BP in the finger (Peñáz, 1969). This method requires the finger artery diameter to be kept constant (clamped) via the use of a finger cuff despite the arterial pressure changes that occur in each heart beat. The clamping at the specific arterial diameter is known as the '*set point*' and if the clamping diameter corresponds to the unstretched or unloaded state of the artery, the transmural pressure is 'zero' (i.e., finger cuff pressure equals intra arterial pressure). The changes in the arterial diameter are detected by the infrared photo-plethysmograph which is embedded into the finger cuff. The arterial changes are opposed by a fast pressure servo controller which changes pressure via an inflatable air bladder which is also built into the finger cuff. Definition and maintenance of the

correct arterial diameter during clamping is obtained by the physiocal algorithm (Wesseling *et al.*, 1995).

The physiocal algorithm uses amplitude and plethysmogram shape interpretation to track the unloaded diameter of the finger artery and the periodic interruption of the BP measurement is referred to as the 'physiocal'. The unloaded diameter is not a constant feature and because normal physiological changes in the arterial wall can bring about change in the unloaded diameter it is necessary to verify the arterial diameter at periodic intervals by the physiocal i.e., physiocal verification. During physiocal verification the BP measurement is temporarily interrupted and this can be troublesome for later analysis of BP data. The physiocal operates at different pressure levels. Firstly, following detection of the systolic phase of the heart beat at the location between diastolic and systolic finger arterial pressure, the shape and amplitude of the plethysmogram are analysed and compared to previous physiocal periods. To confirm optimal unloading an additional verification is made at a different cuff pressure and the physiocal algorithm also checks that the unloaded diameter is not too close to a fully collapsed finger artery state. These normal checks can be observed by a step-like trace in the BP measurement (figure A2).

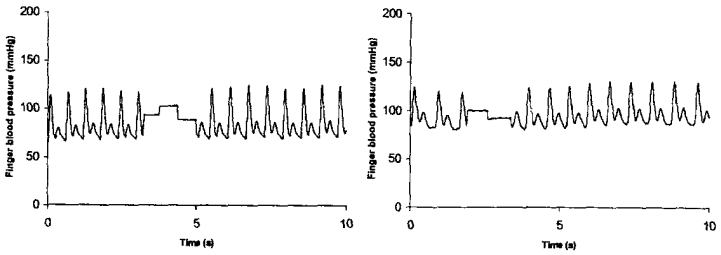


Figure A2. Normal physiocals where correct unloaded diameter has been confirmed. Taken from (FMS, 2005a).

When correct unloaded diameter cannot be confirmed additional steps are added automatically to the physiocal verification (figure A3) and this causes longer interruption to the BP measurement. Clearly, if the multi-step physiocals are observed frequently, the accuracy of the BP measurement would be in doubt. At the start of a measurement there is a pressure staircase until the cuff pressure is above systolic

pressure (figure A4). Once this level is attained a physiocal is performed and BP measurement begins.

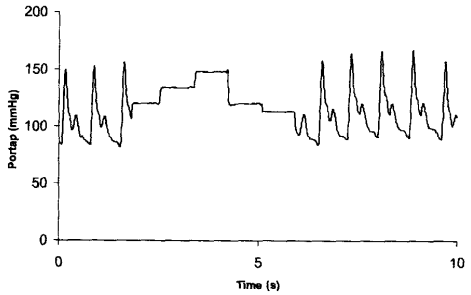


Figure A3. Multi-step physiocal where correct unloaded diameter cannot be confirmed. Taken from (FMS, 2005a).

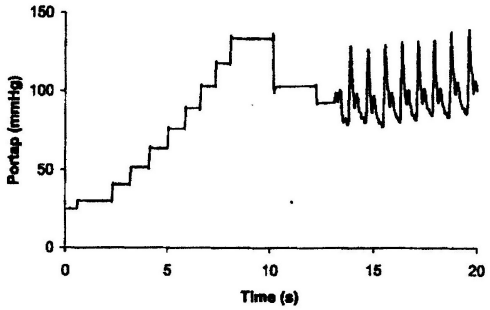


Figure A4. Stairwise step start-up procedure of the physiocal. Taken from (FMS, 2005a).

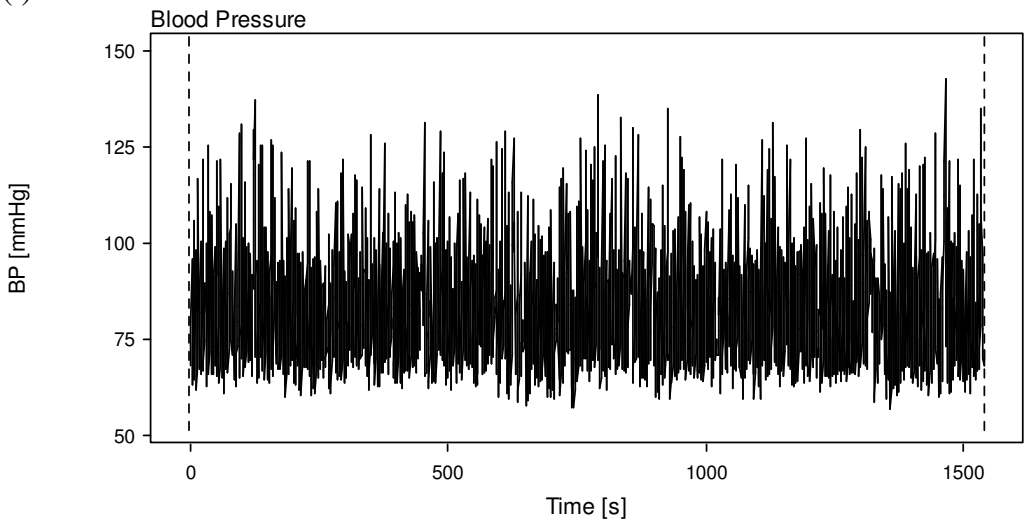
The physiocal procedure starts after every 10th heart beat which increases at 10 beat intervals following achievement of the '*set point*' until 70 beats have been obtained. The 70 beat interval is the highest level of physiocal verification. In practice, if the physiocal cannot verify correct arterial diameter the physiocal procedure will not increase the number of beats or will reduce back to 10 beats until such time it is satisfied with the '*set point*' and will initiate the procedure again. Such procedure is automatic. A normal physiocal procedure (without problems) takes on average approximately 4 min but may take up to 7 min with a slow HR (i.e., 40 – 50 bpm) thus multiple measurement protocols should factor timings accordingly to include physiocal verification procedures. To attain BP measurements without the physiocal interruptions, the physiocal can be switched off following initial set-up. However, due to the possibility of BP drift it is advised that BP measurement > 10 min should not be undertaken without the physiocal connected (FMS, 2005b).

Due to the importance of accurate beat by beat BP measurements for the quantification of BRS via the sequence technique and the need for continuous 10 min BP recordings in the present studies, two protocols were devised (supine and tilt conditions) to assess the extent, if any, of BP drift and the level of physiocal verification following short recordings of 5 min and longer recordings of 10 min with no physiocal servo-adjustment. The tilt protocol was devised to be of shorter duration compared to the supine protocol due to possible orthostatic intolerance from an extended head-up tilt. Following testing, the data was examined to assess any change in physiocal shape during servo-adjustment and evidence of a shift in the BP trace following the servo-adjustment which may have been indicative of BP drift.

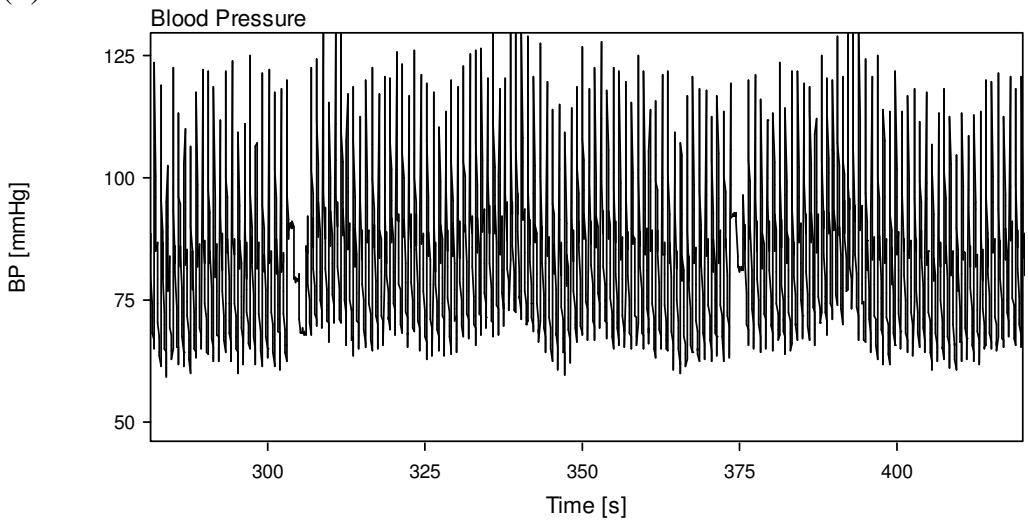
SUPINE (Figure A5)
Physiocal: ON to achieve stability and 70 beats attained
Physiocal: OFF record continuously for ~ 300s
Physiocal: ON
Physiocal: OFF record continuously for ~ 600 s
Physiocal: ON
Physiocal: OFF record continuously for ~ 300s
TILT (Figure A6)
Physiocal: ON to achieve stability and 70 beats attained
Physiocal: OFF *TILT* record continuously ~ 600 s
Physiocal: ON
Physiocal: OFF record continuously ~ 300s

In conclusion, following testing in both conditions no evidence was found for a marked change in the shape of the physiocal servo-adjustment (figures A5; A6) or shift in BP. The physiocal attained 3 continuous 70 beat intervals at all timed junctions thus the highest level of physiocal verification had been achieved without incident. These findings suggested 5 min and 10 min continuous BP measurements during supine and tilt conditions without physiocal verification does not result in BP drift and therefore 10 min continuous BP measurements without physiocal verification were incorporated into the testing procedures.

(i)



(ii)



(iii)

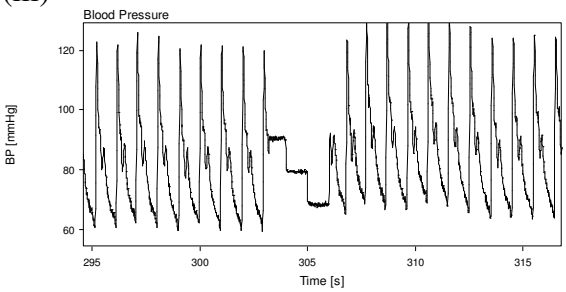
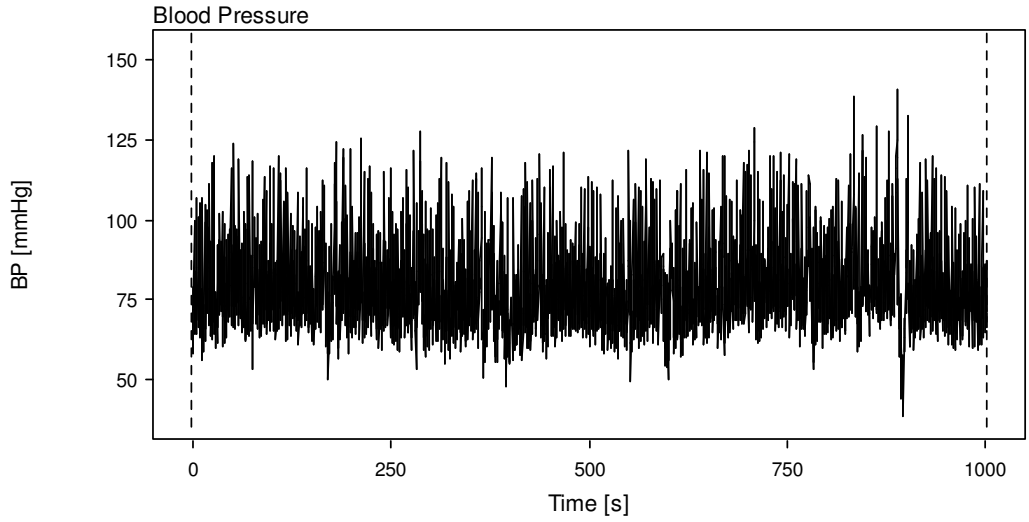
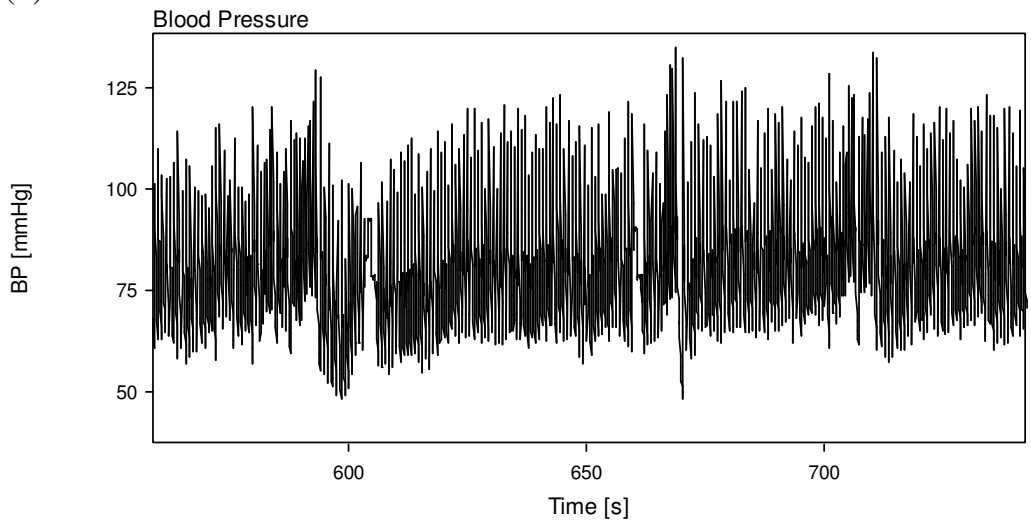


Figure A5. (i) Full recording of BP in supine assessment. (ii) Enlarged section of BP recording with interruption of BP by the physiocal at 300 s and 375 s. (iii) Enlargement of physiocal interruption at 300 s providing evidence of normal physiocal with highest level of verification obtained immediately.

(i)



(ii)



(iii)

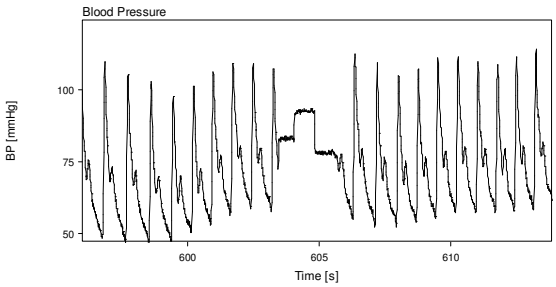


Figure A6. (i) Full recording of BP in tilt assessment. (ii) Enlarged section of BP recording with interruption of BP by the physiocal at 600 s and 660 s. (iii) Enlargement of physiocal interruption at 600 s providing evidence of normal physiocal with highest level of verification obtained immediately.

Physiocal verification during the present reproducibility and exercise studies

Sequence analysis for the quantification of BRS relies on the ability of the Portapres to faithfully reproduce beat by beat BP accurately and prolonged measurement (> 10 min) may result in BP drift which could result in erroneous sequence BRS quantification (Panerai *et al.*, 2007). To reduce the possibility of BP drift occurring during testing in the present reproducibility and exercise studies, a testing protocol was devised whereby the physiocal was switched on between supine and tilt measures and the level of physiocal verification was manually noted for each recording. No BP measurement was undertaken unless a minimum of 40 beats had been achieved to ensure good physiocal verification.

During the present reproducibility study a total of 276 verifications were noted. Of these, 10 min continuous BP measurements were made with a physiocal verification at 70 beats in 258 recordings; 60 beats in 12 recordings; 50 beats in 5 recordings and 40 beats in 1 recording. During the present exercise study a total of 324 verifications were noted. Of these, 10 min continuous BP measurements were made with the physiocal at 70 beats in 286 recordings; 60 beats in 23 recordings; 50 beats in 7 recordings and 40 beats in 7 recordings with one measure lost due to cuff problems. Thus, during the present reproducibility and exercise studies 600 verifications were noted. These findings related to a physiocal verification of 70 beats in 91% of measures; 60 beats in 6% of measures; 50 beats in 2% of measures and 40 beats in 1% of measures which suggested a correct unloaded diameter was confirmed with high verification in 97% of recordings providing optimal conditions for accurate beat by beat BP measurement for the quantification of sequence BRS. Therefore, it was considered unlikely that the extent of BP drift, if any, had influenced the present reproducibility and exercise study findings.

Appendix XVII (c): Hand-warming devices for successful Portapres operation

The achievement of successful beat by beat BP measurement requires warm fingers of the hand because cold hands and fingers may result in unsuccessful BP signal acquisition, with the physiocal unable to confirm optimal unloading and thus the accuracy of the BP measurement becomes uncertain. During preliminary testing it became apparent that participant individual differences with regard to hand and finger warmth could easily disrupt the testing process due to an inability to achieve a BP measurement. Future testing procedures demanded a ready acquirement of BP measurements to ensure time points for data collection purposes could be achieved. For example, the present exercise study required 10 individual BP recordings at set time intervals during a single data collection session and this protocol was to be repeated on 3 separate occasions for each participant. Thus the ability to achieve warm hands and fingers at will in all participants became an essential requirement for data collection purposes.

Hand and finger warmth is essential because the Portapres employs a variable volume clamp method to measure beat-by-beat BP in the finger (Peñáz, 1969) which necessitates the finger artery diameter to be kept constant (clamped) via the use of a finger cuff despite the arterial pressure changes that occur in each heart beat. The clamping at the specific arterial diameter is known as the '*set point*' and if the clamping diameter corresponds to the unstretched or unloaded state of the artery, the transmural pressure is 'zero' (i.e., finger cuff pressure equals intra arterial pressure) which provides optimal conditions for BP measurement (FMS, 2005a; Wesseling *et al.*, 1995). The intra-arterial pressure/ arterial diameter relationship is dependent on the mechanical properties of the artery with arterial compliance dependent on the transmural pressure (i.e., pressure difference between the intra-arterial pressure and the pressure of the surrounding tissue) (Langewouters *et al.*, 1986). A major constituent of the walls of small arteries of the finger is smooth muscle (Marieb, 2003). The contraction of the smooth muscle in the arterial wall occurs during stress and in normal circumstances the stress which negatively affects the ability to achieve a BP measurement is cold. Thus to achieve a relaxed state in smooth muscle in the arterial wall which can readily adapt to changes in blood flow and maintenance of a constant diameter under varying pressures,

the fingers of the hand need to be warm for the achievement of successful BP measurements.

Warm fingers require good blood circulation i.e., relaxed compliant finger arteries and this state may be achieved by the use of hand-warming devices. Thus, preliminary testing was undertaken to assess various devices regarding their hand-warming properties, their ease of use and capability for incorporation into the testing procedures. The devices tested included a hot water bottle, small bottles filled with warm water, blankets, standard hand-warmers and glove hand-warmers.

Hot water bottle

The hot water bottle was filled with hot water and covered for safety. It was held in both hands during the resting period (before finger cuff application) and provided initial success for hand-warming. However, the hot water bottle was bulky to use and required re-filling at regular intervals which could not be incorporated easily into the testing procedures and therefore was discarded as a suitable device.

Small bottles

Small drink bottles were filled with warm water and one bottle was held in each hand. This device was successful during the resting period and provided initial hand-warming properties. However although the small bottles were easy to hold, the water cooled very quickly thus requiring re-filling with warm water at regular intervals and this could not be incorporated easily into the testing procedures. Furthermore, although it was possible for the participant to hold a small bottle continuously in the right hand during testing it was not possible to hold a small bottle in the left hand with the Portapres finger cuff attached. Therefore, the small bottles were also discarded as a suitable hand-warming device.

Blanket

The blanket was found to be useful for overall body warmth but was not successful for specific hand-warming properties.

Standard hand-warmers

The standard hand-warmers were approximately 12 cm x 12 cm, wheat-filled, microfibre covered, microwaveable and able to be held in individual hands (Pixmania, 2009). The small hand-warmers were warmed via a microwave oven which was a simple operation and could be incorporated into the testing procedure with ease. Although this device provided hand-warming properties they did not provide enough adequate warmth for those participants who presented with very cold hands. However, it was found that they could be used with the left hand during BP measurement without interfering with the cuff and were therefore, a useful addition to be used in conjunction with other hand-warming devices.

Glove hand-warmers

The glove hand-warmers were approximately 15 cm x 28 cm, glove shaped with an outer layer of faux fur and an inner layer of 100% brushed cotton flannel (WarmMeUps, 2009). Between the two layers were two non-toxic gel pads that surrounded the hand which were microwaveable and retained heat over a few hours. These hand-warmers were large enough to be worn by all participants and were found to be highly successful for hand-warming properties. Gentle massaging of the gloves following microwave warming allowed the heat to be distributed evenly throughout the glove and thus provided a wholly encompassing heat for each hand. A glove hand-warmer could not be worn during BP measurement on the left hand but if necessary, a small hand-warmer could be placed under the palm of the left hand if required. The glove hand-warmers were an extremely successful and simple hand-warming device which could be used by all participants and incorporated into the testing procedure with ease.

In conclusion, following preliminary testing the hand-warming devices incorporated into the testing procedures included the standard hand-warmers for use by the left hand during BP measurement, glove hand-warmers for use by both hands before BP measurement and for use with the right hand during BP measurement and a blanket for overall body warmth.

Appendix XVII (d) Determination of exercise protocols to equate matching work load across high intensity exercise and moderate intensity exercise conditions

Preliminary testing was undertaken regarding assessment criteria for the two exercise conditions for the present exercise study. This was undertaken to determine a tolerable exercise work load at a high intensity that would be matched to the moderate intensity work load.

A.XVII (d).1. Participants

The participants were recruited from the staff and student body of the University of Gloucestershire on a voluntary basis via direct contact or research presentations during student lecture periods, or through association with research participants from the surrounding community. Participants were non smoking males (n = 10; 21 – 45 y) (table A19) and females (n = 3; 26 – 38 y) (table A20) who were deemed healthy with no history of diabetes, hypertension or cardiac disease, who showed no signs of disease and were undertaking regular exercise (moderate exercise 5 ± 2 $h \cdot wk^{-1}$). Participant age was self reported.

Table A19. Participant (male) physical characteristics

Characteristic (n = 10) (m)	Mean (± SD)
Age (y)	29 (± 8)
Mass (kg)	81.2 (± 12.1)
Stature (m)	1.78 (± 0.07)
HR_{peak} ($b \cdot min^{-1}$)	184 (± 11)
WR_{max} (W)	343 (± 26)
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	47.8 (± 7.5)
RER	1.22 (± 0.09)

Note: HR = heart rate; WR = work rate

Table A20. Participant (female) physical characteristics

Characteristic (n = 3) (f)	Mean (± SD)
Age (y)	31 (± 6)
Mass (kg)	65 (± 7.4)
Stature (m)	1.63 (± 0.07)
HR_{peak} ($b \cdot min^{-1}$)	185 (± 7)
WR_{max} (W)	217 (± 24)

Note: HR = heart rate; WR = work rate

A.XVII (d).2. Ethical considerations

All procedures conformed to those approved and cleared by the University Research Ethics Committee in the Sport & Exercise Laboratory Procedures Manual (UoG, 2008b) and participants received no inducement to participate or were offered or recompensed for inconvenience and no reimbursement of expenses was provided. Participants volunteered after completing a health questionnaire and providing informed consent (Appendix XI; XII). Informed consent included describing the nature of the study, describing any risks or benefits of participation and the right for the participant to be able to withdraw from the study at any time without negative consequences. Participant data was collected and stored with regard to the Data Protection Act (Data Protection Act, 1988) and in accordance with the University of Gloucestershire guidelines (UoG, 2008a).

A.XVII (d).3 Procedures

Procedures undertaken for the preliminary testing exercise conditions conformed to the University of Gloucestershire guidelines as outlined in the Sport & Exercise Laboratory Procedures Manual (UoG, 2008b). All procedures took place in the exercise laboratory of the University of Gloucestershire. Participant descriptive characteristics and environmental characteristics in the physiology laboratory were determined at the start of the progressive exercise test (PET) and are in accordance with those detailed in sections 3.3.1, 3.3.2 and 3.3.9 – 3.3.13.

The participants had previously undertaken a PET (ramp protocol 25W start/ 25W·min^{-1}) for determination of HR_{peak} and WR_{max} and the male participants had also undertaken $\dot{V}O_{2peak}$ testing. The determination of HR_{peak} was taken as the maximal HR (5 s average) recorded immediately prior to the termination of the PET. The determination of WR_{max} was taken as the maximal WR achieved immediately prior to the termination of the PET (Niemelä *et al.*, 2008). In order to standardise work done in the preliminary testing exercise conditions, the total amount of work done by each participant was calculated by multiplying the participant's individual WR (W) by the length in time (s) of each interval exercise bout (adjusted by two decimal places) to provide an index in kilojoules (kJ). This figure was multiplied by the number of exercise bouts (6 or 7) to provide an index of total work done (kJ). Standardisation across exercise conditions was achieved by adjusting length of time (s) appropriately to each of the interval exercise bouts for the 90% WR_{max}, 80% WR_{max}, 75% WR_{max} and 50% WR_{max} preliminary testing exercise conditions respectively and individual participant exercise conditions were calculated and programmed into the cycle ergometer.

The preliminary testing protocols included warm up and cool down periods at 60 W for 5 min respectively at a cadence of 60 – 80 rev.min^{-1} pre and post the preliminary testing exercise condition. Active recovery periods between each interval exercise bout at 60 W for 3 min periods were also included. The WR was controlled independently of cadence so participants were encouraged to keep a cadence of 60 – 80 rev.min^{-1} throughout the testing. These criteria and the use of cycle ergometry would be undertaken in the exercise conditions for the present exercise study. The preliminary testing exercise conditions would provide evidence for participant completion success and adequate intervention exposure. Participant HR was continuously recorded throughout the exercise to provide an indication of intensity of exercise. Individual participant preliminary testing was undertaken 3 – 6 days apart to ensure adequate recovery between tests.

A.XVII (d).4. Results

A.XVII (d).4(i) Workload

The various preliminary exercise conditions provided differences between participants regarding a tolerable workload. The 90% WR_{max} exercise condition was found to be

intolerable for most participants and the 80% WR_{max} exercise condition was also found to be challenging and barely tolerable. The 75% WR_{max} exercise condition was tolerable and manageable by most of the participants and the 50% WR_{max} exercise condition was wholly tolerable by all participants.

90% WR_{max} over 6 interval bouts

Six participants (3 m; 3 f) undertook an exercise condition of 90% WR_{max}. One participant completed 6 bouts, 1 participant completed 4 bouts and 4 participants completed 1 bout. The 2 participants that achieved ≥ 4 bouts were experienced cyclists. The majority of participants experienced extreme leg fatigue over the length of a single interval bout and were unable to continue with testing.

80% WR_{max} over 7 interval bouts

Seven participants (4 m; 3 f) undertook an exercise condition of 80% WR_{max}. Five participants completed 7 bouts (3 participants with extreme difficulty); 1 participant completed 4 bouts and 1 participant 2 bouts. Overall, the participants found the protocol challenging and difficult. The participants experienced leg fatigue and seat discomfort.

75% WR_{max} over 7 interval bouts

Seven participants (6 m; 1 f) undertook an exercise condition of 75% WR_{max}. Six participants completed 7 bouts and 1 participant 4 bouts. Participants found the protocol challenging but manageable. The participants experienced seat discomfort.

50% WR_{max} over 7 interval bouts

Seven participants (4 m; 3 f) undertook an exercise condition of 50% WR_{max}. All participants completed 7 bouts without difficulty. The participants experienced seat discomfort.

A.XVII (d).4(ii) Heart rate response

Heart rate was measured throughout all of the exercise conditions. Only the data for the 80% WR_{max} exercise condition, 75% WR_{max} exercise condition and 50% WR_{max}

exercise condition are provided due to lack of completion of the 90% WR_{max} exercise condition by most of the participants. The data suggested the exercise bouts of 80% WR_{max} and 75% WR_{max} represented high intensity exercise and the exercise bouts of 50% WR_{max} represented moderate intensity exercise. The HR response to 75% WR_{max} and 50% WR_{max} exercise is summarised in figure A7.

Exercise condition: 80% WR_{max}

Only data from 6 participants are included as 1 participant only completed 2 exercise bouts. Heart rate (mean) increased from 139 (124 – 147) to 157 (147 – 171) $b \cdot min^{-1}$. The exercise HR data when compared to the HR_{peak} (174; 151 – 192) $b \cdot min^{-1}$ obtained in the progressive exercise test indicated this exercise condition derived heart rates of 80 – 90% HR_{peak}. The HR data suggested this exercise condition equated to high intensity exercise.

Exercise condition: 75% WRmax

Data from 7 participants are included; 6 participants completed 7 bouts and 1 participant completed 4 bouts of exercise. Heart rate (mean) increased from 144 (134 – 168) to 164 (156 – 173) $b \cdot min^{-1}$. The exercise HR data when compared to the HR_{peak} (187; 167 – 206) $b \cdot min^{-1}$ obtained in the progressive exercise test indicated this condition derived heart rates of 77 – 88% $HR_{peak.}$ The HR data suggested this exercise condition equated to high intensity exercise.

Exercise condition: 50% WR_{max}

Data from 7 participants are included. Heart rate (mean) increased from 128 (117 – 150) to 140 (119 – 174) $b \cdot min^{-1}$. The exercise HR data when compared to the HR_{peak} (174; 151 – 192) $b \cdot min^{-1}$ obtained in the progressive exercise test indicated this condition derived heart rates of 73 – 80% $HR_{peak.}$ The HR data suggested this exercise condition equated to moderate intensity exercise.

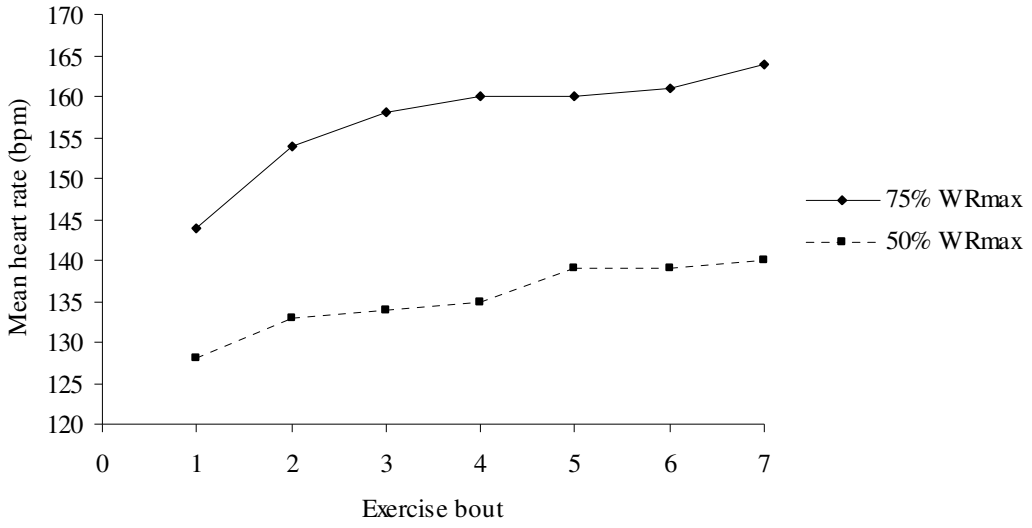


Figure A7. Mean heart rate data over 7 bouts of interval exercise during 75% and 50% WR_{max} preliminary testing exercise conditions

A.XVII (d).5. Conclusion

Preliminary exercise testing was undertaken to assess exercise condition criteria for the present exercise study regarding tolerable exercise work load at a heavy intensity and matched with a moderate intensity work load. Following the completion of the preliminary exercise testing, the 75% WR_{max} exercise condition was found to provide a challenging but manageable exercise intervention and the HR data suggested a level of high intensity exercise. The 50% WR_{max} exercise condition provided a less challenging exercise intervention and the HR data suggested the intensity of exercise was at the high end of the moderate intensity continuum. The distinction between the two intensities of exercise is displayed in figure A7. However, to ensure the exercise conditions in the present exercise study would be manageable and have a greater distinction between the two intensities of exercise, the %WR chosen for the present exercise study were 75% WR_{max} and 40% WR_{max} to provide tolerable exercise conditions of high intensity exercise and moderate intensity exercise of matched equal work load to achieve equal work done.

APPENDIX XVIII: STATISTICAL ANALYSES

Appendix XVIII (a): Relationship between average and absolute difference in BRS indices

Appendix XVIII (b): BRS statistical outcomes (p values) for Kolmogorov-Smirnov tests

Appendix XVIII (c): BRS (± SD) responses at baseline, + 15, 60, 120, 180 min and 24 h for three randomised conditions; control condition (no exercise) and two exercise conditions

Appendix XVIII (d): Statistical analysis HR_{mean} over two exercise conditions
Appendix XVIII (d.i): Two-way ANOVA (bout/condition)
Appendix XVIII (d.ii): One-way ANOVA 40% WR_{max}
Appendix XVIII (d.iii): One-way ANOVA 75% WR_{max}
Appendix XVIII (d.iv): Post hoc Ttest

Appendix XVIII (e): Statistical analysis BRS indices

Two-way ANOVA (time/condition)

Appendix XVIII (e.i): Two-way ANOVA BRS_{UpUp} Supine
Appendix XVIII (e.ii): Two-way ANOVA $BRS_{DownDown}$ Supine
Appendix XVIII (e.iii): Two-way ANOVA $BRS_{\alpha LF}$ Supine
Appendix XVIII (e.iv): Two-way ANOVA BRS_{TFTG} Supine
Appendix XVIII (e.v): Two-way ANOVA BRS_{UpUp} Tilt
Appendix XVIII (e.vi): Two-way ANOVA $BRS_{DownDown}$ Tilt
Appendix XVIII (e.vii): Two-way ANOVA $BRS_{\alpha LF}$ Tilt
Appendix XVIII (e.viii): Two-way ANOVA BRS_{TFTG} Tilt

Paired Ttests

Appendix XVIII (e.ix): Paired Ttests Baseline Supine
Appendix XVIII (e.x): Paired Ttests + 15 min Supine
Appendix XVIII (e.xi): Paired Ttests + 60 min Supine

Appendix XVIII (e.xii): Paired Ttests + 120 min Supine

Appendix XVIII (e.xiii): Paired Ttests + 180 min Supine

Appendix XVIII (e.xiv): Paired Ttests + 24 h Supine

Appendix XVIII (e.xv): Paired Ttests Baseline Tilt

Appendix XVIII (e.xvi): Paired Ttests + 15 min Tilt

Appendix XVIII (e.xvii): Paired Ttests + 60 min Tilt

Appendix XVIII (e.xviii): Paired Ttests + 120 min Tilt

Appendix XVIII (e.xix): Paired Ttests + 180 min Tilt

Appendix XVIII (e.xx): Paired Ttests + 24 h Tilt

Descriptives

Appendix XVIII (e.xxi): Control BRS_{UpUp} Supine

Appendix XVIII (e.xxii): Control $BRS_{DownDown}$ Supine

Appendix XVIII (e.xxiii): Control $BRS_{\alpha LF}$ Supine

Appendix XVIII (e.xxiv): Control BRS_{TFTG} Supine

Appendix XVIII (e.xxv): 40% WR_{max} BRS_{UpUp} Supine

Appendix XVIII (e.xxvi): 40% WR_{max} $BRS_{DownDown}$Supine

Appendix XVIII (e.xxvii): 40% WR_{max} $BRS_{\alpha LF}$ Supine

Appendix XVIII (e.xxviii): 40% WR_{max} BRS_{TFTG} Supine

Appendix XVIII (e.xxix): 75% WR_{max} BRS_{UpUp} Supine

Appendix XVIII (e.xxx): 75% WR_{max} $BRS_{DownDown}$Supine

Appendix XVIII (e.xxxi): 75% WR_{max} $BRS_{\alpha LF}$ Supine

Appendix XVIII (e.xxxii): 75% WR_{max} BRS_{TFTG} Supine

Appendix XVIII (e.xxxiii): Control BRS_{UpUp} Tilt

Appendix XVIII (e.xxxiv): Control $BRS_{DownDown}$ Tilt

Appendix XVIII (e.xxxv): Control $BRS_{\alpha LF}$ Tilt

Appendix XVIII (e.xxxvi): Control BRS_{TFTG} Tilt

Appendix XVIII (e.xxxvii): 40% WR_{max} BRS_{UpUp} Tilt

Appendix XVIII (e.xxxviii): 40% WR_{max} $BRS_{DownDown}$ Tilt

Appendix XVIII (e.xxxix): 40% WR_{max} $BRS_{\alpha LF}$ Tilt

Appendix XVIII (e.xl): 40% WR_{max} BRS_{TFTG} Supine

Appendix XVIII (e.xli): 75% WR_{max} BRS_{UpUp} Tilt

Appendix XVIII (a): Relationship between average and absolute differences in BRS indices

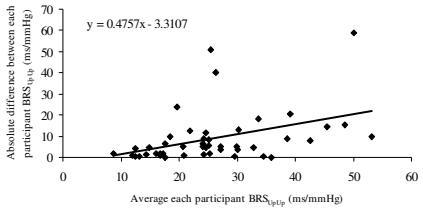


Figure A8. Relationship between average and absolute difference in BRS_{UpUp} in supine between baseline and + 60 min

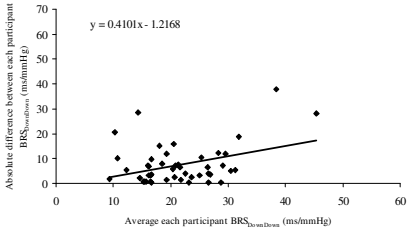


Figure A9. Relationship between average and absolute difference in $BRS_{DownDown}$ in supine between baseline and + 60 min

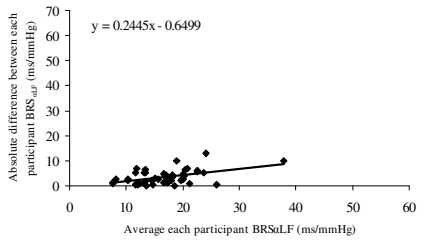


Figure A10. Relationship between average and absolute difference in $BRS_{\alpha LF}$ in supine between baseline and + 60 min

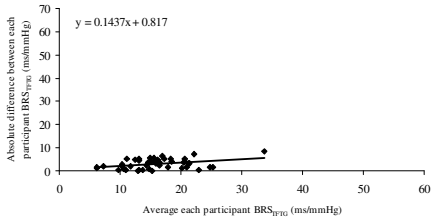


Figure A11. Relationship between average and absolute difference in BRS_{TFTG} in supine between baseline and + 60 min

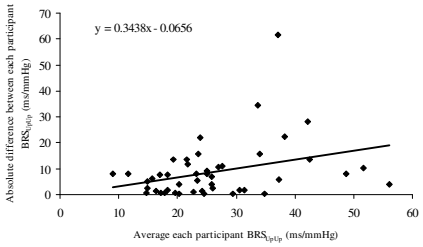


Figure A12. Relationship between average and absolute difference in BRS_{UpUp} in supine between baseline and + 24 h

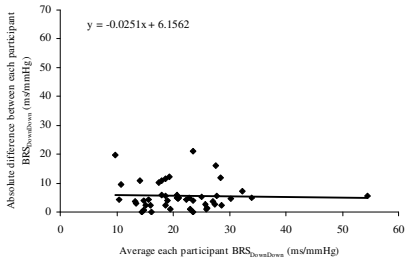


Figure A13. Relationship between average and absolute difference in $BRS_{DownDown}$ in supine between baseline and + 24 h

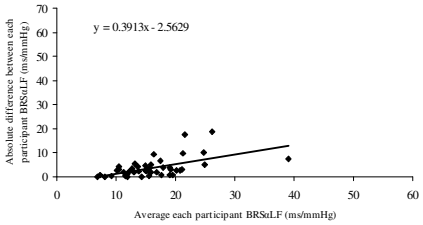


Figure A14. Relationship between average and absolute difference in $BRS_{\alpha LF}$ in supine between baseline and + 24 h

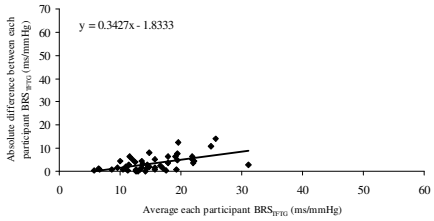


Figure A15. Relationship between average and absolute difference in BRS_{TFTG} in supine between baseline and + 24 h

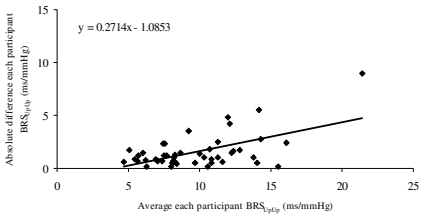


Figure A16. Relationship between average and absolute difference in BRS_{UpUp} in tilt between baseline and + 60 min

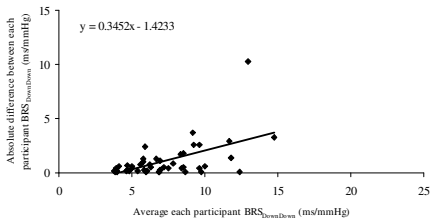


Figure A17. Relationship between average and absolute difference in $BRS_{DownDown}$ in tilt between baseline and + 60 min

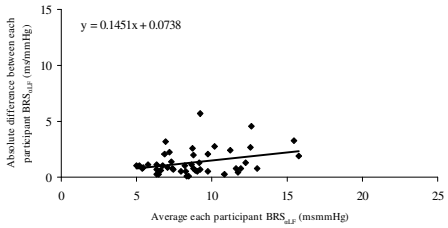


Figure A18. Relationship between average and absolute difference in $BRS_{\alpha LF}$ in tilt between baseline and + 60 min

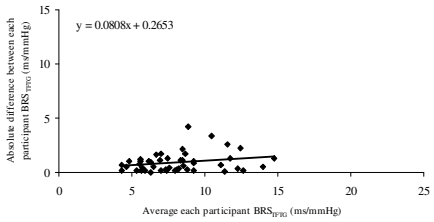


Figure A19. Relationship between average and absolute difference in BRS_{TFTG} in tilt between baseline and + 60 min

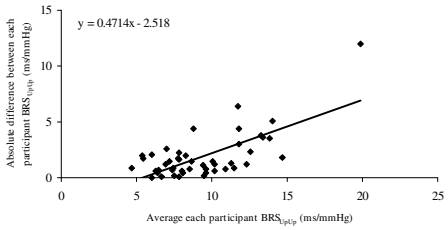


Figure A20. Relationship between average and absolute difference in BRS_{UpUp} in tilt between baseline and + 24 h

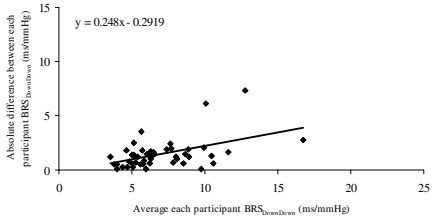


Figure A21. Relationship between average and absolute difference in $BRS_{DownDown}$ in tilt between baseline and + 24 h

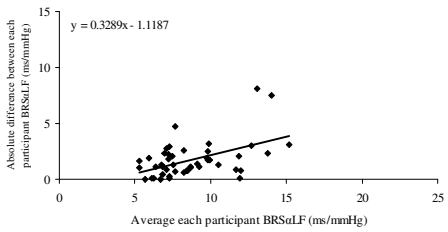


Figure A22. Relationship between average and absolute difference in $BRS_{\alpha LF}$ in tilt between baseline and + 24 h

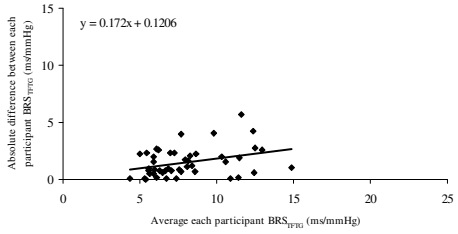


Figure A23. Relationship between average and absolute difference in BRS_{TFTG} in tilt between baseline and + 24 h

Appendix XVIII (b): BRS Statistical outcomes (p values) for Kolmogorov-Smirnov tests

Table A21. Supine and tilt baroreflex sensitivity statistical outcomes (p values) for Kolmogorov-Smirnov tests over three conditions of control condition (no exercise) and two exercise conditions of 40% WR_{max} and 75% WR_{max}

Variable	Control Condition						40% WR_{max} exercise condition						75% WR_{max} exercise condition					
SUPINE			min			h			min			h			min			h
mmHg/ms	Baseline	+ 15	+ 60	+ 120	+ 180	+ 24	Baseline	+ 15	+ 60	+ 120	+ 180	+ 24	Baseline	+ 15	+ 60	+ 120	+ 180	+ 24
BRS_{UpUp}	0.992	0.904	0.321	0.981	0.997	0.988	0.989	0.844	0.903	0.863	0.859	0.968	0.700	0.252	0.742	0.962	0.993	0.650
$BRS_{DownDown}$	0.623	0.820	1.000	0.978	0.855	0.838	0.958	0.989	0.926	0.522	0.900	0.912	0.943	0.430	0.921	0.423	0.509	0.785
$BRS\alpha_{LF}$	0.597	0.623	0.805	0.625	0.860	0.940	0.875	0.796	0.999	0.873	0.757	0.993	0.857	0.189	0.845	0.950	0.746	0.774
BRS_{TFTG}	0.872	0.922	0.601	0.945	0.906	0.961	0.664	0.839	0.955	0.861	0.987	0.845	0.900	0.313	0.990	0.854	0.910	0.793
TILT			min			h			min			h			min			h
BRS_{UpUp}	0.593	0.712	0.676	0.834	0.778	0.630	0.988	0.110	0.556	0.889	0.415	0.290	0.902	0.236	0.802	0.891	0.860	0.988
$BRS_{DownDown}$	0.986	0.989	0.501	0.826	0.684	0.991	0.659	0.478	0.959	0.954	0.591	0.793	0.999	0.552	0.703	1.000	0.988	0.974
$BRS\alpha_{LF}$	0.889	0.646	0.741	0.835	0.819	0.991	0.996	0.973	0.906	0.960	0.676	0.726	0.931	0.825	0.869	0.786	0.344	0.903
BRS_{TFTG}	0.906	0.778	0.997	0.843	0.705	0.964	0.964	0.833	0.979	0.946	0.750	0.960	0.974	0.787	0.817	0.993	0.425	0.426

Note: LF is low frequency; TFTG is transfer function transfer gain; WR_{max} is work rate maximum; min is minute; h is hour. Significance ($p = > 0.05$) indicates a normal distribution at ($p = < 0.05$) level of significance

Appendix XVIII (c): BRS (± SD) responses at baseline, + 15, 60, 120, 180 min and 24 h for three randomised conditions; control condition (no exercise) and two exercise conditions

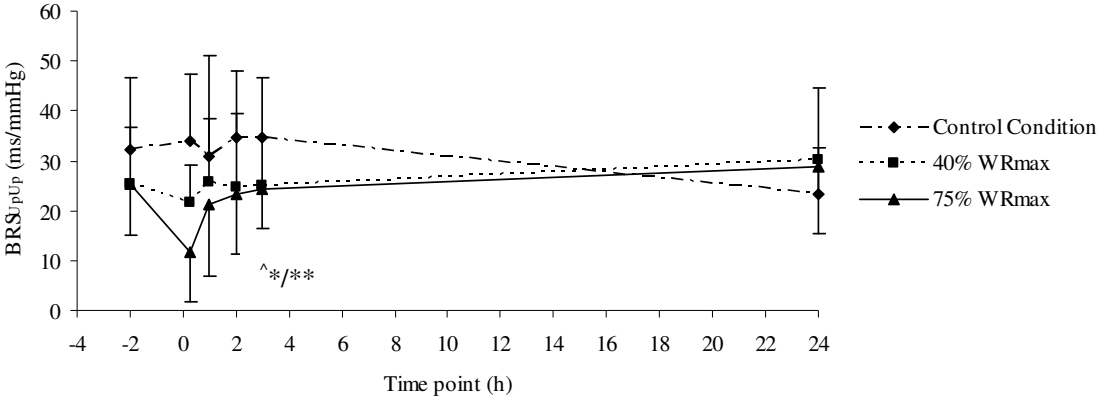


Figure A24. BRS_{UpUp} in supine (± SD) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. No significant condition x time interaction. ^Significant main effect for condition (p = 0.032). */**Significant difference for all condition comparisons at + 15 min (Control vs 40%; p = 0.025; 34 vs 21 ms/mmHg), (Control vs 75%; p = 0.006; 34 vs 11 ms/mmHg) and (40% vs 75%; p = 0.012; 21 vs 11 ms/mmHg) respectively.

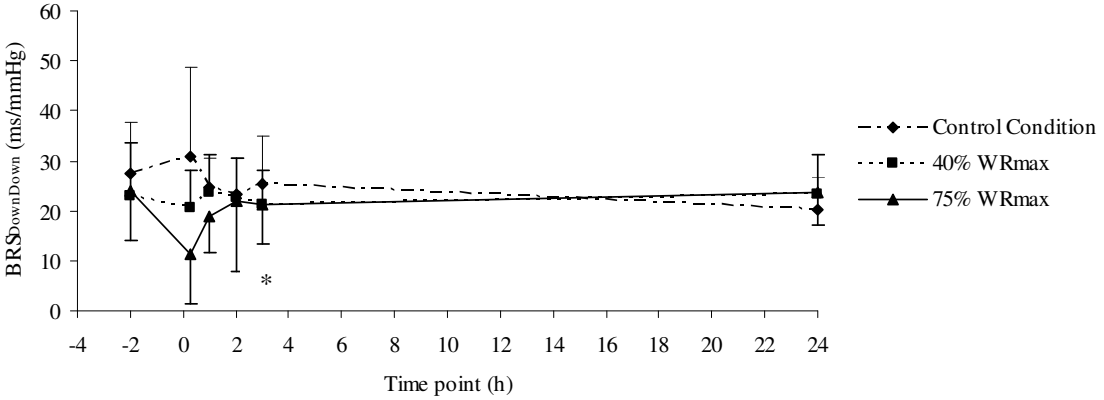


Figure A25. $BRS_{DownDown}$ in supine (± SD) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. Marginal significant condition x time interaction (p = 0.082). Marginal significant main effect for condition (p = 0.084). *Significant difference for condition comparison at + 15 min (Control vs 75%; p = 0.019, 31 vs 11 ms/mmHg) and (40% vs 75%; p = 0.025, 20 vs 11 ms/mmHg) respectively.

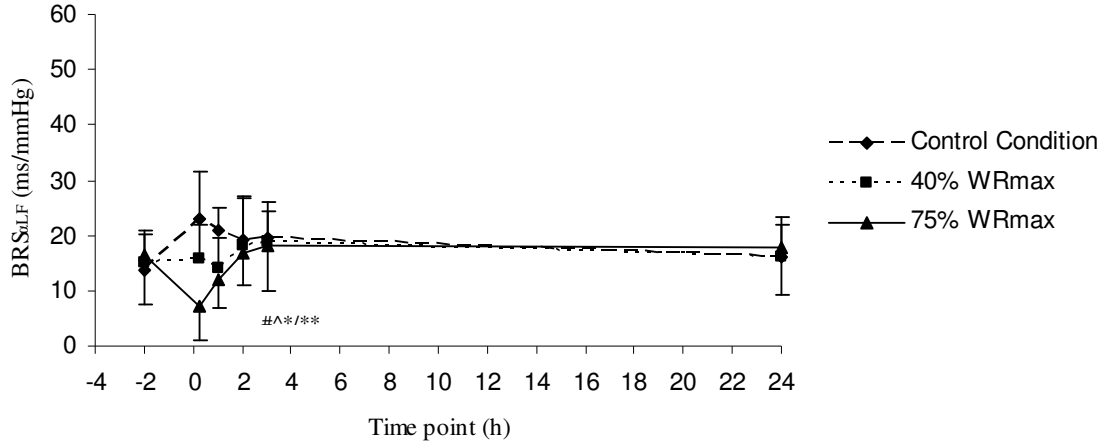


Figure A26. $BRS_{\alpha LF}$ in supine (± SD) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. #Significant condition x time interaction (p = 0.006). ^Significant main effect for condition (p = 0.032). */**Significant difference for condition comparison at + 15 min and + 60 min (Control vs 40%; p = 0.054, 23 vs 16 ms/mmHg; p = 0.013, 21 vs 14 ms/mmHg), (Control vs 75%; p = 0.007, 23 vs 7 ms/mmHg; p = 0.004, 21 vs 12 ms/mmHg) and (40% vs 75%; p = 0.023, 16 vs 7 ms/mmHg; p = 0.016, 14 vs 12 ms/mmHg) respectively.

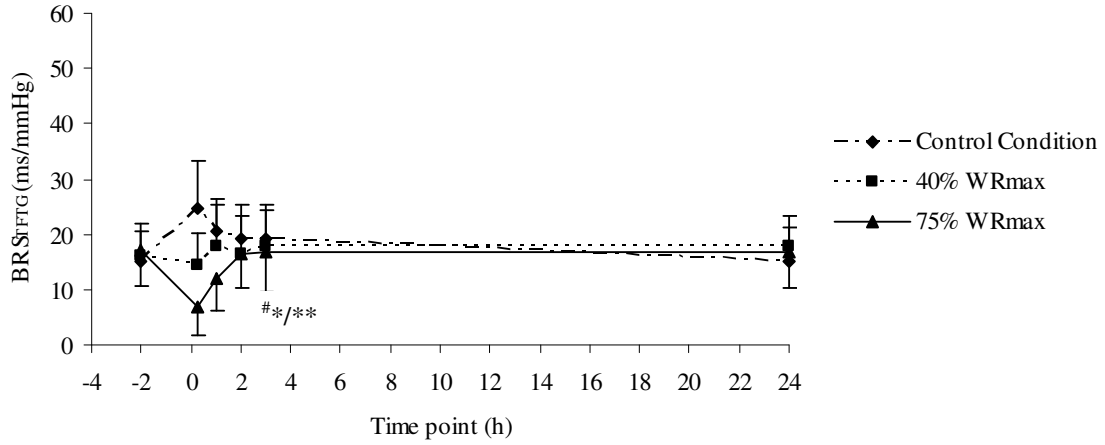


Figure A27. BRS_{TFTG} in supine (± SD) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. #Significant condition x time interaction (p = 0.004). Marginal significant main effect for condition (p = 0.078). */**Significant difference for condition comparison at + 15 min and + 60 min (Control vs 40%; p = 0.010, 25 vs 14 ms/mmHg), (Control vs 75%; p = 0.003, 25 vs 7 ms/mmHg; p = 0.066, 21 vs 12 ms/mmHg) and (40% vs 75%; p = 0.027, 14 vs 7 ms/mmHg; p = 0.015, 18 vs 12 ms/mmHg) respectively.

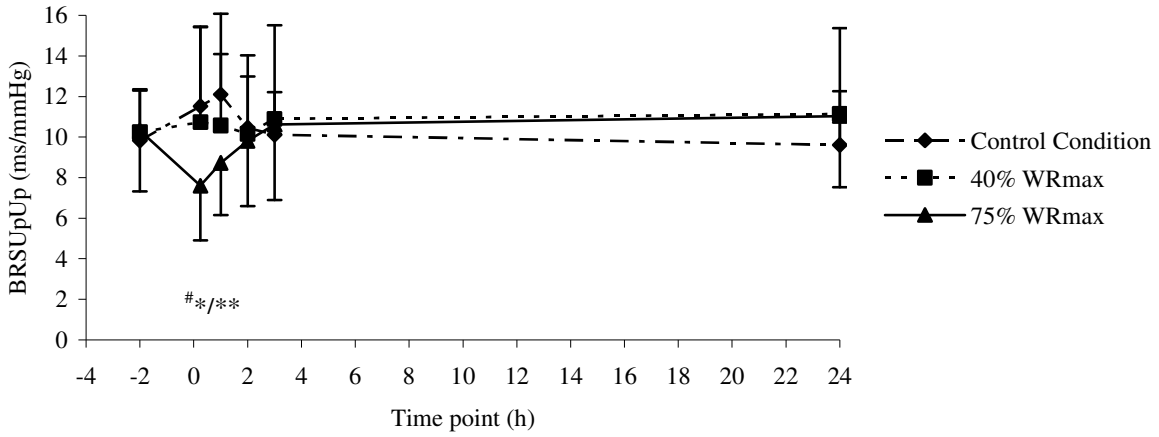


Figure A28. BRS_{UpUp} in tilt (± SD) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. #Significant condition x time interaction (p = 0.027). No significant main effect for condition. */**Significant difference for condition comparison at + 15 min and + 60 min (Control vs 75%; p = 0.031, 12 vs 8 ms/mmHg; p = 0.051, 12 vs 9 ms/mmHg) and (40% vs 75%; p = 0.006, 11 vs 8 ms/mmHg; p = 0.027, 11 vs 9 ms/mmHg) respectively.

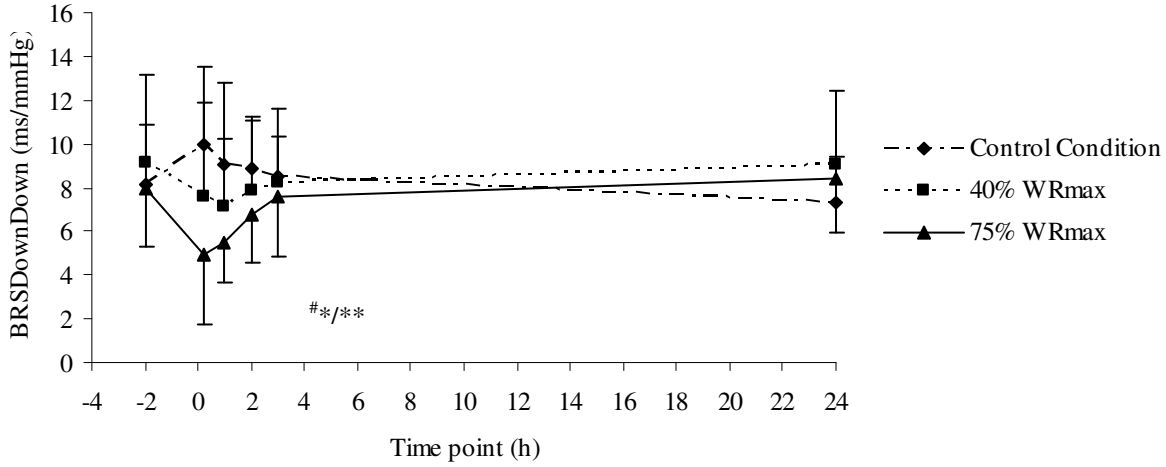


Figure A29. $BRS_{DownDown}$ in tilt (± SD) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. #Significant condition x time interaction (p = 0.004). No significant main effect for condition. */**Significant difference for condition comparison at + 15 min and + 60 min (Control vs 75%; p = 0.008, 10 vs 5 ms/mmHg; p = 0.019, 9 vs 5 ms/mmHg) and (40% vs 75%; p = 0.004, 8 vs 5 ms/mmHg; p = 0.037, 7 vs 5 ms/mmHg) respectively.

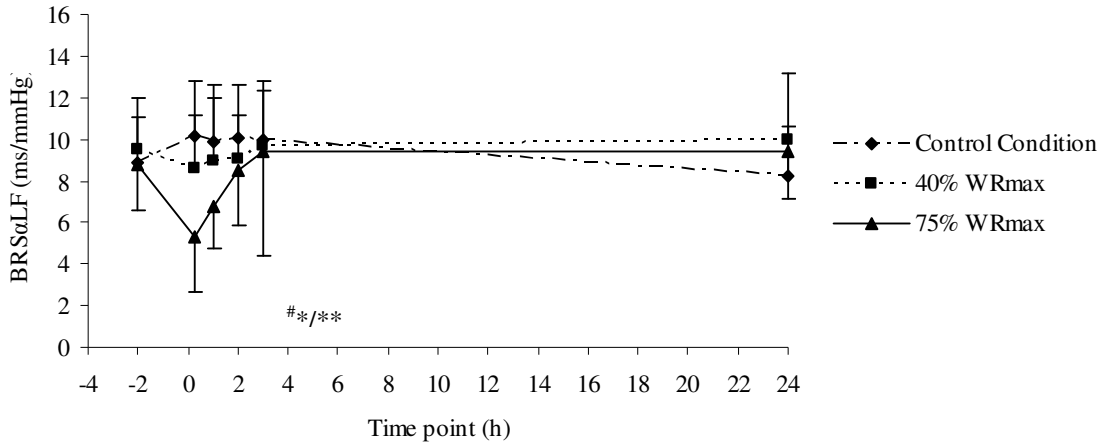


Figure A30. $BRS_{\alpha LF}$ in tilt (± SD) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. #Significant condition x time interaction (p = 0.001). Marginal significant main effect for condition (p = 0.084). */**Significant difference for condition comparison at + 15 min and + 60 min (Control vs 40%; p = 0.024, 10 vs 9 ms/mmHg), (Control vs 75%; p = 0.001, 10 vs 5 ms/mmHg; p = 0.008, 10 vs 7 ms/mmHg) and (40% vs 75%; p = 0.001, 9 vs 5 ms/mmHg; p = 0.007, 9 vs 7 ms/mmHg) respectively.

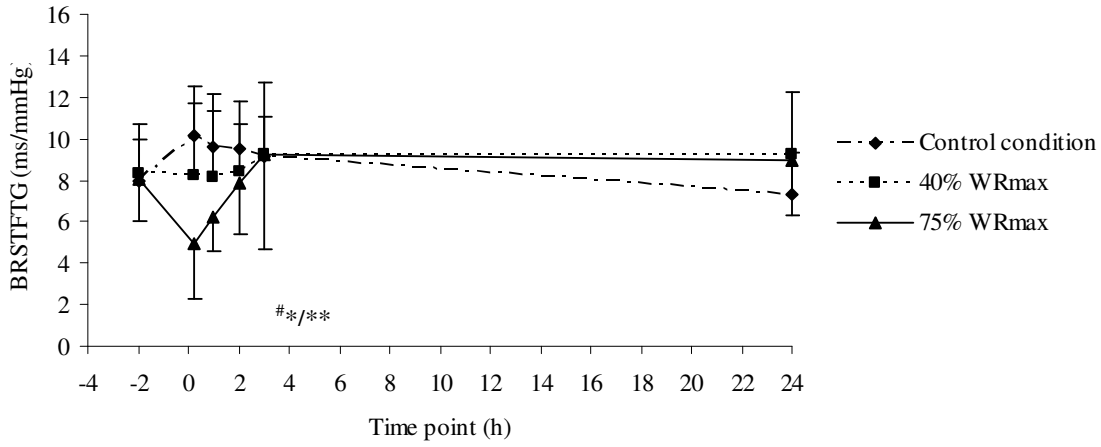


Figure A31. BRS_{TFTG} in tilt (± SD) at baseline (pre-exercise) and + 15, + 60, + 120, + 180 min and + 24 h (post-exercise) for three randomised conditions; control condition (no exercise) and two exercise conditions. #Significant condition x time interaction (p = < 0.001). Marginal significant main effect for condition (p = 0.070). */**Significant difference for condition comparison at + 15 min and + 60 min (Control vs 40%; p = 0.046, 10 vs 8 ms/mmHg), (Control vs 75%; p = < 0.001, 10 vs 5 ms/mmHg; p = 0.005, 10 vs 6 ms/mmHg) and (40% vs 75%; p = 0.001, 8 vs 5 ms/mmHg; p = 0.020, 8 vs 6 ms/mmHg) respectively.

APPENDIX XVIII (d): MEAN HEART RATE OVER TWO EXERCISE CONDITIONS

Appendix XVIII (d.i): Mean heart rate: Two way ANOVA

Within-Subjects Factors

Measure:MEASURE_1

Bout	ConditionHRmean	Dependent Variable
1	1	HRBout140
	2	HRBout175
2	1	HRBout240
	2	HRBout275
3	1	HRBout340
	2	HRBout375
4	1	HRBout440
	2	HRBout475
5	1	HRBout540
	2	HRBout575
6	1	HRBout640
	2	HRBout675
7	1	HRBout740
	2	HRBout775

Descriptive Statistics

	Mean	Std. Deviation	N
HRBout140	112.8889	9.18483	9
HRBout175	134.4444	3.20590	9
HRBout240	119.0000	10.77033	9
HRBout275	146.4444	4.15665	9
HRBout340	120.8889	10.10500	9
HRBout375	151.3333	7.15891	9
HRBout440	123.7778	10.12148	9
HRBout475	156.1111	5.94652	9
HRBout540	124.8889	9.95546	9
HRBout575	159.0000	6.70820	9
HRBout640	127.3333	10.51190	9
HRBout675	161.7778	7.88635	9
HRBout740	128.0000	10.18577	9
HRBout775	164.7778	8.56997	9

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Bout	Pillai's Trace	.977	21.557[a]	6.000	3.000	.015	.977
	Wilks' Lambda	.023	21.557[a]	6.000	3.000	.015	.977
	Hotelling's Trace	43.115	21.557[a]	6.000	3.000	.015	.977
	Roy's Largest Root	43.115	21.557[a]	6.000	3.000	.015	.977
ConditionHRmean	Pillai's Trace	.974	294.995[a]	1.000	8.000	.000	.974
	Wilks' Lambda	.026	294.995[a]	1.000	8.000	.000	.974
	Hotelling's Trace	36.874	294.995[a]	1.000	8.000	.000	.974
	Roy's Largest Root	36.874	294.995[a]	1.000	8.000	.000	.974
Bout * ConditionHRmean	Pillai's Trace	.906	4.795[a]	6.000	3.000	.113	.906
	Wilks' Lambda	.094	4.795[a]	6.000	3.000	.113	.906
	Hotelling's Trace	9.590	4.795[a]	6.000	3.000	.113	.906
	Roy's Largest Root	9.590	4.795[a]	6.000	3.000	.113	.906

a. Exact statistic
b. Design: Intercept
Within Subjects Design: Bout + ConditionHRmean + Bout * ConditionHRmean

Mauchly's Test of Sphericity[b]

Measure:MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Bout	.000	55.551	20	.000	.226	.257	.167
ConditionHRmean	1.000	.000	0	.	1.000	1.000	1.000
Bout * ConditionHRmean	.005	30.541	20	.094	.360	.498	.167

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.
b. Design: Intercept
Within Subjects Design: Bout + ConditionHRmean + Bout * ConditionHRmean

Tests of Within-Subjects Effects

Measure:MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Bout	Sphericity Assumed	6650.857	6	1108.476	101.901	.000	.927
	Greenhouse-Geisser	6650.857	1.358	4895.767	101.901	.000	.927
	Huynh-Feldt	6650.857	1.540	4319.372	101.901	.000	.927
	Lower-bound	6650.857	1.000	6650.857	101.901	.000	.927
Error(Bout)	Sphericity Assumed	522.143	48	10.878			
	Greenhouse-Geisser	522.143	10.868	48.044			
	Huynh-Feldt	522.143	12.318	42.388			
	Lower-bound	522.143	8.000	65.268			
ConditionHRmean	Sphericity Assumed	30302.508	1	30302.508	294.995	.000	.974
	Greenhouse-Geisser	30302.508	1.000	30302.508	294.995	.000	.974
	Huynh-Feldt	30302.508	1.000	30302.508	294.995	.000	.974
	Lower-bound	30302.508	1.000	30302.508	294.995	.000	.974
Error(ConditionHRmean)	Sphericity Assumed	821.778	8	102.722			
	Greenhouse-Geisser	821.778	8.000	102.722			
	Huynh-Feldt	821.778	8.000	102.722			
	Lower-bound	821.778	8.000	102.722			
Bout * ConditionHRmean	Sphericity Assumed	714.825	6	119.138	21.507	.000	.729
	Greenhouse-Geisser	714.825	2.161	330.770	21.507	.000	.729
	Huynh-Feldt	714.825	2.989	239.188	21.507	.000	.729
	Lower-bound	714.825	1.000	714.825	21.507	.002	.729
Error (Bout*ConditionHRmean)	Sphericity Assumed	265.889	48	5.539			
	Greenhouse-Geisser	265.889	17.289	15.379			
	Huynh-Feldt	265.889	23.908	11.121			
	Lower-bound	265.889	8.000	33.236			

Bout: ($p < 0.001$)
Condition: ($p < 0.001$)
Bout*Condition: ($p < 0.001$)

Appendix XVIII (d.ii): Mean heart rate: 40% WR_{max} One way ANOVA

Within-Subjects Factors

Measure:MEASURE_1

BoutHRmean	Dependent Variable
1	HRBout140
2	HRBout240
3	HRBout340
4	HRBout440
5	HRBout540
6	HRBout640
7	HRBout740

Descriptive Statistics

	Mean	Std. Deviation	N
HRBout140	112.8889	9.18483	9
HRBout240	119.0000	10.77033	9
HRBout340	120.8889	10.10500	9
HRBout440	123.7778	10.12148	9
HRBout540	124.8889	9.95546	9
HRBout640	127.3333	10.51190	9
HRBout740	128.0000	10.18577	9

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
BoutHRmean	Pillai's Trace	.949	9.241[a]	6.000	3.000	.048	.949
	Wilks' Lambda	.051	9.241[a]	6.000	3.000	.048	.949
	Hotelling's Trace	18.483	9.241[a]	6.000	3.000	.048	.949
	Roy's Largest Root	18.483	9.241[a]	6.000	3.000	.048	.949

a. Exact statistic
b. Design: Intercept
Within Subjects Design: BoutHRmean

Mauchly's Test of Sphericity[b]

Measure:MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
BoutHRmean	.002	36.107	20	.027	.327	.433	.167

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.
b. Design: Intercept
Within Subjects Design: BoutHRmean

Tests of Within-Subjects Effects

Measure:MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
BoutHRmean	Sphericity Assumed	1512.857	6	252.143	47.224	.000	.855
	Greenhouse-Geisser	1512.857	1.964	770.249	47.224	.000	.855
	Huynh-Feldt	1512.857	2.597	582.472	47.224	.000	.855
	Lower-bound	1512.857	1.000	1512.857	47.224	.000	.855
Error(BoutHRmean)	Sphericity Assumed	256.286	48	5.339			
	Greenhouse-Geisser	256.286	15.713	16.311			
	Huynh-Feldt	256.286	20.778	12.334			
	Lower-bound	256.286	8.000	32.036			

40% WR_{max} Bout: ($p < 0.001$)

Appendix XVIII (d.iii): Mean heart rate: 75% WR_{max} One Way ANOVA

Within-Subjects Factors

Measure:MEASURE_1

Bout	Dependent Variable
1	HRBout175
2	HRBout275
3	HRBout375
4	HRBout475
5	HRBout575
6	HRBout675
7	HRBout775

Descriptive Statistics

	Mean	Std. Deviation	N
HRBout175	134.4444	3.20590	9
HRBout275	146.4444	4.15665	9
HRBout375	151.3333	7.15891	9
HRBout475	156.1111	5.94652	9
HRBout575	159.0000	6.70820	9
HRBout675	161.7778	7.88635	9
HRBout775	164.7778	8.56997	9

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Bout	Pillai's Trace	.976	20.079[a]	6.000	3.000	.016	.976
	Wilks' Lambda	.024	20.079[a]	6.000	3.000	.016	.976
	Hotelling's Trace	40.158	20.079[a]	6.000	3.000	.016	.976
	Roy's Largest Root	40.158	20.079[a]	6.000	3.000	.016	.976

a. Exact statistic
b. Design: Intercept
Within Subjects Design: Bout

Mauchly's Test of Sphericity[b]

Measure:MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Bout	.000	54.744	20	.000	.241	.281	.167

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.
b. Design: Intercept
Within Subjects Design: Bout

Tests of Within-Subjects Effects

Measure:MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Bout	Sphericity Assumed	5852.825	6	975.471	88.054	.000	.917
	Greenhouse-Geisser	5852.825	1.449	4039.457	88.054	.000	.917
	Huynh-Feldt	5852.825	1.685	3472.969	88.054	.000	.917
	Lower-bound	5852.825	1.000	5852.825	88.054	.000	.917
Error(Bout)	Sphericity Assumed	531.746	48	11.078			
	Greenhouse-Geisser	531.746	11.591	45.875			
	Huynh-Feldt	531.746	13.482	39.441			
	Lower-bound	531.746	8.000	66.468			

75% WR_{max} Bout: ($p < 0.001$)

Appendix XVIII (d.iv): Mean heart rate: Ttests

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	HRBout140	112.8889	9	9.18483	3.06161
	HRBout240	119.0000	9	10.77033	3.59011
Pair 2	HRBout240	119.0000	9	10.77033	3.59011
	HRBout340	120.8889	9	10.10500	3.36833
Pair 3	HRBout340	120.8889	9	10.10500	3.36833
	HRBout440	123.7778	9	10.12148	3.37383
Pair 4	HRBout440	123.7778	9	10.12148	3.37383
	HRBout540	124.8889	9	9.95546	3.31849
Pair 5	HRBout540	124.8889	9	9.95546	3.31849
	HRBout640	127.3333	9	10.51190	3.50397
Pair 6	HRBout640	127.3333	9	10.51190	3.50397
	HRBout740	128.0000	9	10.18577	3.39526
Pair 7	HRBout175	134.4444	9	3.20590	1.06863
	HRBout275	146.4444	9	4.15665	1.38555
Pair 8	HRBout275	146.4444	9	4.15665	1.38555
	HRBout375	151.3333	9	7.15891	2.38630
Pair 9	HRBout375	151.3333	9	7.15891	2.38630
	HRBout475	156.1111	9	5.94652	1.98217
Pair 10	HRBout475	156.1111	9	5.94652	1.98217
	HRBout575	159.0000	9	6.70820	2.23607
Pair 11	HRBout575	159.0000	9	6.70820	2.23607
	HRBout675	161.7778	9	7.88635	2.62878
Pair 12	HRBout675	161.7778	9	7.88635	2.62878
	HRBout775	164.7778	9	8.56997	2.85666

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	HRBout140 & HRBout240	9	.962	.000
Pair 2	HRBout240 & HRBout340	9	.982	.000
Pair 3	HRBout340 & HRBout440	9	.976	.000
Pair 4	HRBout440 & HRBout540	9	.980	.000
Pair 5	HRBout540 & HRBout640	9	.988	.000
Pair 6	HRBout640 & HRBout740	9	.992	.000
Pair 7	HRBout175 & HRBout275	9	.696	.037
Pair 8	HRBout275 & HRBout375	9	.788	.012
Pair 9	HRBout375 & HRBout475	9	.918	.000
Pair 10	HRBout475 & HRBout575	9	.971	.000
Pair 11	HRBout575 & HRBout675	9	.971	.000
Pair 12	HRBout675 & HRBout775	9	.989	.000

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	HRBout140 - HRBout240	-6.11111	3.17980	1.05993	-8.55532	-3.66690	-5.766	8	.000
Pair 2	HRBout240 - HRBout340	-1.88889	2.08833	.69611	-3.49412	-.28366	-2.713	8	.027
Pair 3	HRBout340 - HRBout440	-2.88889	2.20479	.73493	-4.58364	-1.19414	-3.931	8	.004
Pair 4	HRBout440 - HRBout540	-1.11111	2.02759	.67586	-2.66965	.44743	-1.644	8	.139
Pair 5	HRBout540 - HRBout640	-2.44444	1.66667	.55556	-3.72556	-1.16333	-4.400	8	.002
Pair 6	HRBout640 - HRBout740	-.66667	1.32288	.44096	-1.68352	.35019	-1.512	8	.169
Pair 7	HRBout175 - HRBout275	-12.00000	3.00000	1.00000	-14.30600	-9.69400	-12.000	8	.000
Pair 8	HRBout275 - HRBout375	-4.88889	4.64878	1.54959	-8.46225	-1.31552	-3.155	8	.013
Pair 9	HRBout375 - HRBout475	-4.77778	2.90593	.96864	-7.01148	-2.54408	-4.932	8	.001
Pair 10	HRBout475 - HRBout575	-2.88889	1.69148	.56383	-4.18908	-1.58870	-5.124	8	.001
Pair 11	HRBout575 - HRBout675	-2.77778	2.10819	.70273	-4.39827	-1.15728	-3.953	8	.004
Pair 12	HRBout675 - HRBout775	-3.00000	1.41421	.47140	-4.08706	-1.91294	-6.364	8	.000

APPENDIX XVIII (e): STATISTICAL ANALYSIS BRS INDICES

Appendix XVIII (e.i): BRS_{UpUp} Supine (Two way ANOVA) (Time/ Condition)

Within-Subjects Factors

Measure:MEASURE_1

Time	Condition	Dependent Variable
1	1	SeqUpCCBS
	2	SeqUp40BS
	3	SeqUp75BS
2	1	SeqUpCC15S
	2	SeqUp4015S
	3	SeqUp7515S
3	1	SeqUpCC60S
	2	SeqUp4060S
	3	SeqUp7560S
4	1	SeqUpCC120S
	2	SeqUp40120S
	3	SeqUp75120S
5	1	SeqUpCC180S
	2	SeqUp40180S
	3	SeqUp75180S
6	1	SeqUpCC24S
	2	SeqUp4024S
	3	SeqUp7524S

Descriptive Statistics

	Mean	Std. Deviation	N
ExCCSeqUpUpBaselineSupine	32.1778	14.44894	9
Ex40%SeqUpUpBaselineSupine	25.2333	11.43624	9
Ex75%SeqUpUpBaselineSupine	25.5000	10.37123	9
ExCCSeqUpUp+15 minSupine	33.9722	13.34801	9
Ex40%SeqUpUp+15minSupine	21.4889	7.69033	9
Ex75%SeqUpUp+15minSupine	11.5000	9.74256	9
ExCCSeqUpUp+60minSupine	30.7111	20.26700	9
Ex40%SeqUpUp+60minSupine	25.8556	12.42277	9
Ex75%SeqUpUp+60minSupine	21.0889	14.24495	9
ExCCSeqUpUp+120minSupine	34.5444	13.32227	9
Ex40%SeqUpUp+120minSupine	24.7111	14.56369	9
Ex75%SeqUpUp+120minSupine	23.4444	12.20114	9
ExCCSeqUpUp+180minSupine	34.6556	11.94823	9
Ex40%SeqUpUp+180minSupine	25.0444	9.72138	9
Ex75%SeqUpUp+180minSupine	24.5000	8.10262	9
ExCCSeqUpUp+24hSupine	23.3000	9.28197	9
Ex40%SeqUpUp+24hSupine	30.1667	14.53418	9
Ex75%SeqUpUp+24hSupine	28.8889	13.51929	9

Multivariate Tests[c]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.581	1.108[a]	5.000	4.000	.474	.581
	Wilks' Lambda	.419	1.108[a]	5.000	4.000	.474	.581
	Hotelling's Trace	1.385	1.108[a]	5.000	4.000	.474	.581
	Roy's Largest Root	1.385	1.108[a]	5.000	4.000	.474	.581
Condition	Pillai's Trace	.601	5.267[a]	2.000	7.000	.040	.601
	Wilks' Lambda	.399	5.267[a]	2.000	7.000	.040	.601
	Hotelling's Trace	1.505	5.267[a]	2.000	7.000	.040	.601
	Roy's Largest Root	1.505	5.267[a]	2.000	7.000	.040	.601
Time * Condition	Pillai's Trace	.[b]	.	.	.	.	.
	Wilks' Lambda	.[b]	.	.	.	.	.
	Hotelling's Trace	.[b]	.	.	.	.	.
	Roy's Largest Root	.[b]	.	.	.	.	.

a. Exact statistic

b. Cannot produce multivariate test statistics because of insufficient residual degrees of freedom.

c. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Mauchly's Test of Sphericity[b]

Measure:MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.074	15.859	14	.359	.609	1.000	.200
Condition	.618	3.366	2	.186	.724	.841	.500
Time * Condition	.000	.	54	.	.331	.594	.100

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Tests of Within-Subjects Effects

Measure:MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	638.213	5	127.643	1.198	.327	.130
	Greenhouse-Geisser	638.213	3.047	209.446	1.198	.332	.130
	Huynh-Feldt	638.213	5.000	127.643	1.198	.327	.130
	Lower-bound	638.213	1.000	638.213	1.198	.306	.130
Error(Time)	Sphericity Assumed	4260.589	40	106.515			
	Greenhouse-Geisser	4260.589	24.377	174.777			
	Huynh-Feldt	4260.589	40.000	106.515			
	Lower-bound	4260.589	8.000	532.574			
Condition	Sphericity Assumed	2315.656	2	1157.828	4.755	.024	.373
	Greenhouse-Geisser	2315.656	1.447	1599.849	4.755	.040	.373
	Huynh-Feldt	2315.656	1.683	1376.058	4.755	.032	.373
	Lower-bound	2315.656	1.000	2315.656	4.755	.061	.373
Error(Condition)	Sphericity Assumed	3896.002	16	243.500			
	Greenhouse-Geisser	3896.002	11.579	336.460			
	Huynh-Feldt	3896.002	13.463	289.396			
	Lower-bound	3896.002	8.000	487.000			
Time * Condition	Sphericity Assumed	2153.503	10	215.350	2.429	.014	.233
	Greenhouse-Geisser	2153.503	3.314	649.729	2.429	.082	.233
	Huynh-Feldt	2153.503	5.940	362.568	2.429	.040	.233
	Lower-bound	2153.503	1.000	2153.503	2.429	.158	.233
Error(Time*Condition)	Sphericity Assumed	7091.320	80	88.642			
	Greenhouse-Geisser	7091.320	26.516	267.439			
	Huynh-Feldt	7091.320	47.517	149.239			
	Lower-bound	7091.320	8.000	886.415			

Time: ($p = 0.327$)
Condition: ($p = 0.032$)
Time*Condition: ($p = 0.082$)

Appendix XVIII (e.ii): $BRS_{DownDown}$ Supine (Two way ANOVA) (Time/ Condition)

Within-Subjects Factors

Measure:MEASURE_1

Time	Condition	Dependent Variable
1	1	SeqDnCCBS
	2	SeqDn40BS
	3	SeqDn75BS
2	1	SeqDnCC15S
	2	SeqDn4015S
	3	SeqDn7515S
3	1	SeqDnCC60S
	2	SeqDn4060S
	3	SeqDn7560S
4	1	SeqDnCC120S
	2	SeqDn40120S
	3	SeqDn75120S
5	1	SeqDnCC180S
	2	SeqDn40180S
	3	SeqDn75180S
6	1	SeqDnCC24S
	2	SeqDn4024S
	3	SeqDn7524S

Descriptive Statistics

	Mean	Std. Deviation	N
ExCCSeqDDownBaselineSupine	27.3000	10.32618	9
Ex40%SeqDDownBaselineSupine	23.0778	10.63823	9
Ex75%SeqDDownBaselineSupine	24.0111	9.78768	9
ExCCSeqDDown+15minSupine	30.9333	17.59822	9
Ex40%SeqDDown+15minSupine	20.4111	7.59711	9
Ex75%SeqDDown+15minSupine	11.3778	10.01022	9
ExCCSeqDDown+60minSupine	24.6444	5.94393	9
Ex40%SeqDDown+60minSupine	23.5111	7.77262	9
Ex75%SeqDDown+60minSupine	18.9056	7.40213	9
ExCCSeqDDown+120minSupine	23.2222	7.30835	9
Ex40%SeqDDown+120minSupine	22.5667	8.04161	9
Ex75%SeqDDown+120minSupine	21.9778	14.23796	9
ExCCSeqDDown+180minSupine	25.5333	9.34131	9
Ex40%SeqDDown+180minSupine	21.0889	7.11994	9
Ex75%SeqDDown+180minSupine	21.3778	7.91656	9
ExCCSeqDDown+24hSupine	20.3333	6.36475	9
Ex40%SeqDDown+24hSupine	23.2056	8.13751	9
Ex75%SeqDDown+24hSupine	23.7778	6.55129	9

Multivariate Tests[c]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.549	.976[a]	5.000	4.000	.524	.549
	Wilks' Lambda	.451	.976[a]	5.000	4.000	.524	.549
	Hotelling's Trace	1.219	.976[a]	5.000	4.000	.524	.549
	Roy's Largest Root	1.219	.976[a]	5.000	4.000	.524	.549
Condition	Pillai's Trace	.370	2.056[a]	2.000	7.000	.198	.370
	Wilks' Lambda	.630	2.056[a]	2.000	7.000	.198	.370
	Hotelling's Trace	.588	2.056[a]	2.000	7.000	.198	.370
	Roy's Largest Root	.588	2.056[a]	2.000	7.000	.198	.370
Time * Condition	Pillai's Trace	.[b]	.	.	.	.	.
	Wilks' Lambda	.[b]	.	.	.	.	.
	Hotelling's Trace	.[b]	.	.	.	.	.
	Roy's Largest Root	.[b]	.	.	.	.	.

a. Exact statistic

b. Cannot produce multivariate test statistics because of insufficient residual degrees of freedom.

c. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Mauchly's Test of Sphericity[b]

Measure:MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.011	27.322	14	.025	.445	.625	.200
Condition	.561	4.047	2	.132	.695	.795	.500
Time * Condition	.000	.	54	.	.313	.536	.100

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Tests of Within-Subjects Effects

Measure:MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	209.950	5	41.990	.770	.577	.088
	Greenhouse-Geisser	209.950	2.227	94.290	.770	.491	.088
	Huynh-Feldt	209.950	3.125	67.192	.770	.526	.088
	Lower-bound	209.950	1.000	209.950	.770	.406	.088
Error(Time)	Sphericity Assumed	2181.487	40	54.537			
	Greenhouse-Geisser	2181.487	17.813	122.465			
	Huynh-Feldt	2181.487	24.997	87.269			
	Lower-bound	2181.487	8.000	272.686			
Condition	Sphericity Assumed	707.511	2	353.756	3.377	.060	.297
	Greenhouse-Geisser	707.511	1.390	509.077	3.377	.084	.297
	Huynh-Feldt	707.511	1.590	445.065	3.377	.075	.297
	Lower-bound	707.511	1.000	707.511	3.377	.103	.297
Error(Condition)	Sphericity Assumed	1676.200	16	104.763			
	Greenhouse-Geisser	1676.200	11.118	150.760			
	Huynh-Feldt	1676.200	12.717	131.803			
	Lower-bound	1676.200	8.000	209.525			
Time * Condition	Sphericity Assumed	1451.154	10	145.115	2.819	.005	.261
	Greenhouse-Geisser	1451.154	3.127	464.113	2.819	.058	.261
	Huynh-Feldt	1451.154	5.364	270.533	2.819	.025	.261
	Lower-bound	1451.154	1.000	1451.154	2.819	.132	.261
Error(Time*Condition)	Sphericity Assumed	4118.277	80	51.478			
	Greenhouse-Geisser	4118.277	25.014	164.640			
	Huynh-Feldt	4118.277	42.912	95.969			
	Lower-bound	4118.277	8.000	514.785			

Time: (p = 0.491)
Condition: (p = 0.084)
Time*Condition: (p = 0.58)

Appendix XVIII (e.iii): $BRS_{\alpha LF}$ Supine (Two way ANOVA) (Time/ Condition)

Within-Subjects Factors

Measure:MEASURE_1

Time	Condition	Dependent Variable
1	1	ALFCCBS
	2	ALF40BS
	3	ALF75BS
2	1	ALFCC15S
	2	ALF4015S
	3	ALF7515S
3	1	ALFCC60S
	2	ALF4060S
	3	ALF7560S
4	1	ALFCC120S
	2	ALF40120S
	3	ALF75120S
5	1	ALFCC180S
	2	ALF40180S
	3	ALF75180S
6	1	ALFCC24S
	2	ALF4024S
	3	ALF7524S

Descriptive Statistics

	Mean	Std. Deviation	N
ExCCAlphaLFBaselineSupine	13.8778	6.42471	9
Ex40%AlphLFBaselineSupine	15.0889	5.95954	9
Ex75%AlphaLFBaselineSupine	16.3444	8.91783	9
ExCCAlphaLF+15minSupine	23.1000	8.48591	9
Ex40%AlphaLF+15minSupine	15.8222	6.10630	9
Ex75%AlphaLF+15minSupine	7.3667	6.42223	9
ExCCAlphaLF+60minSupine	21.0444	4.00846	9
Ex40%AlphLF+60minSupine	13.9000	5.50976	9
Ex75%AlphaLF+60Supine	12.0500	5.09117	9
ExCCAlphaLF+120minSupine	19.3222	7.83801	9
Ex40%AlphaLF+120minSupine	18.1778	8.69882	9
Ex75%AlphaLF+120Supine	16.9444	6.04258	9
ExCCAlphaLF+180minSupine	19.7111	4.75932	9
Ex40%AlphaLF+180minSupine	18.8111	7.14431	9
Ex75%AlphaLF+180Supine	18.1000	7.98984	9
ExCCAlphaLF+24hSupine	16.2333	6.93488	9
Ex40%AlphaLF+24hSupine	15.9722	6.10589	9
Ex75%AlphaLF+24hSupine	17.9889	8.77147	9

Multivariate Tests[c]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.651	1.491[a]	5.000	4.000	.360	.651
	Wilks' Lambda	.349	1.491[a]	5.000	4.000	.360	.651
	Hotelling's Trace	1.864	1.491[a]	5.000	4.000	.360	.651
	Roy's Largest Root	1.864	1.491[a]	5.000	4.000	.360	.651
Condition	Pillai's Trace	.436	2.710[a]	2.000	7.000	.134	.436
	Wilks' Lambda	.564	2.710[a]	2.000	7.000	.134	.436
	Hotelling's Trace	.774	2.710[a]	2.000	7.000	.134	.436
	Roy's Largest Root	.774	2.710[a]	2.000	7.000	.134	.436
Time * Condition	Pillai's Trace	.[b]	.	.	.	.	.
	Wilks' Lambda	.[b]	.	.	.	.	.
	Hotelling's Trace	.[b]	.	.	.	.	.
	Roy's Largest Root	.[b]	.	.	.	.	.

a. Exact statistic

b. Cannot produce multivariate test statistics because of insufficient residual degrees of freedom.

c. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Mauchly's Test of Sphericity[b]

Measure:MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.067	16.522	14	.318	.522	.796	.200
Condition	.735	2.158	2	.340	.790	.952	.500
Time * Condition	.000	.	54	.	.318	.552	.100

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Tests of Within-Subjects Effects

Measure:MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	325.298	5	65.060	2.111	.084	.209
	Greenhouse-Geisser	325.298	2.608	124.730	2.111	.136	.209
	Huynh-Feldt	325.298	3.982	81.687	2.111	.103	.209
	Lower-bound	325.298	1.000	325.298	2.111	.184	.209
Error(Time)	Sphericity Assumed	1233.007	40	30.825			
	Greenhouse-Geisser	1233.007	20.864	59.097			
	Huynh-Feldt	1233.007	31.858	38.703			
	Lower-bound	1233.007	8.000	154.126			
Condition	Sphericity Assumed	460.673	2	230.336	4.401	.030	.355
	Greenhouse-Geisser	460.673	1.581	291.452	4.401	.042	.355
	Huynh-Feldt	460.673	1.904	241.891	4.401	.032	.355
	Lower-bound	460.673	1.000	460.673	4.401	.069	.355
Error(Condition)	Sphericity Assumed	837.385	16	52.337			
	Greenhouse-Geisser	837.385	12.645	66.223			
	Huynh-Feldt	837.385	15.236	54.962			
	Lower-bound	837.385	8.000	104.673			
Time * Condition	Sphericity Assumed	1147.647	10	114.765	5.186	.000	.393
	Greenhouse-Geisser	1147.647	3.178	361.102	5.186	.006	.393
	Huynh-Feldt	1147.647	5.517	208.008	5.186	.001	.393
	Lower-bound	1147.647	1.000	1147.647	5.186	.052	.393
Error(Time*Condition)	Sphericity Assumed	1770.408	80	22.130			
	Greenhouse-Geisser	1770.408	25.425	69.631			
	Huynh-Feldt	1770.408	44.139	40.110			
	Lower-bound	1770.408	8.000	221.301			

Time: (p = 0.136)
Condition: (p = 0.032)
Time*Condition: (p = 0.006)

Appendix XVIII (e.iv): BRS_{TFTG} Supine (Two way ANOVA) (Time/ Condition)

Within-Subjects Factors

Measure:MEASURE_1

Time	Condition	Dependent Variable
1	1	TFTGCCBS
	2	TFTG40BS
	3	TFTG75BS
2	1	TFTGCC15S
	2	TFTG4015S
	3	TFTG7515S
3	1	TFTGCC60S
	2	TFTG4060S
	3	TFTG7560S
4	1	TFTGCC120S
	2	TFTG40120S
	3	TFTG75120S
5	1	TFTGCC180S
	2	TFTG40180S
	3	TFTG75180S
6	1	TFTGCC24S
	2	TFTG4024S
	3	TFTG7524S

Descriptive Statistics

	Mean	Std. Deviation	N
ExCCTFTGBaselineSupine	15.0656	5.47849	9
Ex40%TFTGBaselineSupine	16.0011	5.82167	9
Ex75%TFTGBaselineSupine	17.2556	6.51385	9
ExCCTFTG+15minSupine	24.6533	8.66932	9
Ex40%TFTG+15minSupine	14.4289	5.72707	9
Ex75%TFTG+15minSupine	6.9556	5.37901	9
ExCCTFTG+60minSupine	20.1700	5.72606	9
Ex40%TFTG60minSupine	17.6644	7.60083	9
Ex75%TFTG+60minSupine	12.1189	6.05534	9
ExCCTFTG+120minSupine	19.1011	6.42219	9
Ex40%TFTG120minSupine	16.3022	7.03789	9
Ex75%TFTG+120minSupine	16.2889	5.94696	9
ExCCTFTG+180minSupine	19.3589	5.07145	9
Ex40%TFTG180minSupine	17.9589	7.27542	9
Ex75%TFTG+180minSupine	16.8800	7.22387	9
ExCCTFTG+24hSupine	15.2300	5.98371	9
Ex40%TFTG24hSupine	17.6678	5.70816	9
Ex75%TFTG+24hSupine	16.7956	6.53185	9

Multivariate Tests[c]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.476	.727[a]	5.000	4.000	.639	.476
	Wilks' Lambda	.524	.727[a]	5.000	4.000	.639	.476
	Hotelling's Trace	.908	.727[a]	5.000	4.000	.639	.476
	Roy's Largest Root	.908	.727[a]	5.000	4.000	.639	.476
Condition	Pillai's Trace	.555	4.371[a]	2.000	7.000	.059	.555
	Wilks' Lambda	.445	4.371[a]	2.000	7.000	.059	.555
	Hotelling's Trace	1.249	4.371[a]	2.000	7.000	.059	.555
	Roy's Largest Root	1.249	4.371[a]	2.000	7.000	.059	.555
Time * Condition	Pillai's Trace	.[b]	.	.	.	.	.
	Wilks' Lambda	.[b]	.	.	.	.	.
	Hotelling's Trace	.[b]	.	.	.	.	.
	Roy's Largest Root	.[b]	.	.	.	.	.

a. Exact statistic

b. Cannot produce multivariate test statistics because of insufficient residual degrees of freedom.

c. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Mauchly's Test of Sphericity[b]

Measure:MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.015	25.648	14	.039	.500	.746	.200
Condition	.426	5.978	2	.050	.635	.701	.500
Time * Condition	.000	.	54	.	.310	.528	.100

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Tests of Within-Subjects Effects

Measure:MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	117.281	5	23.456	1.328	.272	.142
	Greenhouse-Geisser	117.281	2.501	46.887	1.328	.291	.142
	Huynh-Feldt	117.281	3.730	31.439	1.328	.283	.142
	Lower-bound	117.281	1.000	117.281	1.328	.282	.142
Error(Time)	Sphericity Assumed	706.654	40	17.666			
	Greenhouse-Geisser	706.654	20.011	35.314			
	Huynh-Feldt	706.654	29.843	23.679			
	Lower-bound	706.654	8.000	88.332			
Condition	Sphericity Assumed	558.338	2	279.169	3.642	.050	.313
	Greenhouse-Geisser	558.338	1.270	439.489	3.642	.078	.313
	Huynh-Feldt	558.338	1.402	398.287	3.642	.072	.313
	Lower-bound	558.338	1.000	558.338	3.642	.093	.313
Error(Condition)	Sphericity Assumed	1226.437	16	76.652			
	Greenhouse-Geisser	1226.437	10.163	120.672			
	Huynh-Feldt	1226.437	11.215	109.359			
	Lower-bound	1226.437	8.000	153.305			
Time * Condition	Sphericity Assumed	1292.253	10	129.225	5.651	.000	.414
	Greenhouse-Geisser	1292.253	3.096	417.332	5.651	.004	.414
	Huynh-Feldt	1292.253	5.275	244.957	5.651	.000	.414
	Lower-bound	1292.253	1.000	1292.253	5.651	.045	.414
Error(Time*Condition)	Sphericity Assumed	1829.407	80	22.868			
	Greenhouse-Geisser	1829.407	24.772	73.851			
	Huynh-Feldt	1829.407	42.203	43.347			
	Lower-bound	1829.407	8.000	228.676			

Time: (P = 0.291)
Condition: (p = 0.078)
Time*Condition: (p = 0.004)

Appendix XVIII (e.v): BRS_{UpUp} Tilt (Two way ANOVA) (Time/ Condition)

Within-Subjects Factors

Measure:MEASURE_1

Time	Conditions	Dependent Variable
1	1	SeqUpCCBT
	2	SeqUp40BT
	3	SeqUp75BT
2	1	SeqUpCC15T
	2	SeqUp4015T
	3	SeqUp7515T
3	1	SeqUpCC60T
	2	SeqUp4060T
	3	SeqUp7560T
4	1	SeqUpCC120T
	2	SeqUp40120T
	3	SeqUp75120T
5	1	SeqUpCC180T
	2	SeqUp40180T
	3	SeqUp75180T
6	1	SeqUpCC24T
	2	SeqUp4024T
	3	SeqUp7524T

Descriptive Statistics

	Mean	Std. Deviation	N
ExCCSeqUpUpBaselineTilt	9.8333	2.52834	9
Ex40%SeqUpUpBaselineTilt	10.2444	2.04824	9
Ex75%SeqUpUpBaselineTilt	10.3333	2.99750	9
ExCCSeqUpUp+15minTilt	11.5278	3.89817	9
Ex40%SeqUpUp+15minTilt	10.7444	4.70986	9
Ex75%SeqUpUp+15minTilt	7.6000	2.69165	9
ExCCSeqUpUp+60minTilt	12.1000	3.98967	9
Ex40%SeqUpUp+60minTilt	10.5722	3.52767	9
Ex75%SeqUpUp+60minTilt	8.7333	2.57973	9
ExCCSeqUpUp+120minTilt	10.4556	3.56970	9
Ex40%SeqUpUp+120minTilt	10.1556	2.82671	9
Ex75%SeqUpUp+120minTilt	9.8111	3.21459	9
ExCCSeqUpUp+180minTilt	10.1222	2.08613	9
Ex40%SeqUpUp+180minTilt	10.9000	4.61979	9
Ex75%SeqUpUp+180minTilt	10.6222	3.72115	9
ExCCSeqUpUp+24hTilt	9.6111	2.65775	9
Ex40%SeqUpUp+24hTilt	11.1444	4.22939	9
Ex75%SeqUpUp+24hTilt	11.0444	3.50646	9

Multivariate Tests[c]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.630	1.362[a]	5.000	4.000	.394	.630
	Wilks' Lambda	.370	1.362[a]	5.000	4.000	.394	.630
	Hotelling's Trace	1.702	1.362[a]	5.000	4.000	.394	.630
	Roy's Largest Root	1.702	1.362[a]	5.000	4.000	.394	.630
Conditions	Pillai's Trace	.327	1.698[a]	2.000	7.000	.250	.327
	Wilks' Lambda	.673	1.698[a]	2.000	7.000	.250	.327
	Hotelling's Trace	.485	1.698[a]	2.000	7.000	.250	.327
	Roy's Largest Root	.485	1.698[a]	2.000	7.000	.250	.327
Time * Conditions	Pillai's Trace	.[b]	.	.	.	.	.
	Wilks' Lambda	.[b]	.	.	.	.	.
	Hotelling's Trace	.[b]	.	.	.	.	.
	Roy's Largest Root	.[b]	.	.	.	.	.

a. Exact statistic

b. Cannot produce multivariate test statistics because of insufficient residual degrees of freedom.

c. Design: Intercept
Within Subjects Design: Time + Conditions + Time * Conditions

Mauchly's Test of Sphericity[b]

Measure:MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.053	17.956	14	.241	.523	.799	.200
Conditions	.610	3.463	2	.177	.719	.834	.500
Time * Conditions	.000	.	54	.	.319	.554	.100

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b. Design: Intercept
Within Subjects Design: Time + Conditions + Time * Conditions

Tests of Within-Subjects Effects

Measure:MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	9.418	5	1.884	.597	.702	.069
	Greenhouse-Geisser	9.418	2.613	3.604	.597	.602	.069
	Huynh-Feldt	9.418	3.995	2.358	.597	.667	.069
	Lower-bound	9.418	1.000	9.418	.597	.462	.069
Error(Time)	Sphericity Assumed	126.201	40	3.155			
	Greenhouse-Geisser	126.201	20.906	6.037			
	Huynh-Feldt	126.201	31.958	3.949			
	Lower-bound	126.201	8.000	15.775			
Conditions	Sphericity Assumed	30.935	2	15.468	.789	.471	.090
	Greenhouse-Geisser	30.935	1.439	21.504	.789	.438	.090
	Huynh-Feldt	30.935	1.668	18.542	.789	.453	.090
	Lower-bound	30.935	1.000	30.935	.789	.400	.090
Error(Conditions)	Sphericity Assumed	313.795	16	19.612			
	Greenhouse-Geisser	313.795	11.508	27.266			
	Huynh-Feldt	313.795	13.347	23.510			
	Lower-bound	313.795	8.000	39.224			
Time * Conditions	Sphericity Assumed	117.196	10	11.720	3.540	.001	.307
	Greenhouse-Geisser	117.196	3.186	36.788	3.540	.027	.307
	Huynh-Feldt	117.196	5.540	21.154	3.540	.007	.307
	Lower-bound	117.196	1.000	117.196	3.540	.097	.307
Error(Time*Conditions)	Sphericity Assumed	264.867	80	3.311			
	Greenhouse-Geisser	264.867	25.486	10.393			
	Huynh-Feldt	264.867	44.322	5.976			
	Lower-bound	264.867	8.000	33.108			

Time: ($p = 0.602$)
Condition: ($p = 0.453$)
Time*Condition: ($p = 0.027$)

Appendix XVIII (e.vi): $BRS_{DownDown}$ Tilt (Two way ANOVA) (Time/ Condition)

Within-Subjects Factors

Measure:MEASURE_1

Time	Condition	Dependent Variable
1	1	SeqDnCCBT
	2	SeqDn40BT
	3	SeqDn75BT
2	1	SeqDnCC15T
	2	SeqDn4015T
	3	SeqDn7515T
3	1	SeqDnCC60T
	2	SeqDn4060T
	3	SeqDn7560T
4	1	SeqDnCC120T
	2	SeqDn40120T
	3	SeqDn75120T
5	1	SeqDnCC180T
	2	SeqDn40180T
	3	SeqDn75180T
6	1	SeqDnCC24T
	2	SeqDn4024T
	3	SeqDn7524T

Descriptive Statistics

	Mean	Std. Deviation	N
ExCCSeqDDownBaselineTilt	8.1333	2.75590	9
Ex40%SeqDDownBaselineTilt	9.1111	4.09831	9
Ex75%SeqDDownBaselineTilt	7.9667	2.68747	9
ExCCSeqDDown+15minTilt	10.0000	3.55739	9
Ex40%SeqDDown+15minTilt	7.6222	4.28538	9
Ex75%SeqDDown+15minTilt	4.9000	3.16149	9
ExCCSeqDDown+60minTilt	9.0778	3.73523	9
Ex40%SeqDDown+60minTilt	7.1389	3.11446	9
Ex75%SeqDDown+60minTilt	5.4444	1.81184	9
ExCCSeqDDown+120minTilt	8.9111	2.37247	9
Ex40%SeqDDown+120minTilt	7.9000	3.12890	9
Ex75%SeqDDown+120minTilt	6.8000	2.20511	9
ExCCSeqDDown+180minTilt	8.4889	1.84285	9
Ex40%SeqDDown+180minTilt	8.2222	3.43285	9
Ex75%SeqDDown+180minTilt	7.5889	2.76245	9
ExCCSeqDDown+24hTilt	7.3000	2.08567	9
Ex40%SeqDDown+24hTilt	9.0778	3.38222	9
Ex75%SeqDDown+24hTilt	8.3667	2.47285	9

Multivariate Tests[c]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.678	1.684[a]	5.000	4.000	.317	.678
	Wilks' Lambda	.322	1.684[a]	5.000	4.000	.317	.678
	Hotelling's Trace	2.105	1.684[a]	5.000	4.000	.317	.678
	Roy's Largest Root	2.105	1.684[a]	5.000	4.000	.317	.678
Condition	Pillai's Trace	.654	6.613[a]	2.000	7.000	.024	.654
	Wilks' Lambda	.346	6.613[a]	2.000	7.000	.024	.654
	Hotelling's Trace	1.889	6.613[a]	2.000	7.000	.024	.654
	Roy's Largest Root	1.889	6.613[a]	2.000	7.000	.024	.654
Time * Condition	Pillai's Trace	.[b]	.	.	.	.	.
	Wilks' Lambda	.[b]	.	.	.	.	.
	Hotelling's Trace	.[b]	.	.	.	.	.
	Roy's Largest Root	.[b]	.	.	.	.	.

a. Exact statistic

b. Cannot produce multivariate test statistics because of insufficient residual degrees of freedom.

c. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Mauchly's Test of Sphericity[b]

Measure:MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.005	32.544	14	.005	.457	.649	.200
Condition	.462	5.410	2	.067	.650	.724	.500
Time * Condition	.000	.	54	.	.294	.484	.100

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Tests of Within-Subjects Effects

Measure:MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	27.848	5	5.570	1.791	.137	.183
	Greenhouse-Geisser	27.848	2.284	12.193	1.791	.192	.183
	Huynh-Feldt	27.848	3.246	8.578	1.791	.170	.183
	Lower-bound	27.848	1.000	27.848	1.791	.218	.183
Error(Time)	Sphericity Assumed	124.366	40	3.109			
	Greenhouse-Geisser	124.366	18.272	6.806			
	Huynh-Feldt	124.366	25.970	4.789			
	Lower-bound	124.366	8.000	15.546			
Condition	Sphericity Assumed	94.875	2	47.438	2.375	.125	.229
	Greenhouse-Geisser	94.875	1.300	72.975	2.375	.151	.229
	Huynh-Feldt	94.875	1.448	65.525	2.375	.145	.229
	Lower-bound	94.875	1.000	94.875	2.375	.162	.229
Error(Condition)	Sphericity Assumed	319.557	16	19.972			
	Greenhouse-Geisser	319.557	10.401	30.724			
	Huynh-Feldt	319.557	11.583	27.588			
	Lower-bound	319.557	8.000	39.945			
Time * Condition	Sphericity Assumed	127.049	10	12.705	5.935	.000	.426
	Greenhouse-Geisser	127.049	2.943	43.177	5.935	.004	.426
	Huynh-Feldt	127.049	4.841	26.245	5.935	.000	.426
	Lower-bound	127.049	1.000	127.049	5.935	.041	.426
Error(Time*Condition)	Sphericity Assumed	171.251	80	2.141			
	Greenhouse-Geisser	171.251	23.540	7.275			
	Huynh-Feldt	171.251	38.727	4.422			
	Lower-bound	171.251	8.000	21.406			

Time: (p = 0.192)
Condition: (p = 0.151)
Time*Condition (p = .004)

Appendix XVIII (e.vii): $BRS_{\alpha LF}$ Tilt (Two way ANOVA) (Time/ Condition)

Within-Subjects Factors

Measure:MEASURE_1

Time	Condition	Dependent Variable
1	1	ALFCCBT
	2	ALF40BT
	3	ALF75BT
2	1	ALFCC15T
	2	ALF4015T
	3	ALF7515T
3	1	ALFCC60T
	2	ALF4060T
	3	ALF7560T
4	1	ALFCC120T
	2	ALF40120T
	3	ALF75120T
5	1	ALFCC180T
	2	ALF40180T
	3	ALF75180T
6	1	ALFCC24T
	2	ALF4024T
	3	ALF7524T

Descriptive Statistics

	Mean	Std. Deviation	N
ExCCAlphaLFBaselineTilt	8.8556	2.16686	9
Ex40%AlphaLFBaselineTilt	9.4889	2.45023	9
Ex75%AlphaLFBaselineTilt	8.7778	2.20951	9
ExCCAlphaLF+15minTilt	10.1722	2.60061	9
Ex40%AlphaLF+15minTilt	8.6333	2.55734	9
Ex75%AlphaLF+15minTilt	5.2778	2.62144	9
ExCCAlphaLF+60minTilt	9.9111	2.69000	9
Ex40%AlphaLF+60minTilt	8.9667	3.00624	9
Ex75%AlphaLF+60minTilt	6.8111	2.04905	9
ExCCAlphaLF+120minTilt	10.0444	2.58172	9
Ex40%AlphaLF+120minTilt	9.0444	2.09172	9
Ex75%AlphaLF+120minTilt	8.5444	2.66979	9
ExCCAlphaLF+180minTilt	9.9333	2.43721	9
Ex40%AlphaLF+180minTilt	9.6778	3.11038	9
Ex75%AlphaLF+180minTilt	9.4333	5.00600	9
ExCCAlphaLF+24hTilt	8.2333	2.34254	9
Ex40%AlphaLF+24hTilt	10.0111	3.18255	9
Ex75%AlphaLF+24hTilt	9.3889	2.29098	9

Multivariate Tests[c]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.809	3.398[a]	5.000	4.000	.130	.809
	Wilks' Lambda	.191	3.398[a]	5.000	4.000	.130	.809
	Hotelling's Trace	4.248	3.398[a]	5.000	4.000	.130	.809
	Roy's Largest Root	4.248	3.398[a]	5.000	4.000	.130	.809
Condition	Pillai's Trace	.824	16.340[a]	2.000	7.000	.002	.824
	Wilks' Lambda	.176	16.340[a]	2.000	7.000	.002	.824
	Hotelling's Trace	4.669	16.340[a]	2.000	7.000	.002	.824
	Roy's Largest Root	4.669	16.340[a]	2.000	7.000	.002	.824
Time * Condition	Pillai's Trace	.[b]	.	.	.	.	.
	Wilks' Lambda	.[b]	.	.	.	.	.
	Hotelling's Trace	.[b]	.	.	.	.	.
	Roy's Largest Root	.[b]	.	.	.	.	.

a. Exact statistic

b. Cannot produce multivariate test statistics because of insufficient residual degrees of freedom.

c. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Mauchly's Test of Sphericity[b]

Measure:MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.006	30.949	14	.009	.459	.655	.200
Condition	.213	10.839	2	.004	.559	.586	.500
Time * Condition	.000	.	54	.	.360	.690	.100

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Tests of Within-Subjects Effects

Measure:MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	45.353	5	9.071	2.335	.060	.226
	Greenhouse-Geisser	45.353	2.297	19.743	2.335	.119	.226
	Huynh-Feldt	45.353	3.275	13.850	2.335	.092	.226
	Lower-bound	45.353	1.000	45.353	2.335	.165	.226
Error(Time)	Sphericity Assumed	155.375	40	3.884			
	Greenhouse-Geisser	155.375	18.377	8.455			
	Huynh-Feldt	155.375	26.196	5.931			
	Lower-bound	155.375	8.000	19.422			
Condition	Sphericity Assumed	69.431	2	34.715	3.712	.047	.317
	Greenhouse-Geisser	69.431	1.119	62.051	3.712	.084	.317
	Huynh-Feldt	69.431	1.173	59.199	3.712	.081	.317
	Lower-bound	69.431	1.000	69.431	3.712	.090	.317
Error(Condition)	Sphericity Assumed	149.631	16	9.352			
	Greenhouse-Geisser	149.631	8.951	16.716			
	Huynh-Feldt	149.631	9.383	15.947			
	Lower-bound	149.631	8.000	18.704			
Time * Condition	Sphericity Assumed	117.778	10	11.778	6.227	.000	.438
	Greenhouse-Geisser	117.778	3.598	32.732	6.227	.001	.438
	Huynh-Feldt	117.778	6.903	17.063	6.227	.000	.438
	Lower-bound	117.778	1.000	117.778	6.227	.037	.438
Error(Time*Condition)	Sphericity Assumed	151.306	80	1.891			
	Greenhouse-Geisser	151.306	28.786	5.256			
	Huynh-Feldt	151.306	55.222	2.740			
	Lower-bound	151.306	8.000	18.913			

Time: (p = 0.119)
Condition: (p = 0.084)
Time*Condition (p = 0.001)

Appendix XVIII (e.viii): BRS_{TFTG} Tilt (Two way ANOVA) (Time/ Condition)

Within-Subjects Factors

Measure:MEASURE_1

Time	Condition	Dependent Variable
1	1	TFTGCCBT
	2	TFTG40BT
	3	TFTG75BT
2	1	TFTGCC15T
	2	TFTG4015T
	3	TFTG7515T
3	1	TFTGCC60T
	2	TFTG4060T
	3	TFTG7560T
4	1	TFTGCC120T
	2	TFTG40120T
	3	TFTG75120T
5	1	TFTGCC180T
	2	TFTG40180T
	3	TFTG75180T
6	1	TFTGCC24T
	2	TFTG4024T
	3	TFTG7524T

Descriptive Statistics

	Mean	Std. Deviation	N
ExCCTFTGBaselineTilt	7.9156	2.06327	9
Ex40%TFTGBaselineTilt	8.3611	2.29684	9
Ex75%TFTGBaselineTilt	8.0889	2.01617	9
ExCCTFTG+15minTilt	10.1428	2.41971	9
Ex40%TFTG+15minTilt	8.2478	3.46114	9
Ex75%TFTG+15minTilt	4.9167	2.67030	9
ExCCTFTG+60minTilt	9.5822	2.58371	9
Ex40%TFTG+60minTilt	8.1544	3.16082	9
Ex75%TFTG+60minTilt	6.2267	1.68516	9
ExCCTFTG+120minTilt	9.5144	2.25066	9
Ex40%TFTG+120minTilt	8.4100	2.27536	9
Ex75%TFTG+120minTilt	7.8244	2.45055	9
ExCCTFTG+180minTilt	9.1533	1.90713	9
Ex40%TFTG+180minTilt	9.2311	3.48128	9
Ex75%TFTG180minTilt	9.1856	4.52062	9
ExCCTFTG24hTilt	7.2867	1.99879	9
Ex40%TFTG+24hTilt	9.2556	2.99585	9
Ex75%TFTG24hTilt	8.9444	2.59288	9

Multivariate Tests[c]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Time	Pillai's Trace	.539	.936[a]	5.000	4.000	.541	.539
	Wilks' Lambda	.461	.936[a]	5.000	4.000	.541	.539
	Hotelling's Trace	1.170	.936[a]	5.000	4.000	.541	.539
	Roy's Largest Root	1.170	.936[a]	5.000	4.000	.541	.539
Condition	Pillai's Trace	.632	6.011[a]	2.000	7.000	.030	.632
	Wilks' Lambda	.368	6.011[a]	2.000	7.000	.030	.632
	Hotelling's Trace	1.717	6.011[a]	2.000	7.000	.030	.632
	Roy's Largest Root	1.717	6.011[a]	2.000	7.000	.030	.632
Time * Condition	Pillai's Trace	.[b]	.	.	.	.	.
	Wilks' Lambda	.[b]	.	.	.	.	.
	Hotelling's Trace	.[b]	.	.	.	.	.
	Roy's Largest Root	.[b]	.	.	.	.	.

a. Exact statistic

b. Cannot produce multivariate test statistics because of insufficient residual degrees of freedom.

c. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Mauchly's Test of Sphericity[b]

Measure:MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[a]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Time	.011	27.758	14	.022	.471	.681	.200
Condition	.598	3.597	2	.166	.713	.825	.500
Time * Condition	.000	.	54	.	.380	.768	.100

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

b. Design: Intercept
Within Subjects Design: Time + Condition + Time * Condition

Tests of Within-Subjects Effects

Measure:MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Time	Sphericity Assumed	35.138	5	7.028	2.026	.096	.202
	Greenhouse-Geisser	35.138	2.357	14.906	2.026	.154	.202
	Huynh-Feldt	35.138	3.405	10.319	2.026	.127	.202
	Lower-bound	35.138	1.000	35.138	2.026	.192	.202
Error(Time)	Sphericity Assumed	138.738	40	3.468			
	Greenhouse-Geisser	138.738	18.858	7.357			
	Huynh-Feldt	138.738	27.243	5.093			
	Lower-bound	138.738	8.000	17.342			
Condition	Sphericity Assumed	58.174	2	29.087	3.438	.057	.301
	Greenhouse-Geisser	58.174	1.427	40.774	3.438	.079	.301
	Huynh-Feldt	58.174	1.649	35.273	3.438	.070	.301
	Lower-bound	58.174	1.000	58.174	3.438	.101	.301
Error(Condition)	Sphericity Assumed	135.364	16	8.460			
	Greenhouse-Geisser	135.364	11.414	11.859			
	Huynh-Feldt	135.364	13.194	10.260			
	Lower-bound	135.364	8.000	16.921			
Time * Condition	Sphericity Assumed	153.225	10	15.322	9.223	.000	.536
	Greenhouse-Geisser	153.225	3.803	40.293	9.223	.000	.536
	Huynh-Feldt	153.225	7.678	19.957	9.223	.000	.536
	Lower-bound	153.225	1.000	153.225	9.223	.016	.536
Error(Time*Condition)	Sphericity Assumed	132.904	80	1.661			
	Greenhouse-Geisser	132.904	30.422	4.369			
	Huynh-Feldt	132.904	61.421	2.164			
	Lower-bound	132.904	8.000	16.613			

Time: ($p = 0.154$)
Condition: ($p = 0.070$)
Time*Condition: ($p = < 0.001$)

Appendix XVIII (e.ix): Baseline Supine (Paired Ttests)

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ExCCSeqUpUpBaselineSupine	32.1778	9	14.44894	4.81631
	Ex40%SeqUpUpBaselineSupine	25.2333	9	11.43624	3.81208
Pair 2	ExCCSeqUpUpBaselineSupine second use	32.1778	9	14.44894	4.81631
	Ex75%SeqUpUpBaselineSupine	25.5000	9	10.37123	3.45708
Pair 3	Ex40%SeqUpUpBaselineSupine second use	25.2333	9	11.43624	3.81208
	Ex75%SeqUpUpBaselineSupine second use	25.5000	9	10.37123	3.45708
Pair 4	ExCCSeqDDownBaselineSupine	27.3000	9	10.32618	3.44206
	Ex40%SeqDDownBaselineSupine	23.0778	9	10.63823	3.54608
Pair 5	ExCCSeqDDownBaselineSupine second use	27.3000	9	10.32618	3.44206
	Ex75%SeqDDownBaselineSupine	24.0111	9	9.78768	3.26256
Pair 6	Ex40%SeqDDownBaselineSupine second use	23.0778	9	10.63823	3.54608
	Ex75%SeqDDownBaselineSupine second use	24.0111	9	9.78768	3.26256
Pair 7	ExCCAlphaLFBaselineSupine	13.8778	9	6.42471	2.14157
	Ex40%AlphaLFBaselineSupine	15.0889	9	5.95954	1.98651
Pair 8	ExCCAlphaLFBaselineSupine second use	13.8778	9	6.42471	2.14157
	Ex75%AlphaLFBaselineSupine	16.3444	9	8.91783	2.97261
Pair 9	Ex40%AlphaLFBaselineSupine second use	15.0889	9	5.95954	1.98651
	Ex75%AlphaLFBaselineSupine second use	16.3444	9	8.91783	2.97261
Pair 10	ExCCTFTGBaselineSupine	15.0656	9	5.47849	1.82616
	Ex40%TFTGBaselineSupine	16.0011	9	5.82167	1.94056
Pair 11	ExCCTFTGBaselineSupine second use	15.0656	9	5.47849	1.82616
	Ex75%TFTGBaselineSupine	17.2556	9	6.51385	2.17128
Pair 12	Ex40%TFTGBaselineSupine second use	16.0011	9	5.82167	1.94056
	Ex75%TFTGBaselineSupine second use	17.2556	9	6.51385	2.17128

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ExCCSeqUpUpBaselineSupine & Ex40%SeqUpUpBaselineSupine	9	.579	.102
Pair 2	ExCCSeqUpUpBaselineSupine second use & Ex75%SeqUpUpBaselineSupine	9	.532	.140
Pair 3	Ex40%SeqUpUpBaselineSupine second use & Ex75%SeqUpUpBaselineSupine second use	9	.462	.210
Pair 4	ExCCSeqDDownBaselineSupine & Ex40%SeqDDownBaselineSupine	9	.715	.030
Pair 5	ExCCSeqDDownBaselineSupine second use & Ex75%SeqDDownBaselineSupine	9	.543	.131
Pair 6	Ex40%SeqDDownBaselineSupine second use & Ex75%SeqDDownBaselineSupine second use	9	.742	.022
Pair 7	ExCCAlphaLFBaselineSupine & Ex40%AlphaLFBaselineSupine	9	.396	.291
Pair 8	ExCCAlphaLFBaselineSupine second use & Ex75%AlphaLFBaselineSupine	9	.582	.100
Pair 9	Ex40%AlphaLFBaselineSupine second use & Ex75%AlphaLFBaselineSupine second use	9	.412	.270
Pair 10	ExCCTFTGBaselineSupine & Ex40%TFTGBaselineSupine	9	.366	.332
Pair 11	ExCCTFTGBaselineSupine second use & Ex75%TFTGBaselineSupine	9	.335	.378
Pair 12	Ex40%TFTGBaselineSupine second use & Ex75%TFTGBaselineSupine second use	9	.308	.421

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	ExCCSeqUpUpBaseline Supine - Ex40% SeqUpUpBaselineSupine	6.94444	12.17057	4.05686	-2.41068	16.29957	1.712	8	.125
Pair 2	ExCCSeqUpUpBaseline Supine second use - Ex75% SeqUpUpBaselineSupine	6.67778	12.52495	4.17498	-2.94975	16.30531	1.599	8	.148
Pair 3	Ex40% SeqUpUpBaselineSupine second use - Ex75% SeqUpUpBaselineSupine second use	-.26667	11.34240	3.78080	-8.98521	8.45187	-.071	8	.946
Pair 4	ExCCSeqDDown BaselineSupine - Ex40% SeqDDownBaseline Supine	4.22222	7.91293	2.63764	-1.86019	10.30464	1.601	8	.148
Pair 5	ExCCSeqDDown BaselineSupine second use - Ex75% SeqDDownBaseline Supine	3.28889	9.62516	3.20839	-4.10966	10.68744	1.025	8	.335
Pair 6	Ex40% SeqDDownBaseline Supine second use - Ex75% SeqDDownBaseline Supine second use	-.93333	7.38563	2.46188	-6.61043	4.74376	-.379	8	.714
Pair 7	ExCCAlphaLFBaseline Supine - Ex40% AlphaLFBaselineSupine	-1.21111	6.81477	2.27159	-6.44941	4.02719	-.533	8	.608
Pair 8	ExCCAlphaLFBaseline Supine second use - Ex75% AlphaLFBaselineSupine	-2.46667	7.35255	2.45085	-8.11834	3.18500	-1.006	8	.344
Pair 9	Ex40% AlphaLFBaselineSupine second use - Ex75% AlphaLFBaselineSupine second use	-1.25556	8.43877	2.81292	-7.74217	5.23105	-.446	8	.667
Pair 10	ExCCTFTGBaseline Supine - Ex40% TFTGBaselineSupine	-.93556	6.36613	2.12204	-5.82899	3.95788	-.441	8	.671
Pair 11	ExCCTFTGBaseline Supine second use - Ex75% TFTGBaselineSupine	-2.19000	6.96664	2.32221	-7.54504	3.16504	-.943	8	.373
Pair 12	Ex40% TFTGBaselineSupine second use - Ex75% TFTGBaselineSupine second use	-1.25444	7.27986	2.42662	-6.85024	4.34135	-.517	8	.619

Appendix XVIII (e.x): + 15 min Supine (Paired Ttests)

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ExCCSeqUpUp+15minSupine	33.9722	9	13.34801	4.44934
	Ex40%SeqUpUp+15minSupine	21.4889	9	7.69033	2.56344
Pair 2	ExCCSeqUpUp+15minSupine second use	33.9722	9	13.34801	4.44934
	Ex75%SeqUpUp+15minSupine	11.5000	9	9.74256	3.24752
Pair 3	Ex40%SeqUpUp+15minSupine second use	21.4889	9	7.69033	2.56344
	Ex75%SeqUpUp+15minSupine second use	11.5000	9	9.74256	3.24752
Pair 4	ExCCSeqDDown+15minSupine	30.9333	9	17.59822	5.86607
	Ex40%SeqDDown+15minSupine	20.4111	9	7.59711	2.53237
Pair 5	ExCCSeqDDown+15minSupine second use	30.9333	9	17.59822	5.86607
	Ex75%SeqDDown+15minSupine	11.3778	9	10.01022	3.33674
Pair 6	Ex40%SeqDDown+15minSupine second use	20.4111	9	7.59711	2.53237
	Ex75%SeqDDown+15minSupine second use	11.3778	9	10.01022	3.33674
Pair 7	ExCCAlphaLF+15minSupine	23.1000	9	8.48591	2.82864
	Ex40%AlphaLF+15minSupine	15.8222	9	6.10630	2.03543
Pair 8	ExCCAlphaLF+15minSupine second use	23.1000	9	8.48591	2.82864
	Ex75%AlphaLF+15minSupine	7.3667	9	6.42223	2.14074
Pair 9	Ex40%AlphaLF+15minSupine second use	15.8222	9	6.10630	2.03543
	Ex75%AlphaLF+15minSupine second use	7.3667	9	6.42223	2.14074
Pair 10	ExCCTFTG+15minSupine	24.6533	9	8.66932	2.88977
	Ex40%TFTG+15minSupine	14.4289	9	5.72707	1.90902
Pair 11	ExCCTFTG+15minSupine second use	24.6533	9	8.66932	2.88977
	Ex75%TFTG+15minSupine	6.9556	9	5.37901	1.79300
Pair 12	Ex40%TFTG+15minSupine second use	14.4289	9	5.72707	1.90902
	Ex75%TFTG+15minSupine second use	6.9556	9	5.37901	1.79300

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ExCCSeqUpUp+15minSupine & Ex40%SeqUpUp+15minSupine	9	.255	.508
Pair 2	ExCCSeqUpUp+15minSupine second use & Ex75%SeqUpUp+15minSupine	9	-.251	.515
Pair 3	Ex40%SeqUpUp+15minSupine second use & Ex75%SeqUpUp+15minSupine second use	9	.455	.218
Pair 4	ExCCSeqDDown+15minSupine & Ex40%SeqDDown+15minSupine	9	-.310	.417
Pair 5	ExCCSeqDDown+15minSupine second use & Ex75%SeqDDown+15minSupine	9	.028	.943
Pair 6	Ex40%SeqDDown+15minSupine second use & Ex75%SeqDDown+15minSupine second use	9	.397	.290
Pair 7	ExCCAlphaLF+15minSupine & Ex40%AlphaLF+15minSupine	9	.156	.689
Pair 8	ExCCAlphaLF+15minSupine second use & Ex75%AlphaLF+15minSupine	9	-.544	.130
Pair 9	Ex40%AlphaLF+15minSupine second use & Ex75%AlphaLF+15minSupine second use	9	-.047	.904
Pair 10	ExCCTFTG+15minSupine & Ex40%TFTG+15minSupine	9	.262	.495
Pair 11	ExCCTFTG+15minSupine second use & Ex75%TFTG+15minSupine	9	-.683	.043
Pair 12	Ex40%TFTG+15minSupine second use & Ex75%TFTG+15minSupine second use	9	-.119	.760

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	ExCCSeqUpUp+15min Supine - Ex40% SeqUpUp+15minSupine	12.48333	13.60129	4.53376	2.02846	22.93821	2.753	8	.025
Pair 2	ExCCSeqUpUp+15min Supine second use - Ex75% SeqUpUp+15minSupine	22.47222	18.39492	6.13164	8.33263	36.61181	3.665	8	.006
Pair 3	Ex40% SeqUpUp+15minSupine second use - Ex75% SeqUpUp+15minSupine second use	9.98889	9.26370	3.08790	2.86818	17.10960	3.235	8	.012
Pair 4	ExCCSeqDDown+15min Supine - Ex40% SeqDDown+15minSupine	10.52222	21.21926	7.07309	-5.78834	26.83279	1.488	8	.175
Pair 5	ExCCSeqDDown+15min Supine second use - Ex75%SeqDDown+15minSupine	19.55556	19.99919	6.66640	4.18281	34.92830	2.933	8	.019
Pair 6	Ex40%SeqDDown+15minSupine second use - Ex75%SeqDDown+15minSupine second use	9.03333	9.87370	3.29123	1.44373	16.62293	2.745	8	.025
Pair 7	ExCCAlphaLF+15min Supine - Ex40% AlphaLF+15minSupine	7.27778	9.65221	3.21740	-.14156	14.69712	2.262	8	.054
Pair 8	ExCCAlphaLF+15min Supine second use - Ex75% AlphaLF+15minSupine	15.73333	13.13718	4.37906	5.63520	25.83147	3.593	8	.007
Pair 9	Ex40% AlphaLF+15minSupine second use - Ex75% AlphaLF+15minSupine second use	8.45556	9.06740	3.02247	1.48573	15.42538	2.798	8	.023
Pair 10	ExCCTFTG+15minSupine - Ex40% TFTG+15minSupine	10.22444	9.05035	3.01678	3.26773	17.18116	3.389	8	.010
Pair 11	ExCCTFTG+15minSupine second use - Ex75% TFTG+15minSupine	17.69778	12.95227	4.31742	7.74178	27.65377	4.099	8	.003
Pair 12	Ex40% TFTG+15minSupine second use - Ex75% TFTG+15minSupine second use	7.47333	8.31086	2.77029	1.08504	13.86163	2.698	8	.027

Appendix XVIII (e.xi): + 60 Supine (Paired Ttests)

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ExCCSeqUpUp+60minSupine	30.7111	9	20.26700	6.75567
	Ex40%SeqUpUp+60minSupine	25.8556	9	12.42277	4.14092
Pair 2	ExCCSeqUpUp+60minSupine second use	30.7111	9	20.26700	6.75567
	Ex75%SeqUpUp+60minSupine	21.0889	9	14.24495	4.74832
Pair 3	Ex40%SeqUpUp+60minSupine second use	25.8556	9	12.42277	4.14092
	Ex75%SeqUpUp+60minSupine second use	21.0889	9	14.24495	4.74832
Pair 4	ExCCSeqDDown+60minSupine	24.6444	9	5.94393	1.98131
	Ex40%SeqDDown+60minSupine	23.5111	9	7.77262	2.59087
Pair 5	ExCCSeqDDown+60minSupine second use	24.6444	9	5.94393	1.98131
	Ex75%SeqDDown+60minSupine	18.9056	9	7.40213	2.46738
Pair 6	Ex40%SeqDDown+60minSupine second use	23.5111	9	7.77262	2.59087
	Ex75%SeqDDown+60minSupine second use	18.9056	9	7.40213	2.46738
Pair 7	ExCCAlphaLF+60minSupine	21.0444	9	4.00846	1.33615
	Ex40%AlphaLF+60minSupine	13.9000	9	5.50976	1.83659
Pair 8	ExCCAlphaLF+60minSupine second use	21.0444	9	4.00846	1.33615
	Ex75%AlphaLF+60minSupine	12.0500	9	5.09117	1.69706
Pair 9	Ex40%AlphaLF+60minSupine second use	13.9000	9	5.50976	1.83659
	Ex75%AlphaLF+60minSupine second use	12.0500	9	5.09117	1.69706
Pair 10	ExCCTFTG+60minSupine	20.1700	9	5.72606	1.90869
	Ex40%TFTG+60minSupine	17.6644	9	7.60083	2.53361
Pair 11	ExCCTFTG+60minSupine second use	20.1700	9	5.72606	1.90869
	Ex75%TFTG+60minSupine	12.1189	9	6.05534	2.01845
Pair 12	Ex40%TFTG+60minSupine second use	17.6644	9	7.60083	2.53361
	Ex75%TFTG+60minSupine second use	12.1189	9	6.05534	2.01845

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ExCCSeqUpUp+60minSupine & Ex40%SeqUpUp+60minSupine	9	-.193	.619
Pair 2	ExCCSeqUpUp+60minSupine second use & Ex75%SeqUpUp+60minSupine	9	-.328	.389
Pair 3	Ex40%SeqUpUp+60minSupine second use & Ex75%SeqUpUp+60minSupine second use	9	.709	.033
Pair 4	ExCCSeqDDown+60minSupine & Ex40%SeqDDown+60minSupine	9	.067	.864
Pair 5	ExCCSeqDDown+60minSupine second use & Ex75%SeqDDown+60minSupine	9	.025	.950
Pair 6	Ex40%SeqDDown+60minSupine second use & Ex75%SeqDDown+60minSupine second use	9	.344	.365
Pair 7	ExCCAlphaLF+60minSupine & Ex40%AlphaLF+60minSupine	9	.018	.963
Pair 8	ExCCAlphaLF+60minSupine second use & Ex75%AlphaLF+60minSupine	9	-.116	.766
Pair 9	Ex40%AlphaLF+60minSupine second use & Ex75%AlphaLF+60minSupine second use	9	.944	.000
Pair 10	ExCCTFTG+60minSupine & Ex40%TFTG+60minSupine	9	-.463	.210
Pair 11	ExCCTFTG+60minSupine second use & Ex75%TFTG+60minSupine	9	-.858	.003
Pair 12	Ex40%TFTG+60minSupine second use & Ex75%TFTG+60minSupine second use	9	.710	.032

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	ExCCSeqUpUp+60min Supine - Ex40% SeqUpUp+60minSupine	4.85556	25.73291	8.57764	-14.92451	24.63562	.566	8	.587
Pair 2	ExCCSeqUpUp+60min Supine second use - Ex75% SeqUpUp+60minSupine	9.62222	28.33989	9.44663	-12.16175	31.40619	1.019	8	.338
Pair 3	Ex40% SeqUpUp+60minSupine second use - Ex75% SeqUpUp+60minSupine second use	4.76667	10.31443	3.43814	-3.16171	12.69504	1.386	8	.203
Pair 4	ExCCSeqDDown+60min Supine - Ex40% SeqDDown+60minSupin e	1.13333	9.46269	3.15423	-6.14033	8.40700	.359	8	.729
Pair 5	ExCCSeqDDown+60min Supine second use - Ex75%SeqDDown+60mi nSupine	5.73889	9.37816	3.12605	-1.46980	12.94758	1.836	8	.104
Pair 6	Ex40%SeqDDown+60mi nSupine second use - Ex75%SeqDDown+60mi nSupine second use	4.60556	8.69772	2.89924	-2.08010	11.29121	1.589	8	.151
Pair 7	ExCCAlphaLF+60min Supine - Ex40% AlphaLF+60minSupine	7.14444	6.75446	2.25149	1.95250	12.33638	3.173	8	.013
Pair 8	ExCCAlphaLF+60min Supine second use - Ex75% AlphaLF+60minSupine	8.99444	6.83614	2.27871	3.73972	14.24916	3.947	8	.004
Pair 9	Ex40% AlphaLF+60minSupine second use - Ex75% AlphaLF+60minSupine second use	1.85000	1.82722	.60907	.44547	3.25453	3.037	8	.016
Pair 10	ExCCTFTG+60minSupine - Ex40% TFTG+60minSupine	2.50556	11.43898	3.81299	-6.28722	11.29833	.657	8	.530
Pair 11	ExCCTFTG+60minSupine second use - Ex75% TFTG+60minSupine	8.05111	11.35526	3.78509	-.67732	16.77954	2.127	8	.066
Pair 12	Ex40% TFTG+60minSupine second use - Ex75% TFTG+60minSupine second use	5.54556	5.39199	1.79733	1.40090	9.69021	3.085	8	.015

Appendix XVIII (e.xii): + 120 min Supine (Paired Ttests)

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ExCCSeqUpUp+120minSupine	34.5444	9	13.32227	4.44076
	Ex40%SeqUpUp+120minSupine	24.7111	9	14.56369	4.85456
Pair 2	ExCCSeqUpUp+120minSupine second use	34.5444	9	13.32227	4.44076
	Ex75%SeqUpUp+120minSupine	23.4444	9	12.20114	4.06705
Pair 3	Ex40%SeqUpUp+120minSupine second use	24.7111	9	14.56369	4.85456
	Ex75%SeqUpUp+120minSupine second use	23.4444	9	12.20114	4.06705
Pair 4	ExCCSeqDDown+120minSupine	23.2222	9	7.30835	2.43612
	Ex40%SeqDDown+120minSupine	22.5667	9	8.04161	2.68054
Pair 5	ExCCSeqDDown+120minSupine second use	23.2222	9	7.30835	2.43612
	Ex75%SeqDDown+120minSupine	21.9778	9	14.23796	4.74599
Pair 6	Ex40%SeqDDown+120minSupine second use	22.5667	9	8.04161	2.68054
	Ex75%SeqDDown+120minSupine second use	21.9778	9	14.23796	4.74599
Pair 7	ExCCAlphaLF+120minSupine	19.3222	9	7.83801	2.61267
	Ex40%AlphaLF+120minSupine	18.1778	9	8.69882	2.89961
Pair 8	ExCCAlphaLF+120minSupine second use	19.3222	9	7.83801	2.61267
	Ex75%AlphaLF+120minSupine	16.9444	9	6.04258	2.01419
Pair 9	Ex40%AlphaLF+120minSupine second use	18.1778	9	8.69882	2.89961
	Ex75%AlphaLF+120minSupine second use	16.9444	9	6.04258	2.01419
Pair 10	ExCCTFTG+120minSupine	19.1011	9	6.42219	2.14073
	Ex40%TFTG+120minSupine	16.3022	9	7.03789	2.34596
Pair 11	ExCCTFTG+120minSupine second use	19.1011	9	6.42219	2.14073
	Ex75%TFTG+120minSupine	16.2889	9	5.94696	1.98232
Pair 12	Ex40%TFTG+120minSupine second use	16.3022	9	7.03789	2.34596
	Ex75%TFTG+120minSupine second use	16.2889	9	5.94696	1.98232

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ExCCSeqUpUp+120minSupine & Ex40%SeqUpUp+120minSupine	9	.327	.390
Pair 2	ExCCSeqUpUp+120minSupine second use & Ex75%SeqUpUp+120minSupine	9	.141	.717
Pair 3	Ex40%SeqUpUp+120minSupine second use & Ex75%SeqUpUp+120minSupine second use	9	.811	.008
Pair 4	ExCCSeqDDown+120minSupine & Ex40%SeqDDown+120minSupine	9	.133	.734
Pair 5	ExCCSeqDDown+120minSupine second use & Ex75%SeqDDown+120minSupine	9	-.281	.465
Pair 6	Ex40%SeqDDown+120minSupine second use & Ex75%SeqDDown+120minSupine second use	9	.851	.004
Pair 7	ExCCAlphaLF+120minSupine & Ex40%AlphaLF+120minSupine	9	.550	.125
Pair 8	ExCCAlphaLF+120minSupine second use & Ex75%AlphaLF+120minSupine	9	.672	.048
Pair 9	Ex40%AlphaLF+120minSupine second use & Ex75%AlphaLF+120minSupine second use	9	.816	.007
Pair 10	ExCCTFTG+120minSupine & Ex40%TFTG+120minSupine	9	-.244	.526
Pair 11	ExCCTFTG+120minSupine second use & Ex75%TFTG+120minSupine	9	-.635	.066
Pair 12	Ex40%TFTG+120minSupine second use & Ex75%TFTG+120minSupine second use	9	.751	.020

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	ExCCSeqUpUp+120min Supine - Ex40% SeqUpUp+120minSupine	9.83333	16.20694	5.40231	-2.62443	22.29109	1.820	8	.106
Pair 2	ExCCSeqUpUp+120min Supine second use - Ex75% SeqUpUp+120minSupine	11.10000	16.74575	5.58192	-1.77192	23.97192	1.989	8	.082
Pair 3	Ex40% SeqUpUp+120minSupine second use - Ex75% SeqUpUp+120minSupine second use	1.26667	8.51968	2.83989	-5.28214	7.81547	.446	8	.667
Pair 4	ExCCSeq DDown+120minSupine - Ex40% SeqDDown+120min Supine	.65556	10.12412	3.37471	-7.12653	8.43764	.194	8	.851
Pair 5	ExCCSeq DDown+120minSupine second use - Ex75% SeqDDown+120min Supine	1.24444	17.73437	5.91146	-12.38740	14.87629	.211	8	.839
Pair 6	Ex40% SeqDDown+120min Supine second use - Ex75% SeqDDown+120min Supine second use	.58889	8.51623	2.83874	-5.95726	7.13504	.207	8	.841
Pair 7	ExCCAlphaLF+120min Supine - Ex40% AlphaLF+120minSupine	1.14444	7.88418	2.62806	-4.91587	7.20476	.435	8	.675
Pair 8	ExCCAlphaLF+120min Supine second use - Ex75% AlphaLF+120minSupine	2.37778	5.85999	1.95333	-2.12661	6.88216	1.217	8	.258
Pair 9	Ex40% AlphaLF+120minSupine second use - Ex75% AlphaLF+120minSupine second use	1.23333	5.13882	1.71294	-2.71672	5.18338	.720	8	.492
Pair 10	ExCCTFTG+120min Supine - Ex40% TFTG+120minSupine	2.79889	10.62419	3.54140	-5.36758	10.96536	.790	8	.452
Pair 11	ExCCTFTG+120min Supine second use - Ex75% TFTG+120minSupine	2.81222	11.18605	3.72868	-5.78614	11.41059	.754	8	.472
Pair 12	Ex40% TFTG+120minSupine second use - Ex75% TFTG+120minSupine second use	.01333	4.69555	1.56518	-3.59598	3.62265	.009	8	.993

Appendix XVIII (e.xiii): + 180 min Supine (Paired Ttests)

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ExCCSeqUpUp+180minSupine	34.6556	9	11.94823	3.98274
	Ex40%SeqUpUp+180minSupine	25.0444	9	9.72138	3.24046
Pair 2	ExCCSeqUpUp+180minSupine second use	34.6556	9	11.94823	3.98274
	Ex75%SeqUpUp+180minSupine	24.5000	9	8.10262	2.70087
Pair 3	Ex40%SeqUpUp+180minSupine second use	25.0444	9	9.72138	3.24046
	Ex75%SeqUpUp+180minSupine second use	24.5000	9	8.10262	2.70087
Pair 4	ExCCSeqDDown+180minSupine	25.5333	9	9.34131	3.11377
	Ex40%SeqDDown+180minSupine	21.0889	9	7.11994	2.37331
Pair 5	ExCCSeqDDown+180minSupine second use	25.5333	9	9.34131	3.11377
	Ex75%SeqDDown+180minSupine	21.3778	9	7.91656	2.63885
Pair 6	Ex40%SeqDDown+180minSupine second use	21.0889	9	7.11994	2.37331
	Ex75%SeqDDown+180minSupine second use	21.3778	9	7.91656	2.63885
Pair 7	ExCCAlphaLF+180minSupine	19.7111	9	4.75932	1.58644
	Ex40%AlphaLF+180minSupine	18.8111	9	7.14431	2.38144
Pair 8	ExCCAlphaLF+180minSupine second use	19.7111	9	4.75932	1.58644
	Ex75%AlphaLF+180minSupine	18.1000	9	7.98984	2.66328
Pair 9	Ex40%AlphaLF+180minSupine second use	18.8111	9	7.14431	2.38144
	Ex75%AlphaLF+180minSupine second use	18.1000	9	7.98984	2.66328
Pair 10	ExCCTFTG+180minSupine	19.3589	9	5.07145	1.69048
	Ex40%TFTG+180minSupine	17.9589	9	7.27542	2.42514
Pair 11	ExCCTFTG+180minSupine second use	19.3589	9	5.07145	1.69048
	Ex75%TFTG+180minSupine	16.8800	9	7.22387	2.40796
Pair 12	Ex40%TFTG+180minSupine second use	17.9589	9	7.27542	2.42514
	Ex75%TFTG+180minSupine second use	16.8800	9	7.22387	2.40796

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ExCCSeqUpUp+180minSupine & Ex40%SeqUpUp+180minSupine	9	.366	.332
Pair 2	ExCCSeqUpUp+180minSupine second use & Ex75%SeqUpUp+180minSupine	9	.598	.089
Pair 3	Ex40%SeqUpUp+180minSupine second use & Ex75%SeqUpUp+180minSupine second use	9	.791	.011
Pair 4	ExCCSeqDDown+180minSupine & Ex40%SeqDDown+180minSupine	9	.453	.220
Pair 5	ExCCSeqDDown+180minSupine second use & Ex75%SeqDDown+180minSupine	9	.542	.131
Pair 6	Ex40%SeqDDown+180minSupine second use & Ex75%SeqDDown+180minSupine second use	9	.574	.106
Pair 7	ExCCAlphaLF+180minSupine & Ex40%AlphaLF+180minSupine	9	.676	.046
Pair 8	ExCCAlphaLF+180minSupine second use & Ex75%AlphaLF+180minSupine	9	.542	.132
Pair 9	Ex40%AlphaLF+180minSupine second use & Ex75%AlphaLF+180minSupine second use	9	.872	.002
Pair 10	ExCCTFTG+180minSupine & Ex40%TFTG+180minSupine	9	.698	.037
Pair 11	ExCCTFTG+180minSupine second use & Ex75%TFTG+180minSupine	9	.795	.010
Pair 12	Ex40%TFTG+180minSupine second use & Ex75%TFTG+180minSupine second use	9	.640	.064

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	ExCCSeqUpUp+180min Supine - Ex40% SeqUpUp+180minSupine	9.61111	12.33475	4.11158	.12978	19.09244	2.338	8	.048
Pair 2	ExCCSeqUpUp+180min Supine second use - Ex75% SeqUpUp+180minSupine	10.15556	9.62160	3.20720	2.75974	17.55138	3.166	8	.013
Pair 3	Ex40% SeqUpUp+180minSupine second use - Ex75% SeqUpUp+180minSupine second use	.54444	5.96785	1.98928	-4.04285	5.13174	.274	8	.791
Pair 4	ExCCSeq DDown+180minSupine - Ex40% SeqDDown+180min Supine	4.44444	8.81109	2.93703	-2.32836	11.21725	1.513	8	.169
Pair 5	ExCCSeq DDown+180minSupine second use - Ex75% SeqDDown+180min Supine	4.15556	8.34882	2.78294	-2.26191	10.57303	1.493	8	.174
Pair 6	Ex40% SeqDDown+180min Supine second use - Ex75% SeqDDown+180min Supine second use	-.28889	6.97880	2.32627	-5.65327	5.07549	-.124	8	.904
Pair 7	ExCCAlphaLF+180min Supine - Ex40% AlphaLF+180minSupine	.90000	5.26474	1.75491	-3.14684	4.94684	.513	8	.622
Pair 8	ExCCAlphaLF+180min Supine second use - Ex75% AlphaLF+180minSupine	1.61111	6.72820	2.24273	-3.56064	6.78286	.718	8	.493
Pair 9	Ex40% AlphaLF+180minSupine second use - Ex75% AlphaLF+180minSupine second use	.71111	3.91677	1.30559	-2.29959	3.72181	.545	8	.601
Pair 10	ExCCTFTG+180min Supine - Ex40% TFTG+180minSupine	1.40000	5.20944	1.73648	-2.60433	5.40433	.806	8	.443
Pair 11	ExCCTFTG+180min Supine second use - Ex75% TFTG+180minSupine	2.47889	4.43606	1.47869	-.93097	5.88874	1.676	8	.132
Pair 12	Ex40% TFTG+180minSupine second use - Ex75% TFTG+180minSupine second use	1.07889	6.15405	2.05135	-3.65153	5.80931	.526	8	.613

Appendix XVIII (e.xiv): + 24 h Supine (Paired Ttests)

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ExCCSeqUpUp24hSupine	23.3000	9	9.28197	3.09399
	Ex40%SeqUpUp24hSupine	30.1667	9	14.53418	4.84473
Pair 2	ExCCSeqUpUp24hSupine second use	23.3000	9	9.28197	3.09399
	Ex75%SeqUpUp24hSupine	28.8889	9	13.51929	4.50643
Pair 3	Ex40%SeqUpUp24hSupine second use	30.1667	9	14.53418	4.84473
	Ex75%SeqUpUp24hSupine second use	28.8889	9	13.51929	4.50643
Pair 4	ExCCSeqDDown24hSupine	20.3333	9	6.36475	2.12158
	Ex40%SeqDDown24hSupine	23.2056	9	8.13751	2.71250
Pair 5	ExCCSeqDDown24hSupine second use	20.3333	9	6.36475	2.12158
	Ex75%SeqDDown24hSupine	23.7778	9	6.55129	2.18376
Pair 6	Ex40%SeqDDown24hSupine second use	23.2056	9	8.13751	2.71250
	Ex75%SeqDDown24hSupine second use	23.7778	9	6.55129	2.18376
Pair 7	ExCCAlphaLF24hSupine	16.2333	9	6.93488	2.31163
	Ex40%AlphaLF24hSupine	15.9722	9	6.10589	2.03530
Pair 8	ExCCAlphaLF24hSupine second use	16.2333	9	6.93488	2.31163
	Ex75%AlphaLF24hSupine	17.9889	9	8.77147	2.92382
Pair 9	Ex40%AlphaLF24hSupine second use	15.9722	9	6.10589	2.03530
	Ex75%AlphaLF24hSupine second use	17.9889	9	8.77147	2.92382
Pair 10	ExCCTFTG24hSupine	15.2300	9	5.98371	1.99457
	Ex40%TFTG24hSupine	17.6678	9	5.70816	1.90272
Pair 11	ExCCTFTG24hSupine second use	15.2300	9	5.98371	1.99457
	Ex75%TFTG24hSupine	16.7956	9	6.53185	2.17728
Pair 12	Ex40%TFTG24hSupine second use	17.6678	9	5.70816	1.90272
	Ex75%TFTG24hSupine second use	16.7956	9	6.53185	2.17728

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ExCCSeqUpUp24hSupine & Ex40%SeqUpUp24hSupine	9	.689	.040
Pair 2	ExCCSeqUpUp24hSupine second use & Ex75%SeqUpUp24hSupine	9	.522	.150
Pair 3	Ex40%SeqUpUp24hSupine second use & Ex75%SeqUpUp24hSupine second use	9	.086	.826
Pair 4	ExCCSeqDDown24hSupine & Ex40%SeqDDown24hSupine	9	.933	.000
Pair 5	ExCCSeqDDown24hSupine second use & Ex75%SeqDDown24hSupine	9	.532	.140
Pair 6	Ex40%SeqDDown24hSupine second use & Ex75%SeqDDown24hSupine second use	9	.765	.016
Pair 7	ExCCAlphaLF24hSupine & Ex40%AlphaLF24hSupine	9	.712	.031
Pair 8	ExCCAlphaLF24hSupine second use & Ex75%AlphaLF24hSupine	9	.406	.278
Pair 9	Ex40%AlphaLF24hSupine second use & Ex75%AlphaLF24hSupine second use	9	.594	.092
Pair 10	ExCCTFTG24hSupine & Ex40%TFTG24hSupine	9	.838	.005
Pair 11	ExCCTFTG24hSupine second use & Ex75%TFTG24hSupine	9	.654	.056
Pair 12	Ex40%TFTG24hSupine second use & Ex75%TFTG24hSupine second use	9	.834	.005

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	ExCCSeqUpUp24h Supine - Ex40% SeqUpUp24hSupine	-6.86667	10.55580	3.51860	-14.98058	1.24724	-1.952	8	.087
Pair 2	ExCCSeqUpUp24h Supine second use - Ex75% SeqUpUp24hSupine	-5.58889	11.74632	3.91544	-14.61791	3.44013	-1.427	8	.191
Pair 3	Ex40% SeqUpUp24hSupine second use - Ex75% SeqUpUp24hSupine second use	1.27778	18.98123	6.32708	-13.31248	15.86804	.202	8	.845
Pair 4	ExCCSeqDDown24h Supine - Ex40% SeqDDown24hSupine	-2.87222	3.18130	1.06043	-5.31759	-.42686	-2.709	8	.027
Pair 5	ExCCSeqDDown24h Supine second use - Ex75% SeqDDown24hSupine	-3.44444	6.24782	2.08261	-8.24695	1.35806	-1.654	8	.137
Pair 6	Ex40% SeqDDown24hSupine second use - Ex75% SeqDDown24hSupine second use	-.57222	5.24757	1.74919	-4.60586	3.46141	-.327	8	.752
Pair 7	ExCCAlphaLF24hSupine - Ex40% AlphaLF24hSupine	.26111	5.00448	1.66816	-3.58568	4.10790	.157	8	.879
Pair 8	ExCCAlphaLF24hSupine second use - Ex75% AlphaLF24hSupine	-1.75556	8.69800	2.89933	-8.44143	4.93032	-.606	8	.562
Pair 9	Ex40% AlphaLF24hSupine second use - Ex75% AlphaLF24hSupine second use	-2.01667	7.11416	2.37139	-7.48509	3.45176	-.850	8	.420
Pair 10	ExCCTFTG24hSupine - Ex40%TFTG24hSupine	-2.43778	3.33348	1.11116	-5.00012	.12456	-2.194	8	.060
Pair 11	ExCCTFTG24hSupine second use - Ex75% TFTG24hSupine	-1.56556	5.23153	1.74384	-5.58687	2.45576	-.898	8	.396
Pair 12	Ex40%TFTG24hSupine second use - Ex75% TFTG24hSupine second use	.87222	3.61352	1.20451	-1.90538	3.64982	.724	8	.490

Appendix XVIII (e.xv): Baseline Tilt (Paired Ttests)

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ExCCSeqUpUpBaselineTilt	9.8333	9	2.52834	.84278
	Ex40%SeqUpUpBaselineTilt	10.2444	9	2.04824	.68275
Pair 2	ExCCSeqUpUpBaselineTilt second use	9.8333	9	2.52834	.84278
	Ex75%SeqUpUpBaselineTilt	10.3333	9	2.99750	.99917
Pair 3	Ex40%SeqUpUpBaselineTilt second use	10.2444	9	2.04824	.68275
	Ex75%SeqUpUpBaselineTilt second use	10.3333	9	2.99750	.99917
Pair 4	ExCCSeqDDownBaselineTilt	8.1333	9	2.75590	.91863
	Ex40%SeqDDownBaselineTilt	9.1111	9	4.09831	1.36610
Pair 5	ExCCSeqDDownBaselineTilt second use	8.1333	9	2.75590	.91863
	Ex75%SeqDDownBaselineTilt	7.9667	9	2.68747	.89582
Pair 6	Ex40%SeqDDownBaselineTilt second use	9.1111	9	4.09831	1.36610
	Ex75%SeqDDownBaselineTilt second use	7.9667	9	2.68747	.89582
Pair 7	ExCCAlphaLFBaselineTilt	8.8556	9	2.16686	.72229
	Ex40%AlphaLFBaselineTilt	9.4889	9	2.45023	.81674
Pair 8	ExCCAlphaLFBaselineTilt second use	8.8556	9	2.16686	.72229
	Ex75%AlphaLFBaselineTilt	8.7778	9	2.20951	.73650
Pair 9	Ex40%AlphaLFBaselineTilt second use	9.4889	9	2.45023	.81674
	Ex75%AlphaLFBaselineTilt second use	8.7778	9	2.20951	.73650
Pair 10	ExCCTFTGBaselineTilt	7.9156	9	2.06327	.68776
	Ex40%TFTGBaselineTilt	8.3611	9	2.29684	.76561
Pair 11	ExCCTFTGBaselineTilt second use	7.9156	9	2.06327	.68776
	Ex75%TFTGBaselineTilt	8.0889	9	2.01617	.67206
Pair 12	Ex40%TFTGBaselineTilt second use	8.3611	9	2.29684	.76561
	Ex75%TFTGBaselineTilt second use	8.0889	9	2.01617	.67206

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ExCCSeqUpUpBaselineTilt & Ex40%SeqUpUpBaselineTilt	9	.204	.599
Pair 2	ExCCSeqUpUpBaselineTilt second use & Ex75%SeqUpUpBaselineTilt	9	.193	.619
Pair 3	Ex40%SeqUpUpBaselineTilt second use & Ex75%SeqUpUpBaselineTilt second use	9	.674	.046
Pair 4	ExCCSeqDDownBaselineTilt & Ex40%SeqDDownBaselineTilt	9	.048	.902
Pair 5	ExCCSeqDDownBaselineTilt second use & Ex75%SeqDDownBaselineTilt	9	.341	.369
Pair 6	Ex40%SeqDDownBaselineTilt second use & Ex75%SeqDDownBaselineTilt second use	9	.840	.005
Pair 7	ExCCAlphaLFBaselineTilt & Ex40%AlphaLFBaselineTilt	9	.191	.623
Pair 8	ExCCAlphaLFBaselineTilt second use & Ex75%AlphaLFBaselineTilt	9	.558	.118
Pair 9	Ex40%AlphaLFBaselineTilt second use & Ex75%AlphaLFBaselineTilt second use	9	.665	.051
Pair 10	ExCCTFTGBaselineTilt & Ex40%TFTGBaselineTilt	9	.185	.634
Pair 11	ExCCTFTGBaselineTilt second use & Ex75%TFTGBaselineTilt	9	.572	.107
Pair 12	Ex40%TFTGBaselineTilt second use & Ex75%TFTGBaselineTilt second use	9	.617	.077

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	ExCCSeqUpUpBaseline Tilt - Ex40% SeqUpUpBaselineTilt	-.41111	2.91181	.97060	-2.64932	1.82710	-.424	8	.683
Pair 2	ExCCSeqUpUpBaseline Tilt second use - Ex75% SeqUpUpBaselineTilt	-.50000	3.52916	1.17639	-3.21276	2.21276	-.425	8	.682
Pair 3	Ex40% SeqUpUpBaselineTilt second use - Ex75% SeqUpUpBaselineTilt second use	-.08889	2.21385	.73795	-1.79060	1.61282	-.120	8	.907
Pair 4	ExCCSeqDDown BaselineTilt - Ex40% SeqDDownBaselineTilt	-.97778	4.82721	1.60907	-4.68830	2.73274	-.608	8	.560
Pair 5	ExCCSeqDDown BaselineTilt second use - Ex75% SeqDDownBaselineTilt	.16667	3.12530	1.04177	-2.23565	2.56898	.160	8	.877
Pair 6	Ex40% SeqDDownBaselineTilt second use - Ex75% SeqDDownBaselineTilt second use	1.14444	2.34740	.78247	-.65993	2.94881	1.463	8	.182
Pair 7	ExCCAlphaLFBaselineTilt - Ex40% AlphaLFBaselineTilt	-.63333	2.94491	.98164	-2.89699	1.63033	-.645	8	.537
Pair 8	ExCCAlphaLFBaselineTilt second use - Ex75% AlphaLFBaselineTilt	.07778	2.05717	.68572	-1.50350	1.65906	.113	8	.912
Pair 9	Ex40% AlphaLFBaselineTilt second use - Ex75% AlphaLFBaselineTilt second use	.71111	1.92058	.64019	-.76517	2.18740	1.111	8	.299
Pair 10	ExCCTFTGBaselineTilt - Ex40%TFTGBaselineTilt	-.44556	2.78958	.92986	-2.58982	1.69870	-.479	8	.645
Pair 11	ExCCTFTGBaselineTilt second use - Ex75% TFTGBaselineTilt	-.17333	1.88656	.62885	-1.62348	1.27681	-.276	8	.790
Pair 12	Ex40%TFTGBaselineTilt second use - Ex75% TFTGBaselineTilt second use	.27222	1.90508	.63503	-1.19215	1.73659	.429	8	.679

Appendix XVIII (e.xvi): + 15 min Tilt (Paired Ttests)

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ExCCSeqUpUp+15minTilt	11.5278	9	3.89817	1.29939
	Ex40%SeqUpUp+15minTilt	10.7444	9	4.70986	1.56995
Pair 2	ExCCSeqUpUp+15minTilt second use	11.5278	9	3.89817	1.29939
	Ex75%SeqUpUp+15minTilt	7.6000	9	2.69165	.89722
Pair 3	Ex40%SeqUpUp+15minTilt second use	10.7444	9	4.70986	1.56995
	Ex75%SeqUpUp+15minTilt second use	7.6000	9	2.69165	.89722
Pair 4	ExCCSeqDDown+15minTilt	10.0000	9	3.55739	1.18580
	Ex40%SeqDDown+15minTilt	7.6222	9	4.28538	1.42846
Pair 5	ExCCSeqDDown+15minTilt second use	10.0000	9	3.55739	1.18580
	Ex75%SeqDDown+15minTilt	4.9000	9	3.16149	1.05383
Pair 6	Ex40%SeqDDown+15minTilt second use	7.6222	9	4.28538	1.42846
	Ex75%SeqDDown+15Tilt second use	4.9000	9	3.16149	1.05383
Pair 7	ExCCAlphaLF+15minTilt	10.1722	9	2.60061	.86687
	Ex40%AlphaLF+15minTilt	8.6333	9	2.55734	.85245
Pair 8	ExCCAlphaLF+15minTilt second use	10.1722	9	2.60061	.86687
	Ex75%AlphaLF+15minTilt	5.2778	9	2.62144	.87381
Pair 9	Ex40%AlphaLF+15minTilt second use	8.6333	9	2.55734	.85245
	Ex75%AlphaLF+15minTilt second use	5.2778	9	2.62144	.87381
Pair 10	ExCCTFTG+15minTilt	10.1428	9	2.41971	.80657
	Ex40%TFTG+15minTilt	8.2478	9	3.46114	1.15371
Pair 11	ExCCTFTG+15minTilt second use	10.1428	9	2.41971	.80657
	Ex75%TFTG+15minTilt	4.9167	9	2.67030	.89010
Pair 12	Ex40%TFTG+15minTilt second use	8.2478	9	3.46114	1.15371
	Ex75%TFTG+15minTilt second use	4.9167	9	2.67030	.89010

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ExCCSeqUpUp+15minTilt & Ex40%SeqUpUp+15minTilt	9	.393	.295
Pair 2	ExCCSeqUpUp+15minTilt second use & Ex75%SeqUpUp+15minTilt	9	.106	.787
Pair 3	Ex40%SeqUpUp+15minTilt second use & Ex75%SeqUpUp+15minTilt second use	9	.905	.001
Pair 4	ExCCSeqDDown+15minTilt & Ex40%SeqDDown+15minTilt	9	.156	.689
Pair 5	ExCCSeqDDown+15minTilt second use & Ex75%SeqDDown+15minTilt	9	.175	.652
Pair 6	Ex40%SeqDDown+15minTilt second use & Ex75%SeqDDown+15Tilt second use	9	.898	.001
Pair 7	ExCCAlphaLF+15minTilt & Ex40%AlphaLF+15minTilt	9	.793	.011
Pair 8	ExCCAlphaLF+15minTilt second use & Ex75%AlphaLF+15minTilt	9	.415	.267
Pair 9	Ex40%AlphaLF+15minTilt second use & Ex75%AlphaLF+15minTilt second use	9	.673	.047
Pair 10	ExCCTFTG+15minTilt & Ex40%TFTG+15minTilt	9	.719	.029
Pair 11	ExCCTFTG+15minTilt second use & Ex75%TFTG+15minTilt	9	.443	.233
Pair 12	Ex40%TFTG+15minTilt second use & Ex75%TFTG+15minTilt second use	9	.793	.011

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	ExCCSeqUpUp+15min Tilt - Ex40% SeqUpUp+15minTilt	.78333	4.78970	1.59657	-2.89836	4.46502	.491	8	.637
Pair 2	ExCCSeqUpUp+15min Tilt second use - Ex75% SeqUpUp+15minTilt	3.92778	4.49702	1.49901	.47106	7.38449	2.620	8	.031
Pair 3	Ex40% SeqUpUp+15minTilt second use - Ex75% SeqUpUp+15minTilt second use	3.14444	2.54564	.84855	1.18769	5.10120	3.706	8	.006
Pair 4	ExCCSeqDDown+15min Tilt - Ex40% SeqDDown+15minTilt	2.37778	5.12610	1.70870	-1.56249	6.31805	1.392	8	.202
Pair 5	ExCCSeqDDown+15min Tilt second use - Ex75% SeqDDown+15minTilt	5.10000	4.32464	1.44155	1.77579	8.42421	3.538	8	.008
Pair 6	Ex40% SeqDDown+15minTilt second use - Ex75% SeqDDown+15Tilt second use	2.72222	2.00797	.66932	1.17876	4.26568	4.067	8	.004
Pair 7	ExCCAlphaLF+15minTilt - Ex40%AlphaLF+15minTilt	1.53889	1.66015	.55338	.26278	2.81500	2.781	8	.024
Pair 8	ExCCAlphaLF+15minTilt second use - Ex75% AlphaLF+15minTilt	4.89444	2.82516	.94172	2.72283	7.06605	5.197	8	.001
Pair 9	Ex40%AlphaLF+15minTilt second use - Ex75% AlphaLF+15minTilt second use	3.35556	2.09530	.69843	1.74497	4.96614	4.804	8	.001
Pair 10	ExCCTFTG+15minTilt - Ex40%TFTG+15minTilt	1.89500	2.40696	.80232	.04485	3.74515	2.362	8	.046
Pair 11	ExCCTFTG+15minTilt second use - Ex75% TFTG+15minTilt	5.22611	2.69554	.89851	3.15413	7.29809	5.816	8	.000
Pair 12	Ex40%TFTG+15minTilt second use - Ex75% TFTG+15minTilt second use	3.33111	2.11147	.70382	1.70809	4.95413	4.733	8	.001

Appendix XVIII (e.xvii): + 60 min Tilt (Paired Ttests)

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ExCCSeqUpUp+60minTilt	12.1000	9	3.98967	1.32989
	Ex40%SeqUpUp+60minTilt	10.5722	9	3.52767	1.17589
Pair 2	ExCCSeqUpUp+60minTilt second use	12.1000	9	3.98967	1.32989
	Ex75%SeqUpUp+60minTilt	8.7333	9	2.57973	.85991
Pair 3	Ex40%SeqUpUp+60minTilt second use	10.5722	9	3.52767	1.17589
	Ex75%SeqUpUp+60minTilt second use	8.7333	9	2.57973	.85991
Pair 4	ExCCSeqDDown+60minTilt	9.0778	9	3.73523	1.24508
	Ex40%SeqDDown+60minTilt	7.1389	9	3.11446	1.03815
Pair 5	ExCCSeqDDown+60minTilt second use	9.0778	9	3.73523	1.24508
	Ex75%SeqDDown+60minTilt	5.4444	9	1.81184	.60395
Pair 6	Ex40%SeqDDown+60minTilt second use	7.1389	9	3.11446	1.03815
	Ex75%SeqDDown+60minTilt second use	5.4444	9	1.81184	.60395
Pair 7	ExCCAlphaLF+60minTilt	9.9111	9	2.69000	.89667
	Ex40%AlphaLF+60minTilt	8.9667	9	3.00624	1.00208
Pair 8	ExCCAlphaLF+60minTilt second use	9.9111	9	2.69000	.89667
	Ex75%AlphaLF+60minTilt	6.8111	9	2.04905	.68302
Pair 9	Ex40%AlphaLF+60minTilt second use	8.9667	9	3.00624	1.00208
	Ex75%AlphaLF+60minTilt second use	6.8111	9	2.04905	.68302
Pair 10	ExCCTFTG+60minTilt	9.5822	9	2.58371	.86124
	Ex40%TFTG+60minTilt	8.1544	9	3.16082	1.05361
Pair 11	ExCCTFTG+60minTilt second use	9.5822	9	2.58371	.86124
	Ex75%TFTG+60minTilt	6.2267	9	1.68516	.56172
Pair 12	Ex40%TFTG+60minTilt second use	8.1544	9	3.16082	1.05361
	Ex75%TFTG+60minTilt second use	6.2267	9	1.68516	.56172

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ExCCSeqUpUp+60minTilt & Ex40%SeqUpUp+60minTilt	9	.465	.207
Pair 2	ExCCSeqUpUp+60minTilt second use & Ex75%SeqUpUp+60minTilt	9	.159	.683
Pair 3	Ex40%SeqUpUp+60minTilt second use & Ex75%SeqUpUp+60minTilt second use	9	.819	.007
Pair 4	ExCCSeqDDown+60minTilt & Ex40%SeqDDown+60minTilt	9	.431	.247
Pair 5	ExCCSeqDDown+60minTilt second use & Ex75%SeqDDown+60minTilt	9	.245	.526
Pair 6	Ex40%SeqDDown+60minTilt second use & Ex75%SeqDDown+60minTilt second use	9	.784	.012
Pair 7	ExCCAlphaLF+60minTilt & Ex40%AlphaLF+60minTilt	9	.449	.226
Pair 8	ExCCAlphaLF+60minTilt second use & Ex75%AlphaLF+60minTilt	9	.391	.298
Pair 9	Ex40%AlphaLF+60minTilt second use & Ex75%AlphaLF+60minTilt second use	9	.807	.009
Pair 10	ExCCTFTG+60minTilt & Ex40%TFTG+60minTilt	9	.578	.103
Pair 11	ExCCTFTG+60minTilt second use & Ex75%TFTG+60minTilt	9	.275	.473
Pair 12	Ex40%TFTG+60minTilt second use & Ex75%TFTG+60minTilt second use	9	.828	.006

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	ExCCSeqUpUp+60min Tilt - Ex40% SeqUpUp+60minTilt	1.52778	3.90713	1.30238	-1.47551	4.53107	1.173	8	.275
Pair 2	ExCCSeqUpUp+60min Tilt second use - Ex75% SeqUpUp+60minTilt	3.36667	4.39375	1.46458	-.01067	6.74400	2.299	8	.051
Pair 3	Ex40% SeqUpUp+60minTilt second use - Ex75% SeqUpUp+60minTilt second use	1.83889	2.04600	.68200	.26619	3.41158	2.696	8	.027
Pair 4	ExCCSeqDDown+60min Tilt - Ex40% SeqDDown+60minTilt	1.93889	3.69254	1.23085	-.89945	4.77723	1.575	8	.154
Pair 5	ExCCSeqDDown+60min Tilt second use - Ex75% SeqDDown+60minTilt	3.63333	3.73162	1.24387	.76496	6.50171	2.921	8	.019
Pair 6	Ex40% SeqDDown+60minTilt second use - Ex75% SeqDDown+60minTilt second use	1.69444	2.03446	.67815	.13062	3.25827	2.499	8	.037
Pair 7	ExCCAlphaLF+60minTilt - Ex40%AlphaLF+60minTilt	.94444	3.00296	1.00099	-1.36384	3.25272	.944	8	.373
Pair 8	ExCCAlphaLF+60minTilt second use - Ex75% AlphaLF+60minTilt	3.10000	2.66880	.88960	1.04858	5.15142	3.485	8	.008
Pair 9	Ex40%AlphaLF+60minTilt second use - Ex75% AlphaLF+60minTilt second use	2.15556	1.81529	.60510	.76020	3.55091	3.562	8	.007
Pair 10	ExCCTFTG+60minTilt - Ex40%TFTG+60minTilt	1.42778	2.68946	.89649	-.63952	3.49508	1.593	8	.150
Pair 11	ExCCTFTG+60minTilt second use - Ex75% TFTG+60minTilt	3.35556	2.66777	.88926	1.30493	5.40618	3.773	8	.005
Pair 12	Ex40%TFTG+60minTilt second use - Ex75% TFTG+60minTilt second use	1.92778	2.00197	.66732	.38893	3.46663	2.889	8	.020

Appendix XVIII (e.xviii): + 120 min Tilt (Paired Ttests)

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ExCCSeqUpUp+120minTilt	10.4556	9	3.56970	1.18990
	Ex40%SeqUpUp+120minTilt	10.1556	9	2.82671	.94224
Pair 2	ExCCSeqUpUp+120minTilt second use	10.4556	9	3.56970	1.18990
	Ex75%SeqUpUp+120minTilt	9.8111	9	3.21459	1.07153
Pair 3	Ex40%SeqUpUp+120minTilt second use	10.1556	9	2.82671	.94224
	Ex75%SeqUpUp+120minTilt second use	9.8111	9	3.21459	1.07153
Pair 4	ExCCSeqDDown+120minTilt	8.9111	9	2.37247	.79082
	Ex40%SeqDDown+120minTilt	7.9000	9	3.12890	1.04297
Pair 5	ExCCSeqDDown+120minTilt second use	8.9111	9	2.37247	.79082
	Ex75%SeqDDown+120minTilt	6.8000	9	2.20511	.73504
Pair 6	Ex40%SeqDDown+120minTilt second use	7.9000	9	3.12890	1.04297
	Ex75%SeqDDown+120minTilt second use	6.8000	9	2.20511	.73504
Pair 7	ExCCAlphaLF+120minTilt	10.0444	9	2.58172	.86057
	Ex40%AlphaLF+120minTilt	9.0444	9	2.09172	.69724
Pair 8	ExCCAlphaLF+120minTilt second use	10.0444	9	2.58172	.86057
	Ex75%AlphaLF+120minTilt	8.5444	9	2.66979	.88993
Pair 9	Ex40%AlphaLF+120minTilt second use	9.0444	9	2.09172	.69724
	Ex75%AlphaLF+120minTilt second use	8.5444	9	2.66979	.88993
Pair 10	ExCCTFTG+120minTilt	9.5144	9	2.25066	.75022
	Ex40%TFTG+120minTilt	8.4100	9	2.27536	.75845
Pair 11	ExCCTFTG+120minTilt second use	9.5144	9	2.25066	.75022
	Ex75%TFTG+120minTilt	7.8244	9	2.45055	.81685
Pair 12	Ex40%TFTG+120minTilt second use	8.4100	9	2.27536	.75845
	Ex75%TFTG+120minTilt second use	7.8244	9	2.45055	.81685

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ExCCSeqUpUp+120minTilt & Ex40%SeqUpUp+120minTilt	9	.515	.156
Pair 2	ExCCSeqUpUp+120minTilt second use & Ex75%SeqUpUp+120minTilt	9	.419	.262
Pair 3	Ex40%SeqUpUp+120minTilt second use & Ex75%SeqUpUp+120minTilt second use	9	.875	.002
Pair 4	ExCCSeqDDown+120minTilt & Ex40%SeqDDown+120minTilt	9	.351	.354
Pair 5	ExCCSeqDDown+120minTilt second use & Ex75%SeqDDown+120minTilt	9	.286	.456
Pair 6	Ex40%SeqDDown+120minTilt second use & Ex75%SeqDDown+120minTilt second use	9	.912	.001
Pair 7	ExCCAlphaLF+120minTilt & Ex40%AlphaLF+120minTilt	9	.402	.283
Pair 8	ExCCAlphaLF+120minTilt second use & Ex75%AlphaLF+120minTilt	9	.397	.290
Pair 9	Ex40%AlphaLF+120minTilt second use & Ex75%AlphaLF+120minTilt second use	9	.891	.001
Pair 10	ExCCTFTG+120minTilt & Ex40%TFTG+120minTilt	9	.486	.184
Pair 11	ExCCTFTG+120minTilt second use & Ex75%TFTG+120minTilt	9	.434	.243
Pair 12	Ex40%TFTG+120minTilt second use & Ex75%TFTG+120minTilt second use	9	.945	.000

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	ExCCSeqUpUp+120min Tilt - Ex40% SeqUpUp+120minTilt	.30000	3.21636	1.07212	-2.17232	2.77232	.280	8	.787
Pair 2	ExCCSeqUpUp+120min Tilt second use - Ex75% SeqUpUp+120minTilt	.64444	3.66848	1.22283	-2.17540	3.46429	.527	8	.612
Pair 3	Ex40% SeqUpUp+120minTilt second use - Ex75% SeqUpUp+120minTilt second use	.34444	1.55653	.51884	-.85201	1.54090	.664	8	.525
Pair 4	ExCCSeq DDown+120minTilt - Ex40% SeqDDown+120minTilt	1.01111	3.19392	1.06464	-1.44395	3.46617	.950	8	.370
Pair 5	ExCCSeq DDown+120minTilt second use - Ex75% SeqDDown+120minTilt	2.11111	2.73882	.91294	.00587	4.21635	2.312	8	.050
Pair 6	Ex40% SeqDDown+120minTilt second use - Ex75% SeqDDown+120minTilt second use	1.10000	1.43701	.47900	-.00458	2.20458	2.296	8	.051
Pair 7	ExCCAlphaLF+120minTilt - Ex40% AlphaLF+120minTilt	1.00000	2.58795	.86265	-.98928	2.98928	1.159	8	.280
Pair 8	ExCCAlphaLF+120minTilt second use - Ex75% AlphaLF+120minTilt	1.50000	2.88401	.96134	-.71684	3.71684	1.560	8	.157
Pair 9	Ex40% AlphaLF+120minTilt second use - Ex75% AlphaLF+120minTilt second use	.50000	1.24499	.41500	-.45698	1.45698	1.205	8	.263
Pair 10	ExCCTFTG+120minTilt - Ex40%TFTG+120minTilt	1.10444	2.29356	.76452	-.65854	2.86743	1.445	8	.187
Pair 11	ExCCTFTG+120minTilt second use - Ex75% TFTG+120minTilt	1.69000	2.50603	.83534	-.23630	3.61630	2.023	8	.078
Pair 12	Ex40%TFTG+120minTilt second use - Ex75% TFTG+120minTilt second use	.58556	.80396	.26799	-.03242	1.20353	2.185	8	.060

Appendix XVIII (e.xix): + 180 min Tilt (Paired Ttests)

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ExCCSeqUpUp+180minTilt	10.1222	9	2.08613	.69538
	Ex40%SeqUpUp+180minTilt	10.9000	9	4.61979	1.53993
Pair 2	ExCCSeqUpUp+180minTilt second use	10.1222	9	2.08613	.69538
	Ex75%SeqUpUp+180minTilt	10.6222	9	3.72115	1.24038
Pair 3	Ex40%SeqUpUp+180minTilt second use	10.9000	9	4.61979	1.53993
	Ex75%SeqUpUp+180minTilt second use	10.6222	9	3.72115	1.24038
Pair 4	ExCCSeqDDown+180minTilt	8.4889	9	1.84285	.61428
	Ex40%SeqDDown+180minTilt	8.2222	9	3.43285	1.14428
Pair 5	ExCCSeqDDown+180minTilt second use	8.4889	9	1.84285	.61428
	Ex75%SeqDDown+180minTilt	7.5889	9	2.76245	.92082
Pair 6	Ex40%SeqDDown+180minTilt second use	8.2222	9	3.43285	1.14428
	Ex75%SeqDDown+180minTilt second use	7.5889	9	2.76245	.92082
Pair 7	ExCCAlphaLF+180minTilt	9.9333	9	2.43721	.81240
	Ex40%AlphaLF+180minTilt	9.6778	9	3.11038	1.03679
Pair 8	ExCCAlphaLF+180minTilt second use	9.9333	9	2.43721	.81240
	Ex75%AlphaLF+180minTilt	9.4333	9	5.00600	1.66867
Pair 9	Ex40%AlphaLF+180minTilt second use	9.6778	9	3.11038	1.03679
	Ex75%AlphaLF+180minTilt second use	9.4333	9	5.00600	1.66867
Pair 10	ExCCTFTG+180minTilt	9.1533	9	1.90713	.63571
	Ex40%TFTG+180minTilt	9.2311	9	3.48128	1.16043
Pair 11	ExCCTFTG+180minTilt second use	9.1533	9	1.90713	.63571
	Ex75%TFTG+180minTilt	9.1856	9	4.52062	1.50687
Pair 12	Ex40%TFTG+180minTilt second use	9.2311	9	3.48128	1.16043
	Ex75%TFTG+180minTilt second use	9.1856	9	4.52062	1.50687

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ExCCSeqUpUp+180minTilt & Ex40%SeqUpUp+180minTilt	9	.339	.373
Pair 2	ExCCSeqUpUp+180minTilt second use & Ex75%SeqUpUp+180minTilt	9	-.030	.940
Pair 3	Ex40%SeqUpUp+180minTilt second use & Ex75%SeqUpUp+180minTilt second use	9	.703	.034
Pair 4	ExCCSeqDDown+180minTilt & Ex40%SeqDDown+180minTilt	9	.201	.603
Pair 5	ExCCSeqDDown+180minTilt second use & Ex75%SeqDDown+180minTilt	9	.194	.616
Pair 6	Ex40%SeqDDown+180minTilt second use & Ex75%SeqDDown+180minTilt second use	9	.939	.000
Pair 7	ExCCAlphaLF+180minTilt & Ex40%AlphaLF+180minTilt	9	.543	.131
Pair 8	ExCCAlphaLF+180minTilt second use & Ex75%AlphaLF+180minTilt	9	.414	.268
Pair 9	Ex40%AlphaLF+180minTilt second use & Ex75%AlphaLF+180minTilt second use	9	.896	.001
Pair 10	ExCCTFTG+180minTilt & Ex40%TFTG+180minTilt	9	.644	.061
Pair 11	ExCCTFTG+180minTilt second use & Ex75%TFTG+180minTilt	9	.456	.217
Pair 12	Ex40%TFTG+180minTilt second use & Ex75%TFTG+180minTilt second use	9	.923	.000

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	ExCCSeqUpUp+180min Tilt - Ex40% SeqUpUp+180minTilt	-.77778	4.37829	1.45943	-4.14323	2.58768	-.533	8	.609
Pair 2	ExCCSeqUpUp+180min Tilt second use - Ex75% SeqUpUp+180minTilt	-.50000	4.31943	1.43981	-3.82021	2.82021	-.347	8	.737
Pair 3	Ex40% SeqUpUp+180minTilt second use - Ex75% SeqUpUp+180minTilt second use	.27778	3.31729	1.10576	-2.27212	2.82768	.251	8	.808
Pair 4	ExCCSeq DDown+180minTilt - Ex40% SeqDDown+180minTilt	.26667	3.55422	1.18474	-2.46535	2.99868	.225	8	.828
Pair 5	ExCCSeq DDown+180minTilt second use - Ex75% SeqDDown+180minTilt	.90000	3.00791	1.00264	-1.41208	3.21208	.898	8	.396
Pair 6	Ex40% SeqDDown+180minTilt second use - Ex75% SeqDDown+180minTilt second use	.63333	1.26984	.42328	-.34275	1.60942	1.496	8	.173
Pair 7	ExCCAlphaLF+180minTilt - Ex40% AlphaLF+180minTilt	.25556	2.71713	.90571	-1.83301	2.34412	.282	8	.785
Pair 8	ExCCAlphaLF+180minTilt second use - Ex75% AlphaLF+180minTilt	.50000	4.57138	1.52379	-3.01387	4.01387	.328	8	.751
Pair 9	Ex40% AlphaLF+180minTilt second use - Ex75% AlphaLF+180minTilt second use	.24444	2.61109	.87036	-1.76262	2.25150	.281	8	.786
Pair 10	ExCCTFTG+180minTilt - Ex40%TFTG+180minTilt	-.07778	2.68360	.89453	-2.14058	1.98502	-.087	8	.933
Pair 11	ExCCTFTG+180minTilt second use - Ex75% TFTG+180minTilt	-.03222	4.02521	1.34174	-3.12627	3.06183	-.024	8	.981
Pair 12	Ex40%TFTG+180minTilt second use - Ex75% TFTG+180minTilt second use	.04556	1.86967	.62322	-1.39160	1.48271	.073	8	.944

Appendix XVIII (e.xx): + 24 h Tilt (Paired Ttests)

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ExCCSeqUpUp24hTilt	9.6111	9	2.65775	.88592
	Ex40%SeqUpUp24hTilt	11.1444	9	4.22939	1.40980
Pair 2	ExCCSeqUpUp24hTilt second use	9.6111	9	2.65775	.88592
	Ex75%SeqUpUp24hTilt	11.0444	9	3.50646	1.16882
Pair 3	Ex40%SeqUpUp24hTilt second use	11.1444	9	4.22939	1.40980
	Ex75%SeqUpUp24hTilt second use	11.0444	9	3.50646	1.16882
Pair 4	ExCCSeqDDown24hTilt	7.3000	9	2.08567	.69522
	Ex40%SeqDDown24hTilt	9.0778	9	3.38222	1.12741
Pair 5	ExCCSeqDDown24hTilt second use	7.3000	9	2.08567	.69522
	Ex75%SeqDDown24hTilt	8.3667	9	2.47285	.82428
Pair 6	Ex40%SeqDDown24hTilt second use	9.0778	9	3.38222	1.12741
	Ex75%SeqDDown24hTilt second use	8.3667	9	2.47285	.82428
Pair 7	ExCCAlphaLF24hTilt	8.2333	9	2.34254	.78085
	Ex40%AlphaLF24hTilt	10.0111	9	3.18255	1.06085
Pair 8	ExCCAlphaLF24hTilt second use	8.2333	9	2.34254	.78085
	Ex75%AlphaLF24hTilt	9.3889	9	2.29098	.76366
Pair 9	Ex40%AlphalF24hTilt second use	10.0111	9	3.18255	1.06085
	Ex75%AlphaLF24hTilt second use	9.3889	9	2.29098	.76366
Pair 10	ExCCTFTG24hTilt	7.2867	9	1.99879	.66626
	Ex40%TFTG24hTilt	9.2556	9	2.99585	.99862
Pair 11	ExCCTFTG24hTilt second use	7.2867	9	1.99879	.66626
	Ex75%TFTG24hTilt	8.9444	9	2.59288	.86429
Pair 12	Ex40%TFTG24hTilt second use	9.2556	9	2.99585	.99862
	Ex75%TFTG24hTilt second use	8.9444	9	2.59288	.86429

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	ExCCSeqUpUp24hTilt & Ex40%SeqUpUp24hTilt	9	.847	.004
Pair 2	ExCCSeqUpUp24hTilt second use & Ex75%SeqUpUp24hTilt	9	.592	.093
Pair 3	Ex40%SeqUpUp24hTilt second use & Ex75%SeqUpUp24hTilt second use	9	.564	.114
Pair 4	ExCCSeqDDown24hTilt & Ex40%SeqDDown24hTilt	9	.659	.053
Pair 5	ExCCSeqDDown24hTilt second use & Ex75%SeqDDown24hTilt	9	.628	.070
Pair 6	Ex40%SeqDDown24hTilt second use & Ex75%SeqDDown24hTilt second use	9	.378	.315
Pair 7	ExCCAlphaLF24hTilt & Ex40%AlphaLF24hTilt	9	.846	.004
Pair 8	ExCCAlphaLF24hTilt second use & Ex75%AlphaLF24hTilt	9	.711	.032
Pair 9	Ex40%AlphaIF24hTilt second use & Ex75%AlphaLF24hTilt second use	9	.785	.012
Pair 10	ExCCTFTG24hTilt & Ex40%TFTG24hTilt	9	.865	.003
Pair 11	ExCCTFTG24hTilt second use & Ex75%TFTG24hTilt	9	.820	.007
Pair 12	Ex40%TFTG24hTilt second use & Ex75%TFTG24hTilt second use	9	.634	.067

Paired Samples Test

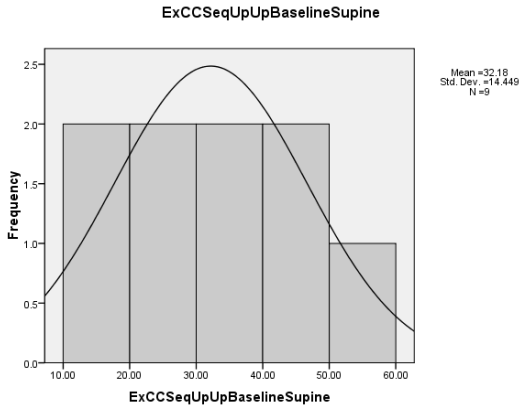
		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	ExCCSeqUpUp24hTilt - Ex40%SeqUpUp24hTilt	-1.53333	2.43105	.81035	-3.40200	.33534	-1.892	8	.095
Pair 2	ExCCSeqUpUp24hTilt second use - Ex75% SeqUpUp24hTilt	-1.43333	2.88574	.96191	-3.65151	.78484	-1.490	8	.175
Pair 3	Ex40%SeqUpUp24hTilt second use - Ex75% SeqUpUp24hTilt second use	.10000	3.66981	1.22327	-2.72087	2.92087	.082	8	.937
Pair 4	ExCCSeqDDown24hTilt - Ex40%SeqDDown24hTilt	-1.77778	2.54695	.84898	-3.73554	.17998	-2.094	8	.070
Pair 5	ExCCSeqDDown24hTilt second use - Ex75% SeqDDown24hTilt	-1.06667	1.99750	.66583	-2.60208	.46875	-1.602	8	.148
Pair 6	Ex40%SeqDDown24hTilt second use - Ex75% SeqDDown24hTilt second use	.71111	3.35054	1.11685	-1.86434	3.28656	.637	8	.542
Pair 7	ExCCAlphaLF24hTilt - Ex40%AlphaLF24hTilt	-1.77778	1.73189	.57730	-3.10903	-.44653	-3.079	8	.015
Pair 8	ExCCAlphaLF24hTilt second use - Ex75% AlphaLF24hTilt	-1.15556	1.76076	.58692	-2.50900	.19788	-1.969	8	.084
Pair 9	Ex40%AlphaIF24hTilt second use - Ex75% AlphaLF24hTilt second use	.62222	1.98291	.66097	-.90198	2.14642	.941	8	.374
Pair 10	ExCCTFTG24hTilt - Ex40%TFTG24hTilt	-1.96889	1.61517	.53839	-3.21042	-.72736	-3.657	8	.006
Pair 11	ExCCTFTG24hTilt second use - Ex75%TFTG24hTilt	-1.65778	1.48795	.49598	-2.80152	-.51404	-3.342	8	.010
Pair 12	Ex40%TFTG24hTilt second use - Ex75% TFTG24hTilt second use	.31111	2.41772	.80591	-1.54732	2.16954	.386	8	.710

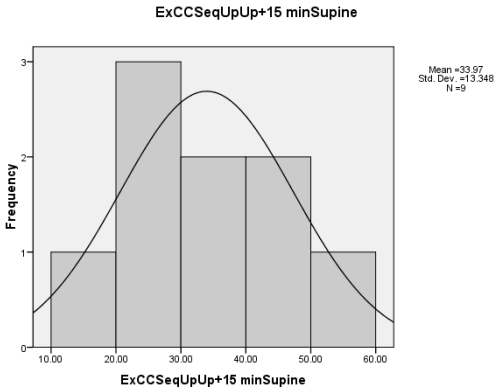
DESCRIPTIVES: Appendix XVIII (e.xxi): Control BRS_{UpUp} Supine

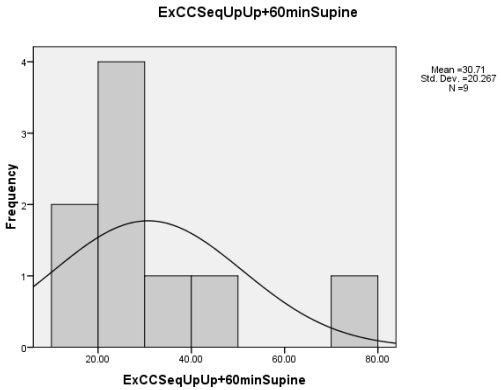
Statistics

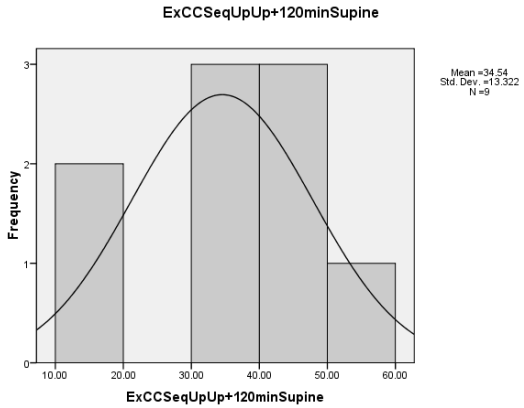
		ExCCSeqUpUpBaselineSupine	ExCCSeqUpUp+15 minSupine	ExCCSeqUpUp+60minSupine	ExCCSeqUpUp+120minSupine	ExCCSeqUpUp+180minSupine	ExCCSeqUpUp+24hSupine
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	32.1778	33.9722	30.7111	34.5444	34.6556	23.3000
	Median	30.7000	33.3000	22.0000	31.2000	34.8000	21.2000
	Mode	13.40[a]	13.90[a]	20.90	15.10[a]	13.60[a]	10.40[a]
	Std. Deviation	14.44894	13.34801	20.26700	13.32227	11.94823	9.28197
	Skewness	.265	-.021	1.926	-.157	-.289	.464
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-1.006	-1.354	3.960	-1.003	-.406	-.557
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	13.40	13.90	11.80	15.10	13.60	10.40
	Maximum	55.60	50.30	78.40	53.80	50.30	39.40

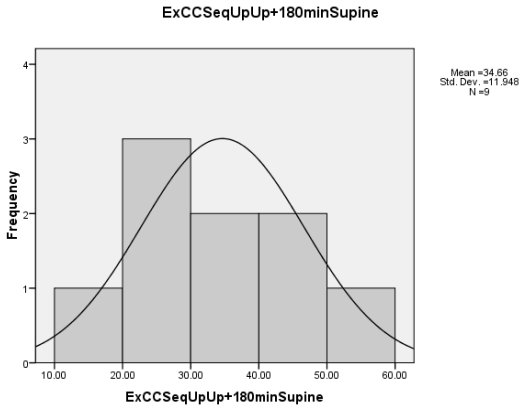
a. Multiple modes exist. The smallest value is shown

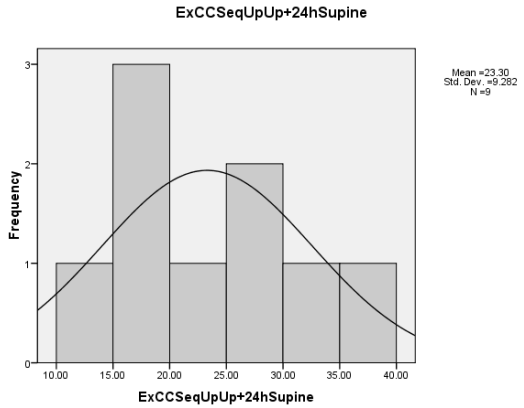

ExCCSeqUpUpBaselineSupine
Mean =32.18
Std. Dev. =14.449
N =9
Frequency
ExCCSeqUpUpBaselineSupine


ExCCSeqUpUp+15 minSupine
Mean =33.97
Std. Dev. =13.348
N =9
Frequency
ExCCSeqUpUp+15 minSupine


ExCCSeqUpUp+60minSupine
Mean =30.71
Std. Dev. =20.267
N =9
Frequency
ExCCSeqUpUp+60minSupine


ExCCSeqUpUp+120minSupine
Mean =34.54
Std. Dev. =13.322
N =9
Frequency
ExCCSeqUpUp+120minSupine


ExCCSeqUpUp+180minSupine
Mean =34.66
Std. Dev. =11.948
N =9
Frequency
ExCCSeqUpUp+180minSupine

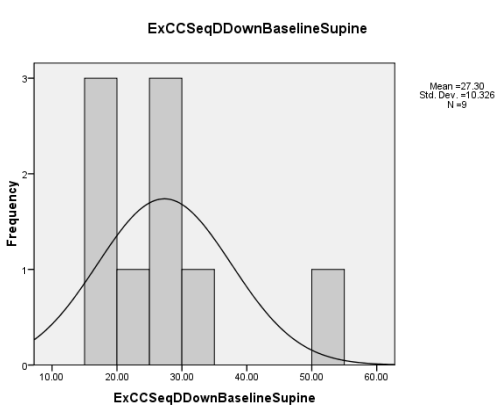

ExCCSeqUpUp+24hSupine
Mean =23.30
Std. Dev. =9.282
N =9
Frequency
ExCCSeqUpUp+24hSupine

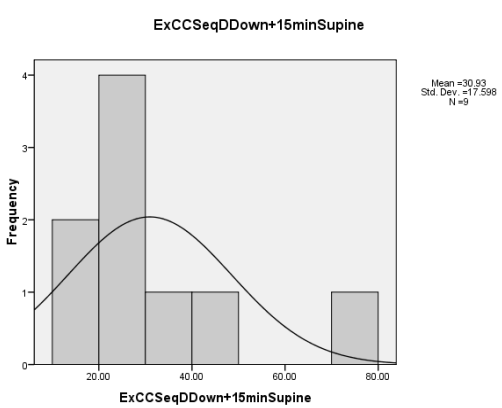
Appendix XVIII (e.xxii): Control $BRS_{DownDown}$ Supine

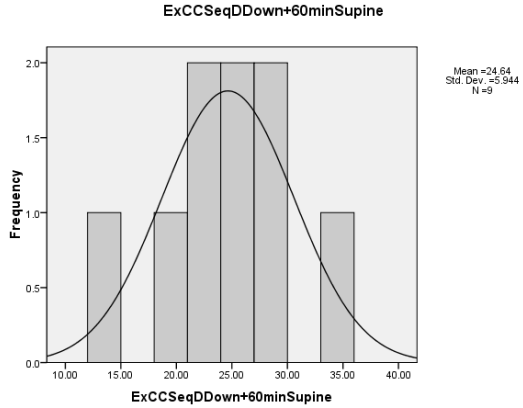
Statistics

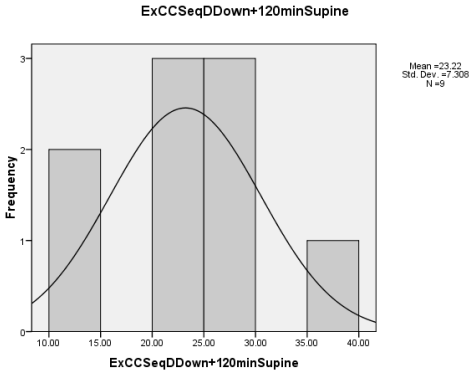
		ExCCSeqDDown BaselineSupine	ExCCSeqDDown +15minSupine	ExCCSeqDDown +60minSupine	ExCCSeqDDown +120minSupine	ExCCSeqDDown +180minSupine	ExCCSeqDDown +24hSupine
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	27.3000	30.9333	24.6444	23.2222	25.5333	20.3333
	Median	27.8000	24.7000	24.1000	23.3000	23.3000	20.0000
	Mode	16.50[a]	12.60[a]	14.60[a]	21.00	18.50	12.90[a]
	Std. Deviation	10.32618	17.59822	5.94393	7.30835	9.34131	6.36475
	Skewness	1.547	1.723	.064	-.172	.486	.241
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	3.212	3.555	.474	-.298	-1.250	-1.772
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	16.50	12.60	14.60	11.70	13.60	12.90
	Maximum	50.80	71.60	35.10	35.00	40.20	29.10

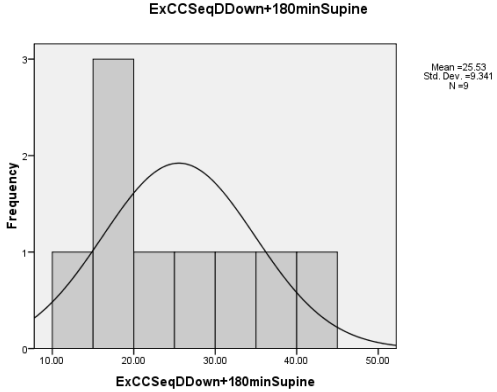
a. Multiple modes exist. The smallest value is shown

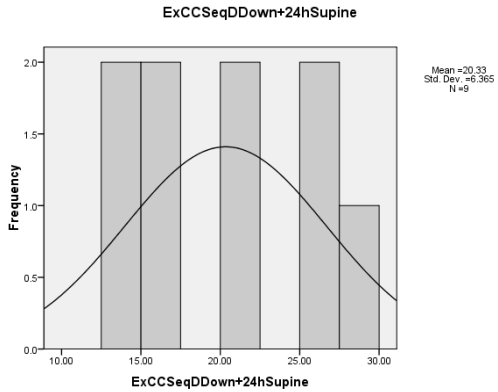

ExCCSeqDDownBaselineSupine
Mean =27.30
Std. Dev. =10.326
N =9
Frequency
ExCCSeqDDownBaselineSupine


ExCCSeqDDown+15minSupine
Mean =30.93
Std. Dev. =17.598
N =9
Frequency
ExCCSeqDDown+15minSupine


ExCCSeqDDown+60minSupine
Mean =24.64
Std. Dev. =5.944
N =9
Frequency
ExCCSeqDDown+60minSupine


ExCCSeqDDown+120minSupine
Mean =23.22
Std. Dev. =7.308
N =9
Frequency
ExCCSeqDDown+120minSupine


ExCCSeqDDown+180minSupine
Mean =25.53
Std. Dev. =9.341
N =9
Frequency
ExCCSeqDDown+180minSupine

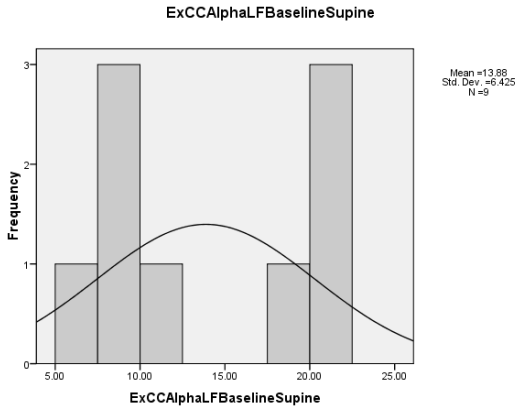

ExCCSeqDDown+24hSupine
Mean =20.33
Std. Dev. =6.365
N =9
Frequency
ExCCSeqDDown+24hSupine

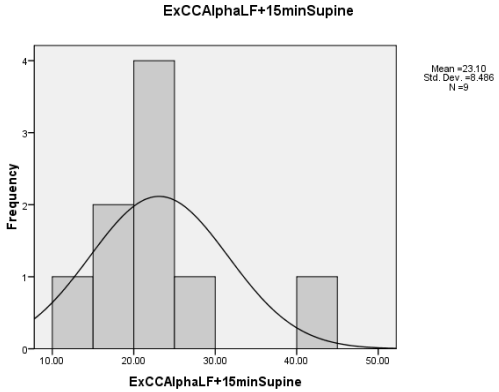
Appendix XVIII (e.xxiii): Control $BRS_{\alpha LF}$ Supine

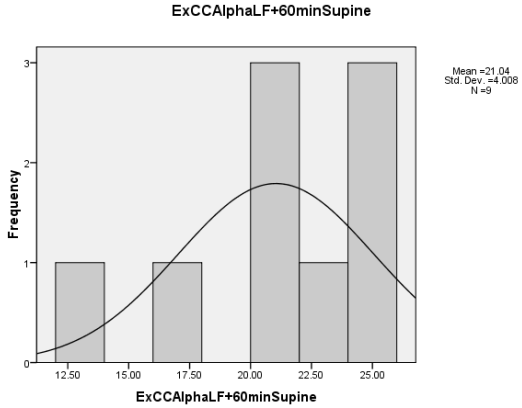
Statistics

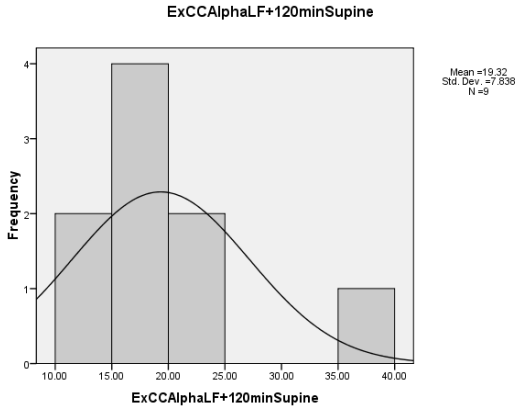
		ExCCAlphaLFBaselineSupine	ExCCAlphaLF+15minSupine	ExCCAlphaLF+60minSupine	ExCCAlphaLF+120minSupine	ExCCAlphaLF+180minSupine	ExCCAlphaLF+24hSupine
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	13.8778	23.1000	21.0444	19.3222	19.7111	16.2333
	Median	10.5000	23.3500	21.6000	19.0000	19.1000	17.3000
	Mode	5.40[a]	10.85[a]	12.30[a]	10.30[a]	13.40[a]	18.00
	Std. Deviation	6.42471	8.48591	4.00846	7.83801	4.75932	6.93488
	Skewness	.167	1.190	-1.433	1.522	.637	.789
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-2.058	3.141	2.139	3.599	-.107	.894
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	5.40	10.85	12.30	10.30	13.40	7.00
	Maximum	22.20	41.90	25.10	37.30	28.10	30.10

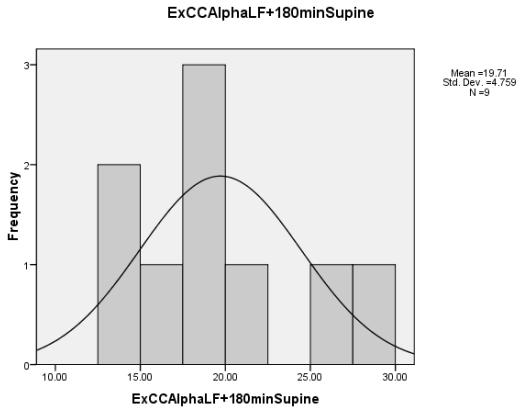
a. Multiple modes exist. The smallest value is shown

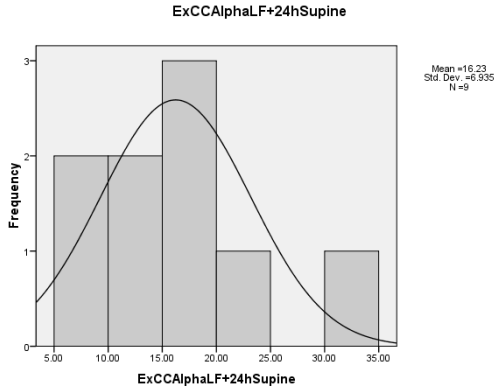

ExCCAlphaLFBaselineSupine
Mean =13.88
Std. Dev. =6.425
N =9
Frequency
ExCCAlphaLFBaselineSupine


ExCCAlphaLF+15minSupine
Mean =23.10
Std. Dev. =8.486
N =9
Frequency
ExCCAlphaLF+15minSupine


ExCCAlphaLF+60minSupine
Mean =21.04
Std. Dev. =4.008
N =9
Frequency
ExCCAlphaLF+60minSupine


ExCCAlphaLF+120minSupine
Mean =19.32
Std. Dev. =7.838
N =9
Frequency
ExCCAlphaLF+120minSupine


ExCCAlphaLF+180minSupine
Mean =19.71
Std. Dev. =4.759
N =9
Frequency
ExCCAlphaLF+180minSupine

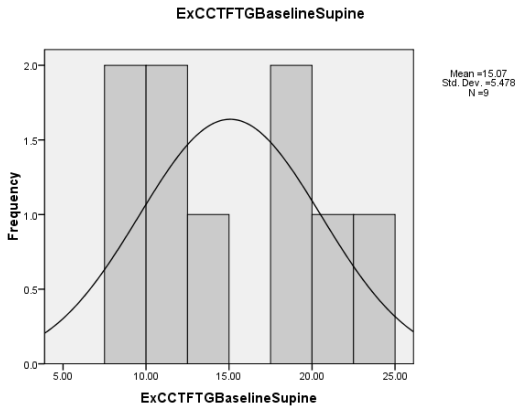

ExCCAlphaLF+24hSupine
Mean =16.23
Std. Dev. =6.935
N =9
Frequency
ExCCAlphaLF+24hSupine

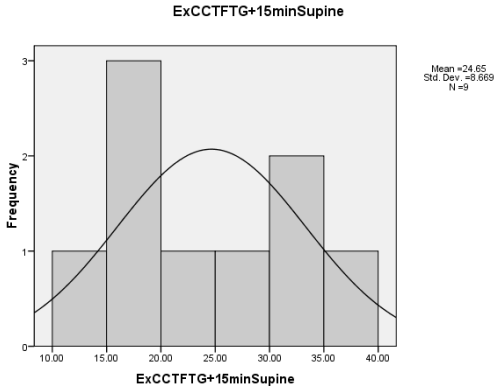
Appendix XVIII (e.xxiv): Control BRS_{TFTG} Supine

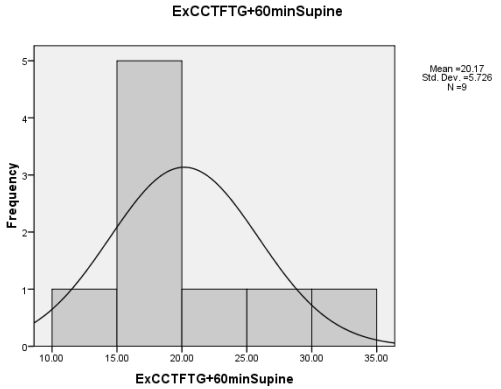
Statistics

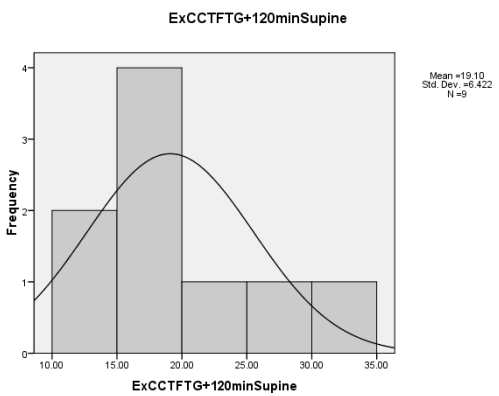
		ExCCTFTGBaselineSupine	ExCCTFTG+15minSupine	ExCCTFTG+60minSupine	ExCCTFTG+120minSupine	ExCCTFTG+180minSupine	ExCCTFTG+24hSupine
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	15.0656	24.6533	20.1700	19.1011	19.3589	15.2300
	Median	14.1600	23.7500	18.7700	17.6400	18.4300	13.7600
	Mode	7.58[a]	12.79[a]	12.00[a]	10.56[a]	12.21[a]	9.02[a]
	Std. Deviation	5.47849	8.66932	5.72606	6.42219	5.07145	5.98371
	Skewness	.188	.204	.756	.943	.320	.840
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-1.431	-1.398	.379	.772	-1.150	-.191
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	7.58	12.79	12.00	10.56	12.21	9.02
	Maximum	23.52	37.85	30.71	31.75	26.93	26.54

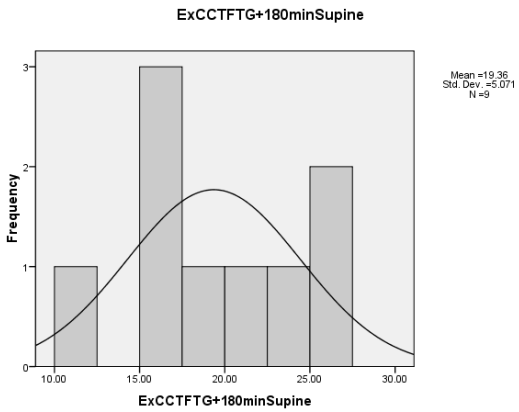
a. Multiple modes exist. The smallest value is shown

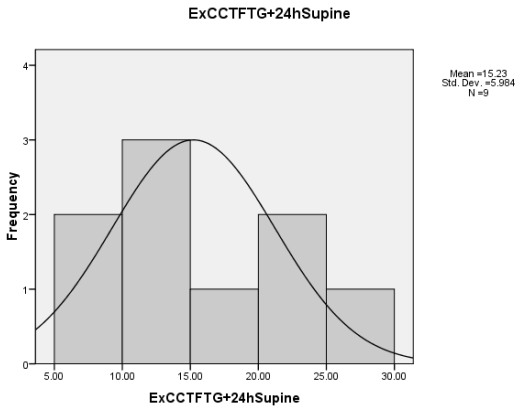

ExCCTFTGBaselineSupine
Mean =15.07
Std. Dev. =5.478
N =9
Frequency
ExCCTFTGBaselineSupine


ExCCTFTG+15minSupine
Mean =24.65
Std. Dev. =8.669
N =9
Frequency
ExCCTFTG+15minSupine


ExCCTFTG+60minSupine
Mean =20.17
Std. Dev. =5.726
N =9
Frequency
ExCCTFTG+60minSupine


ExCCTFTG+120minSupine
Mean =19.10
Std. Dev. =6.422
N =9
Frequency
ExCCTFTG+120minSupine


ExCCTFTG+180minSupine
Mean =19.36
Std. Dev. =5.071
N =9
Frequency
ExCCTFTG+180minSupine

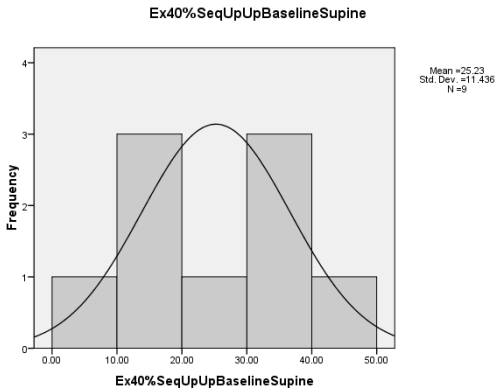

ExCCTFTG+24hSupine
Mean =15.23
Std. Dev. =5.984
N =9
Frequency
ExCCTFTG+24hSupine

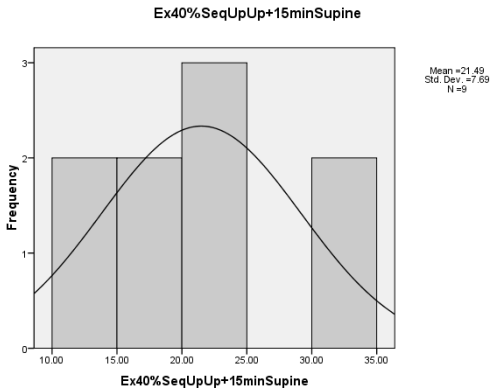
Appendix XVIII (e.xxv): 40% BRS_{UpUp} Supine

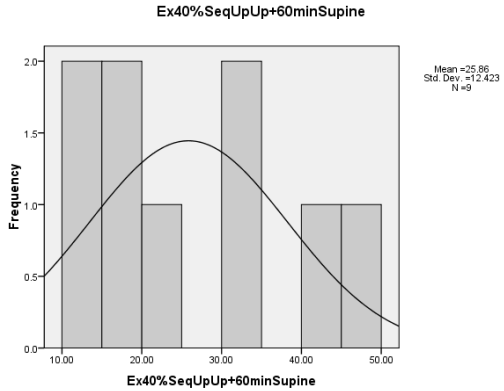
Statistics

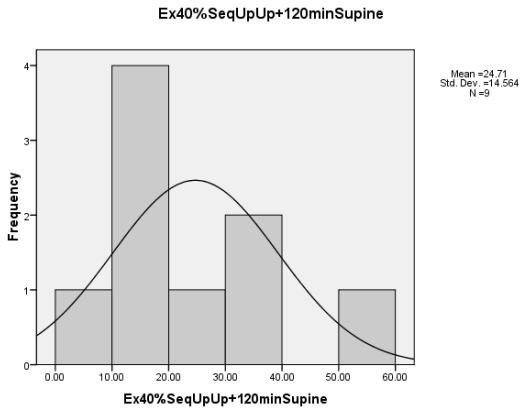
		Ex40%SeqUpUp BaselineSupine	Ex40%SeqUpUp +15minSupine	Ex40%SeqUpUp +60minSupine	Ex40%SeqUpUp +120minSupine	Ex40%SeqUpUp +180minSupine	Ex40%SeqUpUp +24hSupine
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	25.2333	21.4889	25.8556	24.7111	25.0444	30.1667
	Median	25.1000	21.2000	21.6000	19.3000	22.1000	29.5000
	Mode	8.30[a]	12.00[a]	12.00[a]	6.80[a]	9.90[a]	10.40[a]
	Std. Deviation	11.43624	7.69033	12.42277	14.56369	9.72138	14.53418
	Skewness	.225	.697	.533	.889	.080	.604
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-.583	-.401	-1.188	.200	-1.176	-.096
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	8.30	12.00	12.00	6.80	9.90	10.40
	Maximum	44.60	34.40	46.20	52.80	37.80	56.90

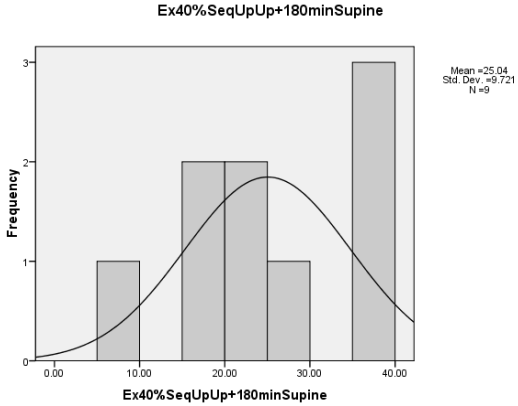
a. Multiple modes exist. The smallest value is shown

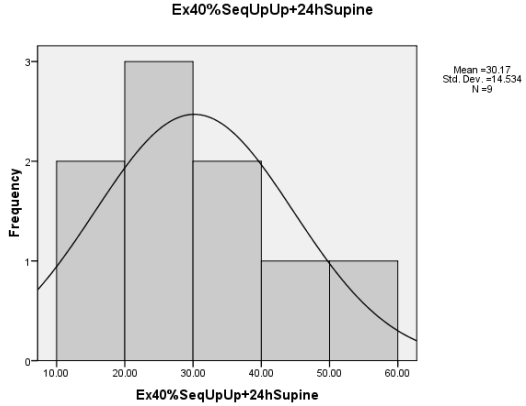

Ex40%SeqUpUpBaselineSupine
Mean =25.23
Std. Dev. =11.436
N =9
Frequency
Ex40%SeqUpUpBaselineSupine


Ex40%SeqUpUp+15minSupine
Mean =21.49
Std. Dev. =7.69
N =9
Frequency
Ex40%SeqUpUp+15minSupine


Ex40%SeqUpUp+60minSupine
Mean =25.86
Std. Dev. =12.423
N =9
Frequency
Ex40%SeqUpUp+60minSupine


Ex40%SeqUpUp+120minSupine
Mean =24.71
Std. Dev. =14.564
N =9
Frequency
Ex40%SeqUpUp+120minSupine


Ex40%SeqUpUp+180minSupine
Mean =25.04
Std. Dev. =9.721
N =9
Frequency
Ex40%SeqUpUp+180minSupine

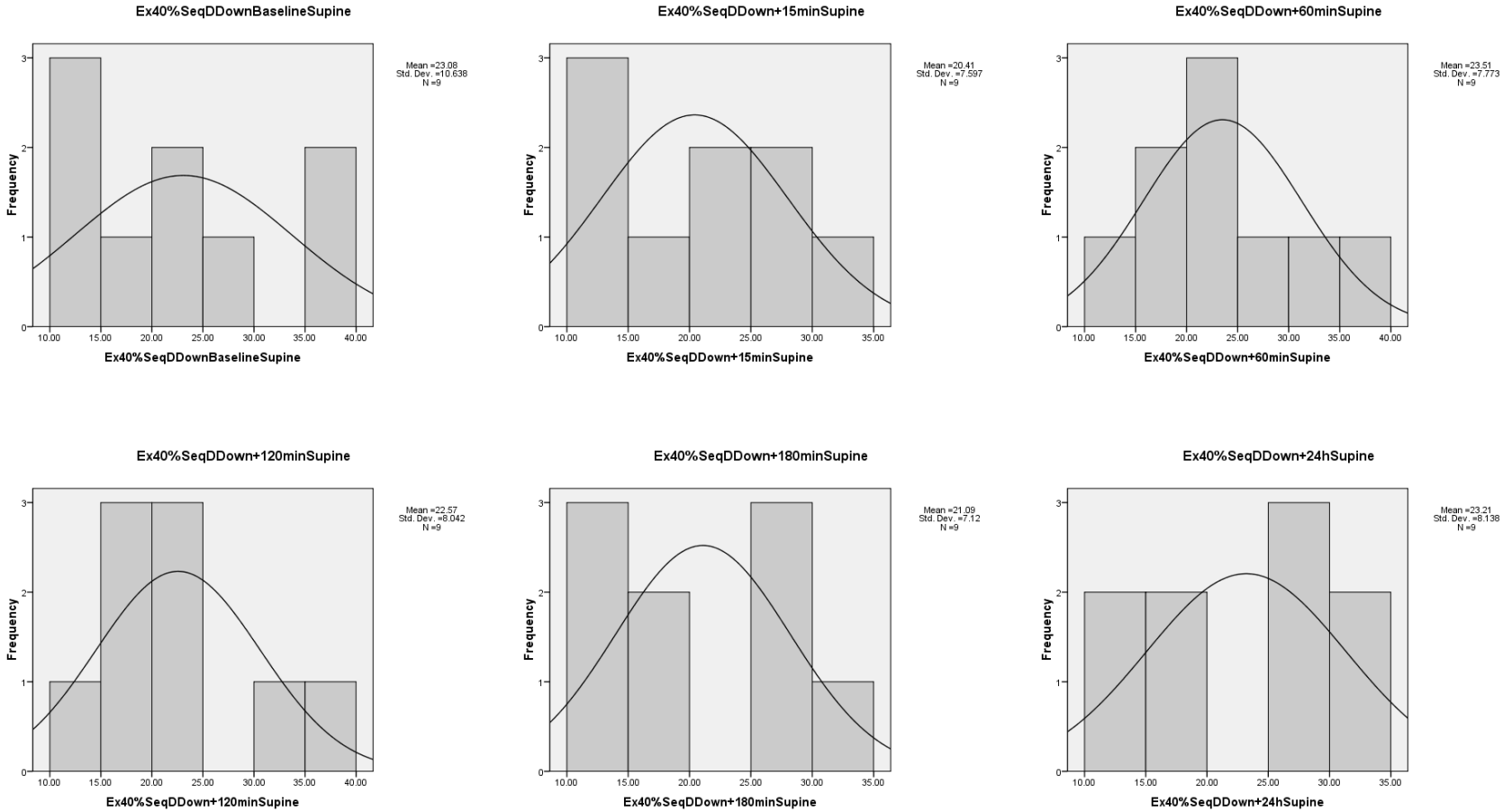

Ex40%SeqUpUp+24hSupine
Mean =30.17
Std. Dev. =14.534
N =9
Frequency
Ex40%SeqUpUp+24hSupine

Appendix XVIII (e.xxvi): 40% $BRS_{DownDown}$ Supine

Statistics

		Ex40%SeqDDownBaselineSupine	Ex40%SeqDDown+15minSupine	Ex40%SeqDDown+60minSupine	Ex40%SeqDDown+120minSupine	Ex40%SeqDDown+180minSupine	Ex40%SeqDDown+24hSupine
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	23.0778	20.4111	23.5111	22.5667	21.0889	23.2056
	Median	21.6000	21.8000	21.0000	20.7000	19.6000	25.7000
	Mode	11.80[a]	10.20[a]	13.90[a]	12.40[a]	11.80[a]	11.80[a]
	Std. Deviation	10.63823	7.59711	7.77262	8.04161	7.11994	8.13751
	Skewness	.580	.040	.617	1.130	.297	-.231
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-1.113	-1.190	-.672	.811	-.912	-1.734
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	11.80	10.20	13.90	12.40	11.80	11.80
	Maximum	39.40	32.20	37.10	38.30	33.20	33.70

a. Multiple modes exist. The smallest value is shown

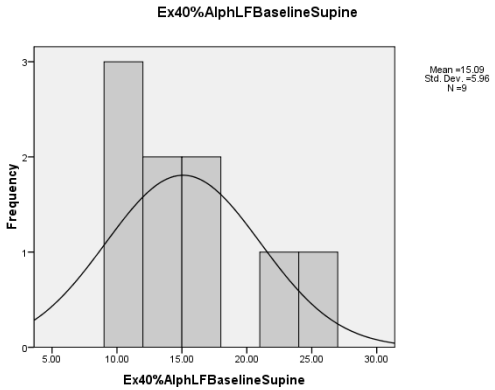

Ex40%SeqDDownBaselineSupine
Mean =23.08
Std. Dev. =10.638
N =9
Frequency
Ex40%SeqDDownBaselineSupine
Ex40%SeqDDown+15minSupine
Mean =20.41
Std. Dev. =7.597
N =9
Frequency
Ex40%SeqDDown+15minSupine
Ex40%SeqDDown+60minSupine
Mean =23.51
Std. Dev. =7.773
N =9
Frequency
Ex40%SeqDDown+60minSupine
Ex40%SeqDDown+120minSupine
Mean =22.57
Std. Dev. =8.042
N =9
Frequency
Ex40%SeqDDown+120minSupine
Ex40%SeqDDown+180minSupine
Mean =21.09
Std. Dev. =7.12
N =9
Frequency
Ex40%SeqDDown+180minSupine
Ex40%SeqDDown+24hSupine
Mean =23.21
Std. Dev. =8.138
N =9
Frequency
Ex40%SeqDDown+24hSupine

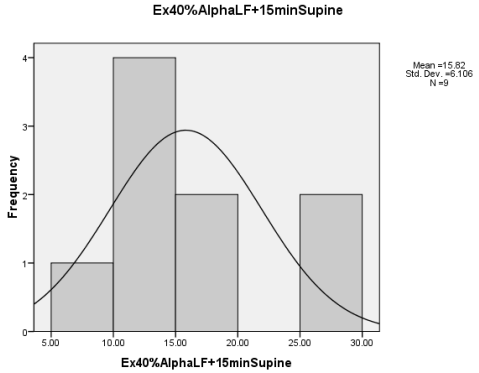
Appendix XVIII (e.xxvii): 40% $BRS_{\alpha LF}$ Supine

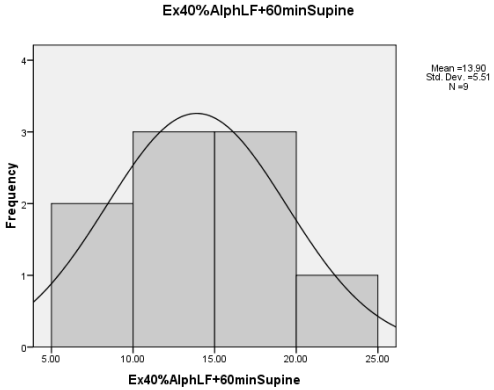
Statistics

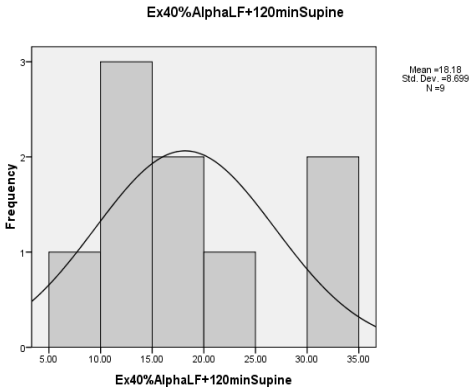
		Ex40%AlphLFBaselineSupine	Ex40%AlphaLF+15minSupine	Ex40%AlphLF+60minSupine	Ex40%AlphaLF+120minSupine	Ex40%AlphaLF+180minSupine	Ex40%AlphaLF+24hSupine
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	15.0889	15.8222	13.9000	18.1778	18.8111	15.9722
	Median	14.5000	13.3000	13.5000	16.2000	15.7000	16.8000
	Mode	9.30	12.50	5.20[a]	7.20[a]	9.80[a]	7.50[a]
	Std. Deviation	5.95954	6.10630	5.50976	8.69882	7.14431	6.10589
	Skewness	.782	.924	.113	.709	.534	.277
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-.515	-.171	.047	-.704	-1.153	-.978
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	9.10	8.20	5.20	7.20	9.80	7.50
	Maximum	25.10	26.10	23.50	32.40	29.90	24.80

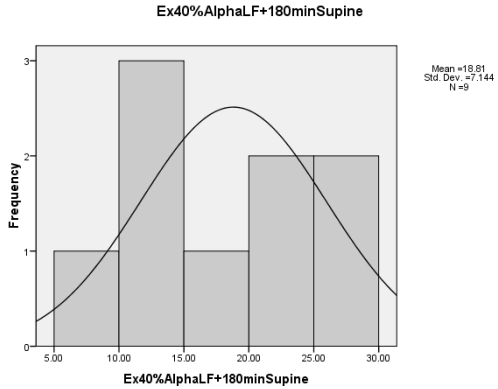
a. Multiple modes exist. The smallest value is shown

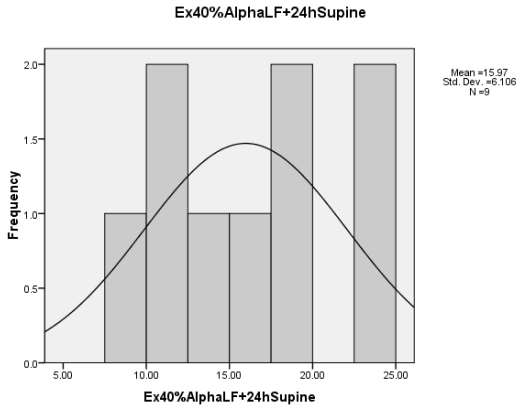

Ex40%AlphLFBaselineSupine
Mean =15.09
Std. Dev. =5.96
N =9
Frequency
Ex40%AlphLFBaselineSupine


Ex40%AlphaLF+15minSupine
Mean =15.82
Std. Dev. =6.106
N =9
Frequency
Ex40%AlphaLF+15minSupine


Ex40%AlphLF+60minSupine
Mean =13.90
Std. Dev. =5.51
N =9
Frequency
Ex40%AlphLF+60minSupine


Ex40%AlphaLF+120minSupine
Mean =18.18
Std. Dev. =8.699
N =9
Frequency
Ex40%AlphaLF+120minSupine


Ex40%AlphaLF+180minSupine
Mean =18.81
Std. Dev. =7.144
N =9
Frequency
Ex40%AlphaLF+180minSupine

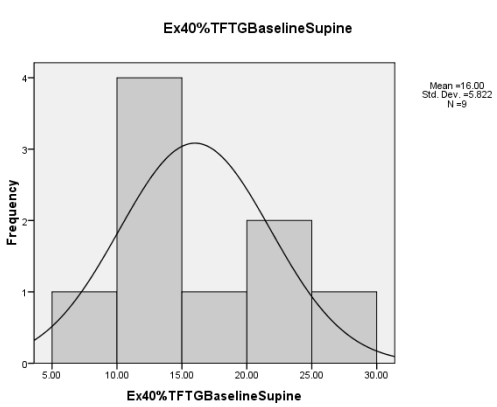

Ex40%AlphaLF+24hSupine
Mean =15.97
Std. Dev. =6.106
N =9
Frequency
Ex40%AlphaLF+24hSupine

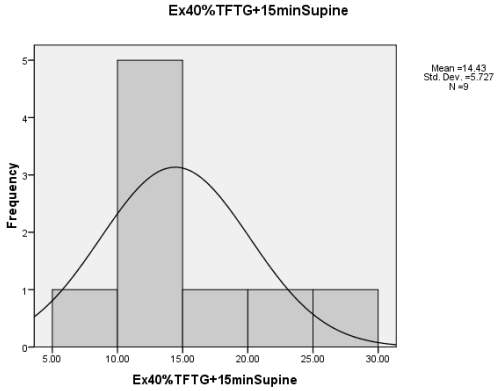
Appendix XVIII (e.xxviii): 40% BRS_{TFTG} Supine

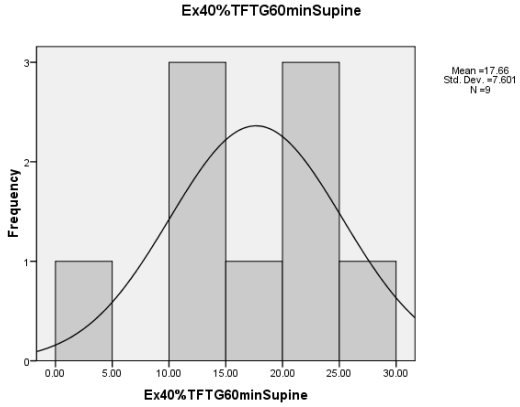
Statistics

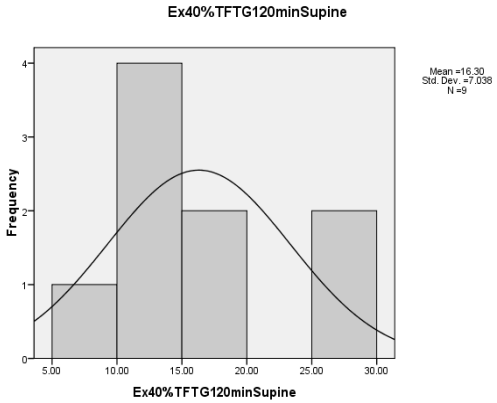
		Ex40%TFTGBaselineSupine	Ex40%TFTG+15minSupine	Ex40%TFTG60minSupine	Ex40%TFTG120minSupine	Ex40%TFTG180minSupine	Ex40%TFTG24hSupine
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	16.0011	14.4289	17.6644	16.3022	17.9589	17.6678
	Median	13.1600	13.2200	19.9000	13.6800	18.1800	15.4800
	Mode	7.58[a]	7.46[a]	4.25[a]	7.02[a]	9.93[a]	9.55[a]
	Std. Deviation	5.82167	5.72707	7.60083	7.03789	7.27542	5.70816
	Skewness	.509	1.087	-.435	.703	1.163	.185
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-.584	.818	-.606	-.486	1.669	-1.265
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	7.58	7.46	4.25	7.02	9.93	9.55
	Maximum	25.86	25.87	27.90	27.23	33.42	26.56

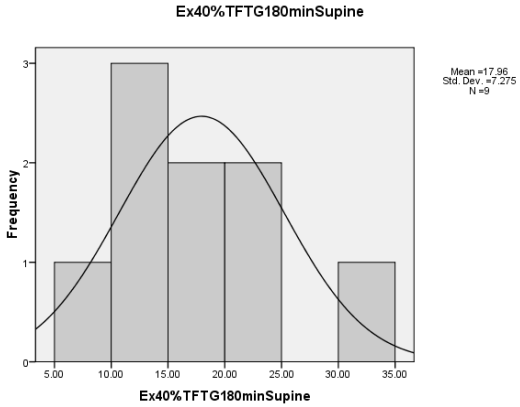
a. Multiple modes exist. The smallest value is shown

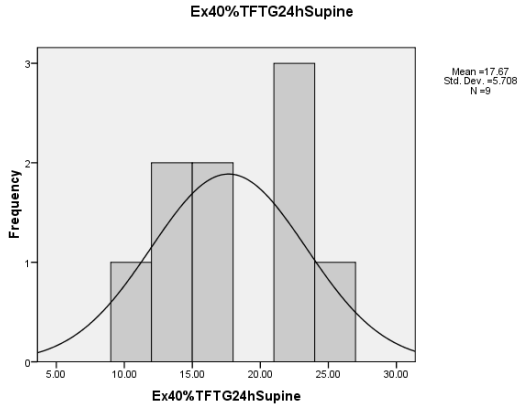

Ex40%TFTGBaselineSupine
Mean =16.00
Std. Dev. =5.822
N =9
Frequency
Ex40%TFTGBaselineSupine


Ex40%TFTG+15minSupine
Mean =14.43
Std. Dev. =5.727
N =9
Frequency
Ex40%TFTG+15minSupine


Ex40%TFTG60minSupine
Mean =17.66
Std. Dev. =7.601
N =9
Frequency
Ex40%TFTG60minSupine


Ex40%TFTG120minSupine
Mean =16.30
Std. Dev. =7.038
N =9
Frequency
Ex40%TFTG120minSupine


Ex40%TFTG180minSupine
Mean =17.96
Std. Dev. =7.275
N =9
Frequency
Ex40%TFTG180minSupine

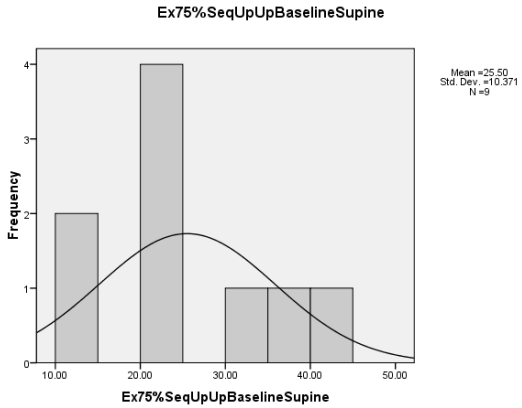

Ex40%TFTG24hSupine
Mean =17.67
Std. Dev. =5.708
N =9
Frequency
Ex40%TFTG24hSupine

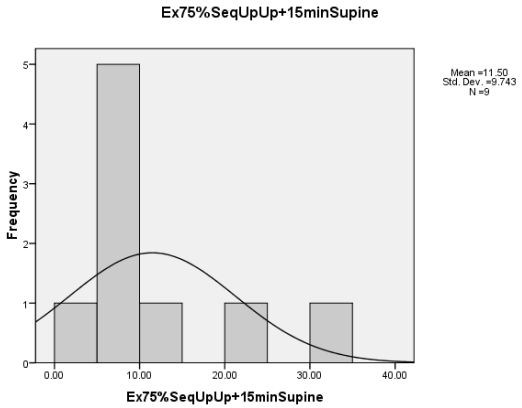
Appendix XVIII (e.xxix): 75% BRS_{UpUp} Supine

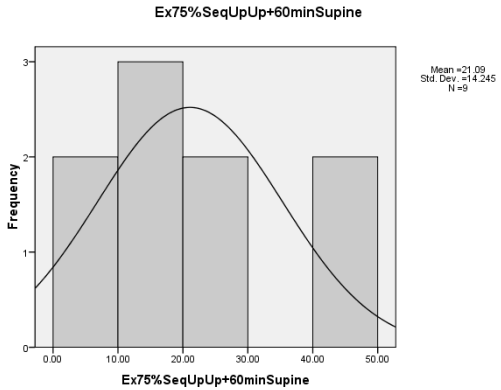
Statistics

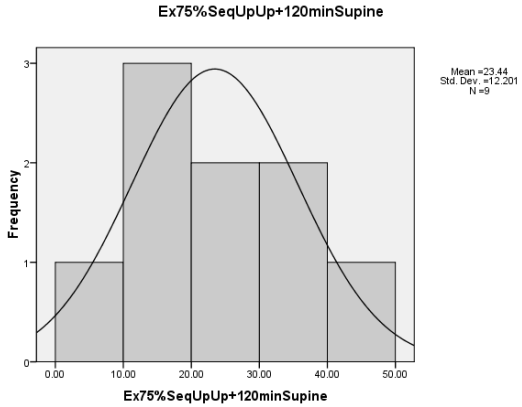
		Ex75%SeqUpUp BaselineSupine	Ex75%SeqUpUp +15minSupine	Ex75%SeqUpUp +60minSupine	Ex75%SeqUpUp +120minSupine	Ex75%SeqUpUp +180minSupine	Ex75%SeqUpUp +24hSupine
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	25.5000	11.5000	21.0889	23.4444	24.5000	28.8889
	Median	22.6000	8.4000	16.2000	21.4000	26.1000	23.0000
	Mode	12.10[a]	4.20[a]	5.90[a]	8.00[a]	9.90[a]	10.50[a]
	Std. Deviation	10.37123	9.74256	14.24495	12.20114	8.10262	13.51929
	Skewness	.728	1.803	.995	.771	-.413	.616
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	.060	2.682	-.250	.525	.291	-.780
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	12.10	4.20	5.90	8.00	9.90	10.50
	Maximum	44.70	33.30	44.90	47.50	36.90	51.20

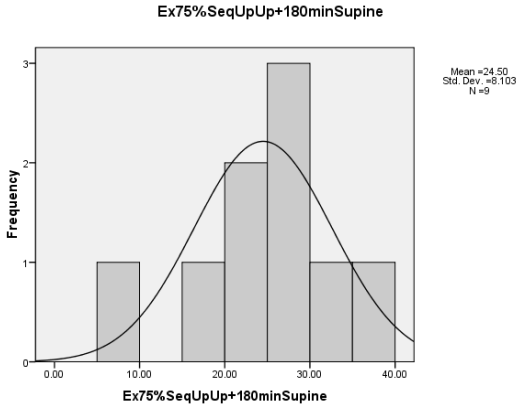
a. Multiple modes exist. The smallest value is shown

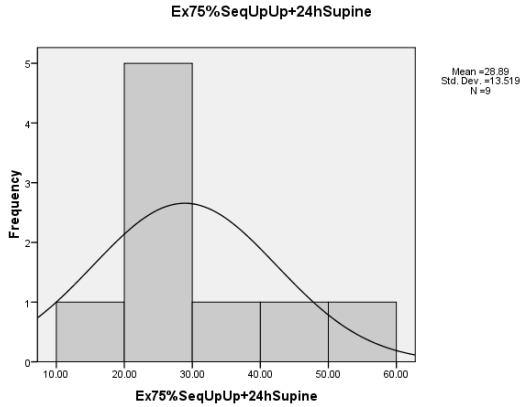

Ex75%SeqUpUpBaselineSupine
Mean =25.50
Std. Dev. =10.371
N =9
Frequency
Ex75%SeqUpUpBaselineSupine


Ex75%SeqUpUp+15minSupine
Mean =11.50
Std. Dev. =9.743
N =9
Frequency
Ex75%SeqUpUp+15minSupine


Ex75%SeqUpUp+60minSupine
Mean =21.09
Std. Dev. =14.245
N =9
Frequency
Ex75%SeqUpUp+60minSupine


Ex75%SeqUpUp+120minSupine
Mean =23.44
Std. Dev. =12.201
N =9
Frequency
Ex75%SeqUpUp+120minSupine


Ex75%SeqUpUp+180minSupine
Mean =24.50
Std. Dev. =8.103
N =9
Frequency
Ex75%SeqUpUp+180minSupine

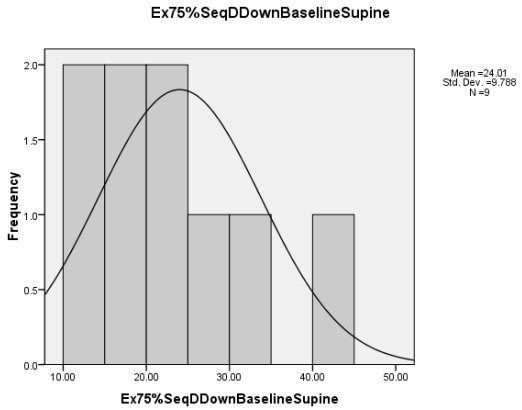

Ex75%SeqUpUp+24hSupine
Mean =28.89
Std. Dev. =13.519
N =9
Frequency
Ex75%SeqUpUp+24hSupine

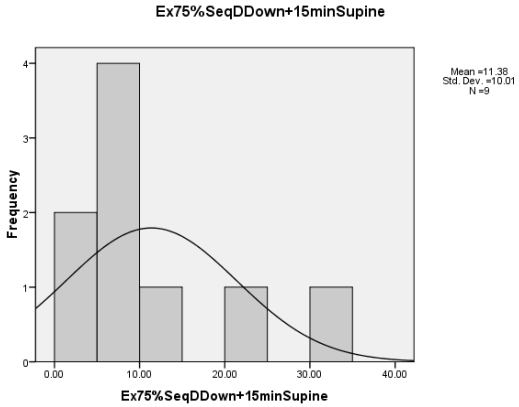
Appendix XVIII (e.xxx): 75% $BRS_{DownDown}$ Supine

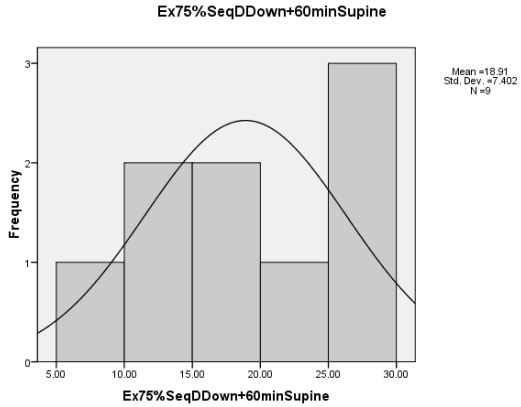
Statistics

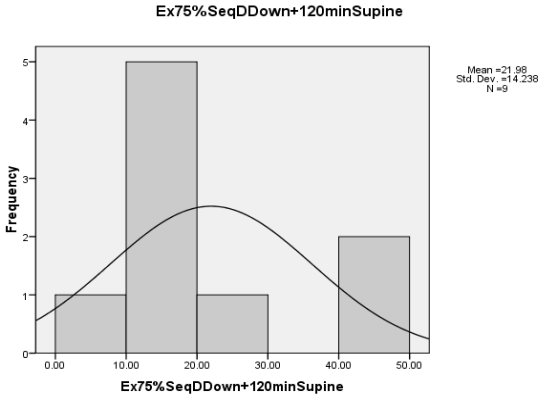
		Ex75%SeqDDownBaselineSupine	Ex75%SeqDDown+15minSupine	Ex75%SeqDDown+60minSupine	Ex75%SeqDDown+120minSupine	Ex75%SeqDDown+180minSupine	Ex75%SeqDDown+24hSupine
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	24.0111	11.3778	18.9056	21.9778	21.3778	23.7778
	Median	21.1000	6.9000	19.2000	16.8000	16.8000	25.4000
	Mode	14.90	3.70[a]	8.25[a]	8.60[a]	16.10	13.80[a]
	Std. Deviation	9.78768	10.01022	7.40213	14.23796	7.91656	6.55129
	Skewness	1.254	1.652	-.054	1.378	.639	-.425
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	1.422	2.366	-1.410	.551	-1.411	-1.591
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	14.90	3.70	8.25	8.60	12.40	13.80
	Maximum	44.70	33.60	28.70	49.10	34.00	31.50

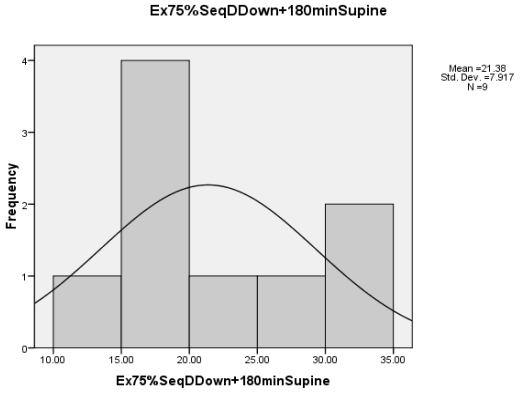
a. Multiple modes exist. The smallest value is shown

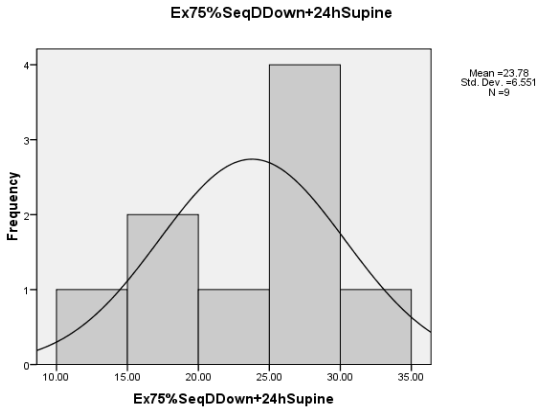

Ex75%SeqDDownBaselineSupine
Mean =24.01
Std. Dev. =9.788
N =9
Frequency
Ex75%SeqDDownBaselineSupine


Ex75%SeqDDown+15minSupine
Mean =11.38
Std. Dev. =10.01
N =9
Frequency
Ex75%SeqDDown+15minSupine


Ex75%SeqDDown+60minSupine
Mean =18.91
Std. Dev. =7.402
N =9
Frequency
Ex75%SeqDDown+60minSupine


Ex75%SeqDDown+120minSupine
Mean =21.98
Std. Dev. =14.238
N =9
Frequency
Ex75%SeqDDown+120minSupine


Ex75%SeqDDown+180minSupine
Mean =21.38
Std. Dev. =7.917
N =9
Frequency
Ex75%SeqDDown+180minSupine

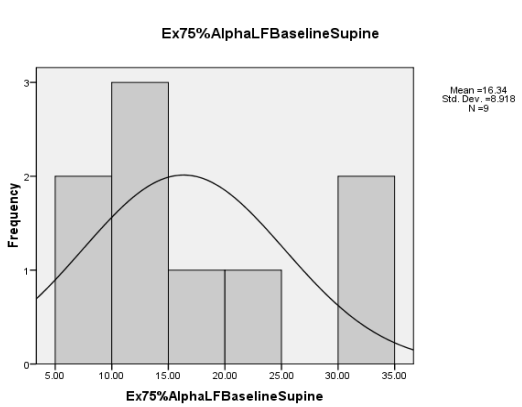

Ex75%SeqDDown+24hSupine
Mean =23.78
Std. Dev. =6.551
N =9
Frequency
Ex75%SeqDDown+24hSupine

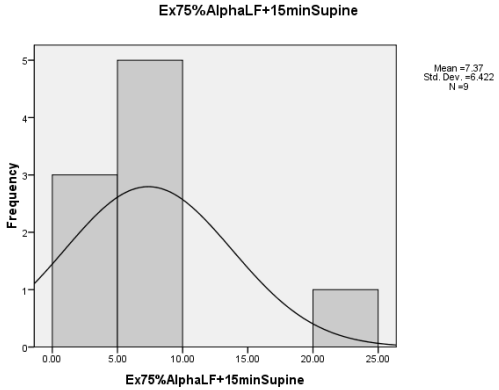
Appendix XVIII (e.xxxi): 75% $BRS_{\alpha LF}$ Supine

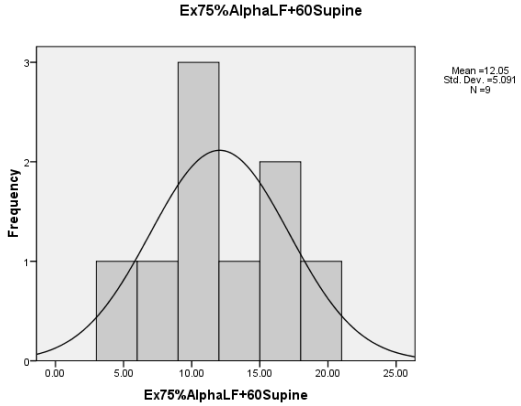
Statistics

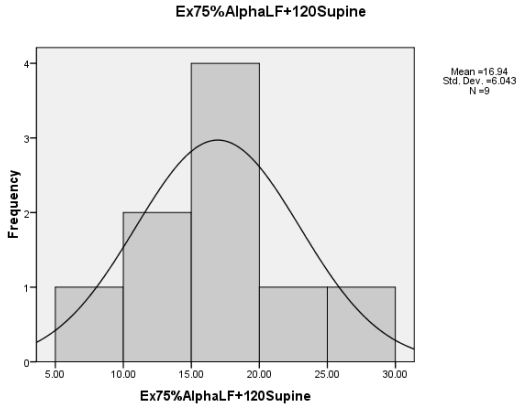
		Ex75%AlphaLFBaselineSupine	Ex75%AlphaLF+15minSupine	Ex75%AlphaLF+60Supine	Ex75%AlphaLF+120Supine	Ex75%AlphaLF+180Supine	Ex75%AlphaLF+24hSupine
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	16.3444	7.3667	12.0500	16.9444	18.1000	17.9889
	Median	13.0000	6.4000	10.1000	16.5000	16.4000	14.5000
	Mode	6.30[a]	2.10[a]	3.90[a]	5.80[a]	26.40	9.60[a]
	Std. Deviation	8.91783	6.42223	5.09117	6.04258	7.98984	8.77147
	Skewness	.826	2.471	.216	.017	.434	1.130
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-.736	6.850	-.066	1.730	-1.145	-.090
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	6.30	2.10	3.90	5.80	8.00	9.60
	Maximum	30.40	23.70	20.90	28.10	30.80	32.60

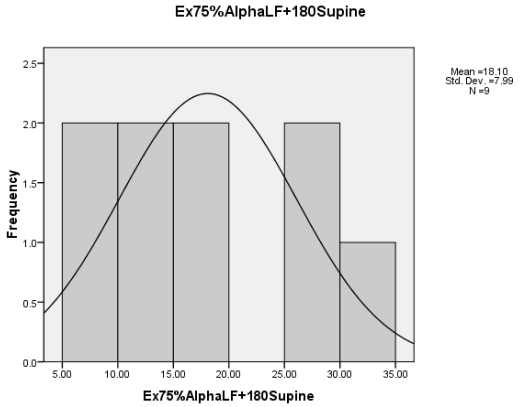
a. Multiple modes exist. The smallest value is shown

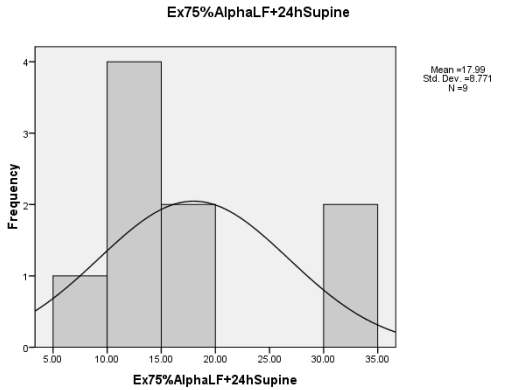

Ex75%AlphaLFBaselineSupine
Mean =16.34
Std. Dev. =8.918
N =9
Frequency
Ex75%AlphaLFBaselineSupine


Ex75%AlphaLF+15minSupine
Mean =7.37
Std. Dev. =6.422
N =9
Frequency
Ex75%AlphaLF+15minSupine


Ex75%AlphaLF+60Supine
Mean =12.05
Std. Dev. =5.091
N =9
Frequency
Ex75%AlphaLF+60Supine


Ex75%AlphaLF+120Supine
Mean =16.94
Std. Dev. =6.043
N =9
Frequency
Ex75%AlphaLF+120Supine


Ex75%AlphaLF+180Supine
Mean =18.10
Std. Dev. =7.99
N =9
Frequency
Ex75%AlphaLF+180Supine

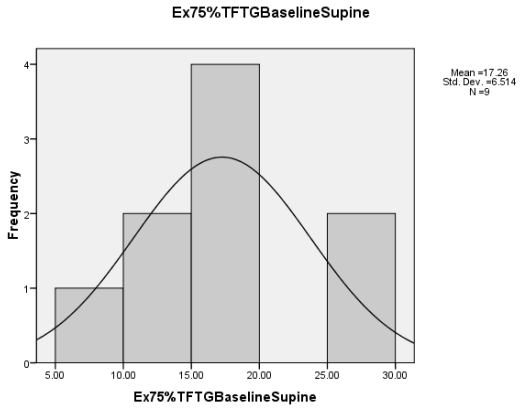

Ex75%AlphaLF+24hSupine
Mean =17.99
Std. Dev. =8.771
N =9
Frequency
Ex75%AlphaLF+24hSupine

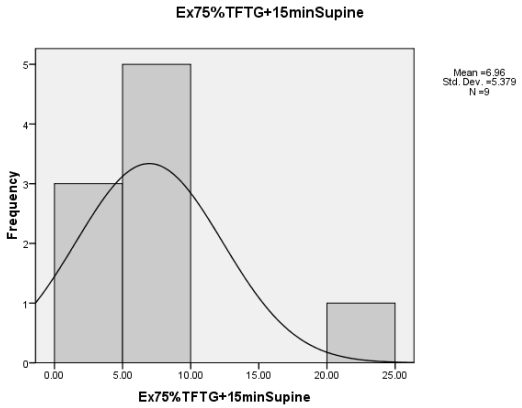
Appendix XVIII (e.xxxii): 75% BRS_{TFTG} Supine

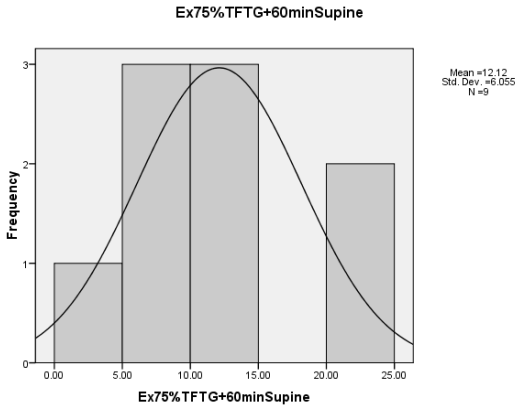
Statistics

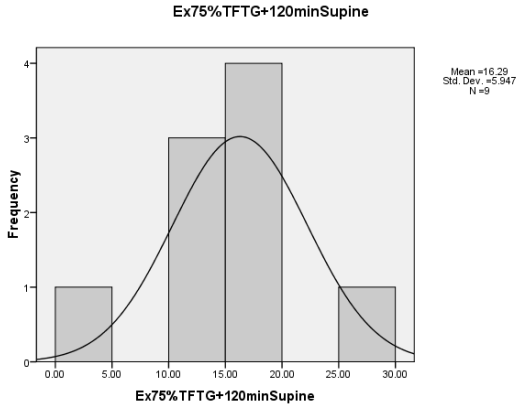
		Ex75%TFTGBaselineSupine	Ex75%TFTG+15minSupine	Ex75%TFTG+60minSupine	Ex75%TFTG+120minSupine	Ex75%TFTG+180minSupine	Ex75%TFTG+24hSupine
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	17.2556	6.9556	12.1189	16.2889	16.8800	16.7956
	Median	16.7500	5.4600	11.8200	16.9700	14.4500	14.5300
	Mode	8.77[a]	1.73[a]	2.36[a]	4.92[a]	6.29[a]	9.76[a]
	Std. Deviation	6.51385	5.37901	6.05534	5.94696	7.22387	6.53185
	Skewness	.626	2.292	.125	-.221	.219	.924
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-.206	6.112	-.453	1.670	-1.104	-.444
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	8.77	1.73	2.36	4.92	6.29	9.76
	Maximum	28.79	20.38	20.78	26.76	27.73	28.45

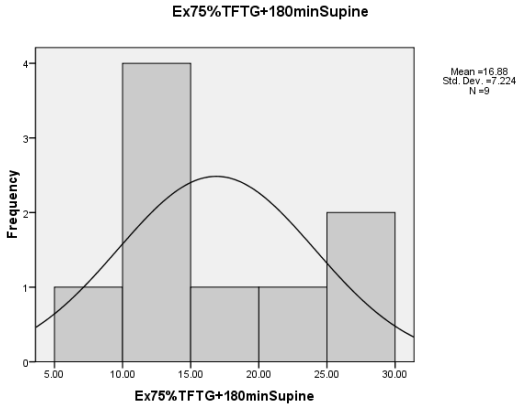
a. Multiple modes exist. The smallest value is shown

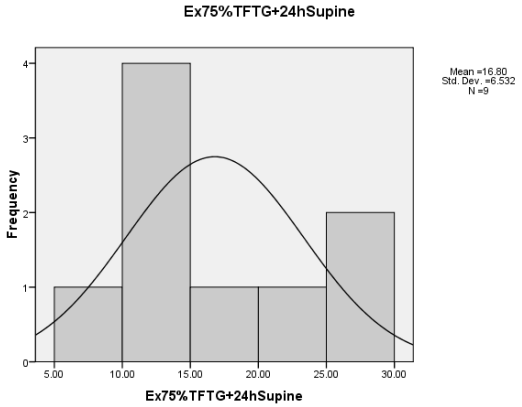

Ex75%TFTGBaselineSupine
Mean =17.26
Std. Dev. =6.514
N =9
Frequency
Ex75%TFTGBaselineSupine


Ex75%TFTG+15minSupine
Mean =6.96
Std. Dev. =5.379
N =9
Frequency
Ex75%TFTG+15minSupine


Ex75%TFTG+60minSupine
Mean =12.12
Std. Dev. =6.055
N =9
Frequency
Ex75%TFTG+60minSupine


Ex75%TFTG+120minSupine
Mean =16.29
Std. Dev. =5.947
N =9
Frequency
Ex75%TFTG+120minSupine


Ex75%TFTG+180minSupine
Mean =16.88
Std. Dev. =7.224
N =9
Frequency
Ex75%TFTG+180minSupine

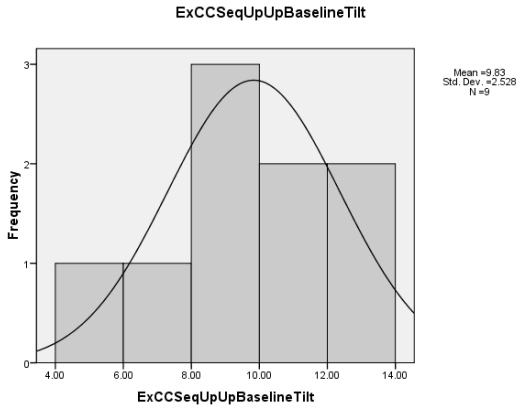

Ex75%TFTG+24hSupine
Mean =16.80
Std. Dev. =6.532
N =9
Frequency
Ex75%TFTG+24hSupine

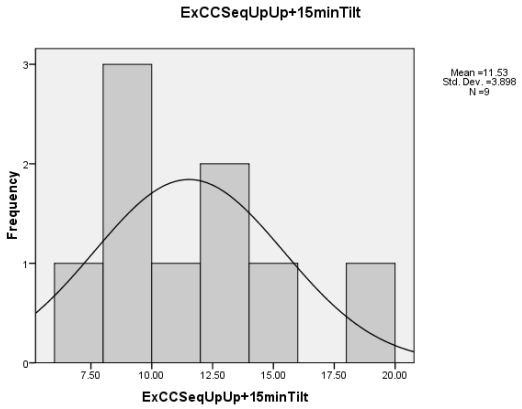
Appendix XVIII (e.xxxiii): Control BRS_{UpUp} Tilt

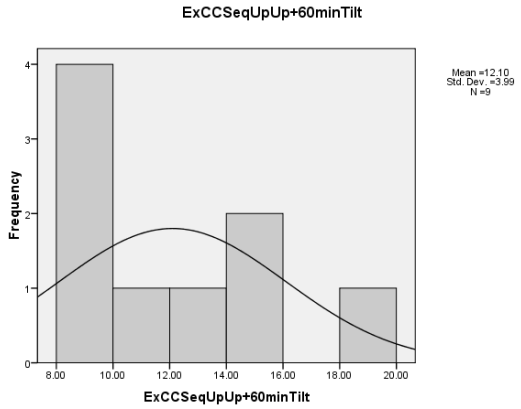
Statistics

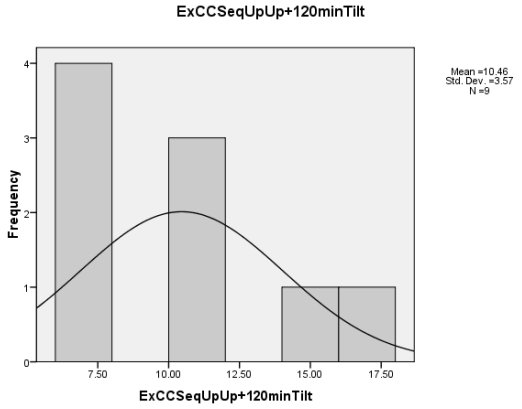
		ExCCSeqUpUpBaselineTilt	ExCCSeqUpUp+15minTilt	ExCCSeqUpUp+60minTilt	ExCCSeqUpUp+120minTilt	ExCCSeqUpUp+180minTilt	ExCCSeqUpUp+24hTilt
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	9.8333	11.5278	12.1000	10.4556	10.1222	9.6111
	Median	9.9000	10.9000	11.8000	10.3000	9.4000	8.8000
	Mode	5.00[a]	7.00[a]	8.20[a]	6.40[a]	11.80	6.70[a]
	Std. Deviation	2.52834	3.89817	3.98967	3.56970	2.08613	2.65775
	Skewness	-.798	.474	.838	.968	.253	1.179
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	.507	-1.102	-.024	.452	-1.526	.567
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	5.00	7.00	8.20	6.40	7.60	6.70
	Maximum	13.20	18.20	19.80	17.50	13.40	14.80

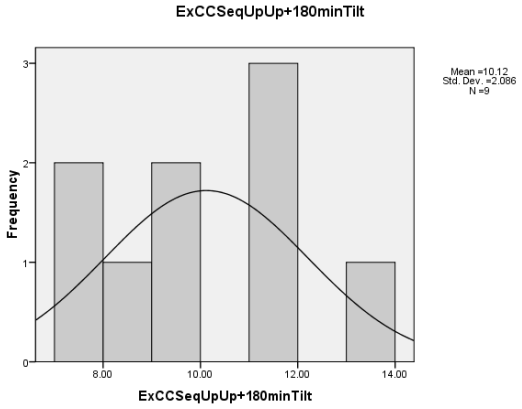
a. Multiple modes exist. The smallest value is shown

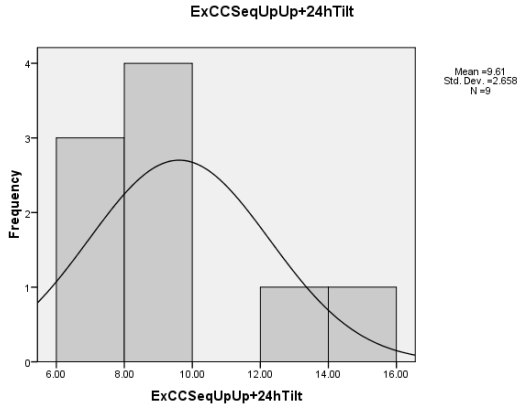

ExCCSeqUpUpBaselineTilt
Mean =9.83
Std. Dev. =2.528
N =9
Frequency
ExCCSeqUpUpBaselineTilt


ExCCSeqUpUp+15minTilt
Mean =11.53
Std. Dev. =3.898
N =9
Frequency
ExCCSeqUpUp+15minTilt


ExCCSeqUpUp+60minTilt
Mean =12.10
Std. Dev. =3.99
N =9
Frequency
ExCCSeqUpUp+60minTilt


ExCCSeqUpUp+120minTilt
Mean =10.46
Std. Dev. =3.57
N =9
Frequency
ExCCSeqUpUp+120minTilt


ExCCSeqUpUp+180minTilt
Mean =10.12
Std. Dev. =2.086
N =9
Frequency
ExCCSeqUpUp+180minTilt

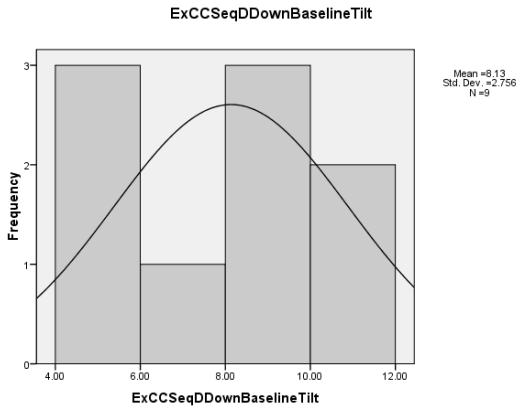

ExCCSeqUpUp+24hTilt
Mean =9.61
Std. Dev. =2.658
N =9
Frequency
ExCCSeqUpUp+24hTilt

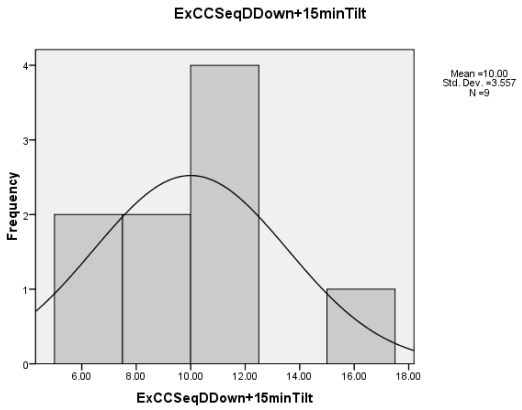
Appendix XVIII (e.xxxiv): Control $BRS_{DownDown}$ Tilt

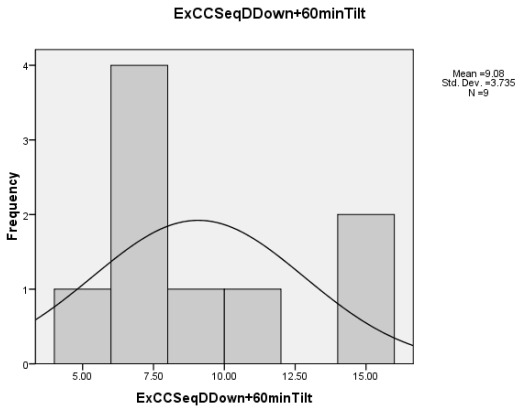
Statistics

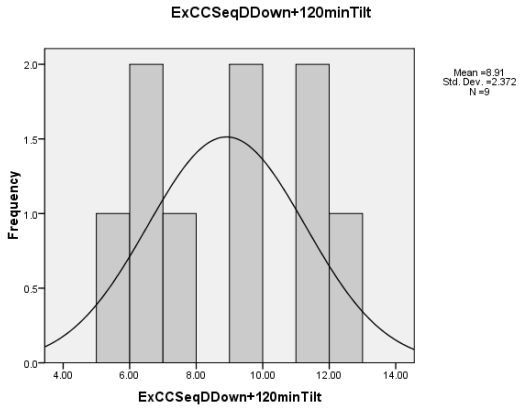
		ExCCSeqDDown BaselineTilt	ExCCSeqDDown +15minTilt	ExCCSeqDDown +60minTilt	ExCCSeqDDown +120minTilt	ExCCSeqDDown +180minTilt	ExCCSeqDDown +24hTilt
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	8.1333	10.0000	9.0778	8.9111	8.4889	7.3000
	Median	8.8000	10.4000	6.9000	9.6000	8.7000	7.6000
	Mode	4.20[a]	5.20[a]	6.60	5.60[a]	5.60[a]	4.40[a]
	Std. Deviation	2.75590	3.55739	3.73523	2.37247	1.84285	2.08567
	Skewness	-.149	.463	.744	-.068	.334	-.021
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-1.511	.252	-.929	-1.819	1.536	-1.112
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	4.20	5.20	4.80	5.60	5.60	4.40
	Maximum	11.70	16.70	15.20	12.00	12.10	10.50

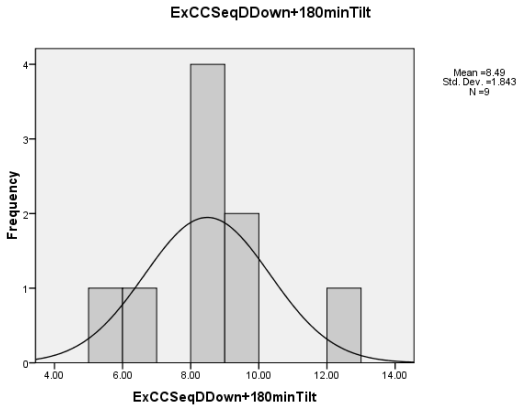
a. Multiple modes exist. The smallest value is shown

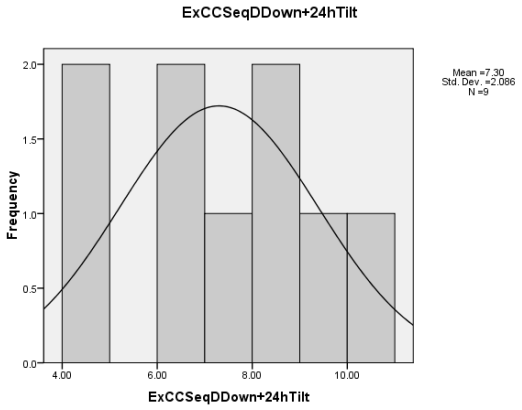

ExCCSeqDDownBaselineTilt
Mean =8.13
Std. Dev. =2.756
N =9
Frequency
ExCCSeqDDownBaselineTilt


ExCCSeqDDown+15minTilt
Mean =10.00
Std. Dev. =3.557
N =9
Frequency
ExCCSeqDDown+15minTilt


ExCCSeqDDown+60minTilt
Mean =9.08
Std. Dev. =3.735
N =9
Frequency
ExCCSeqDDown+60minTilt


ExCCSeqDDown+120minTilt
Mean =8.91
Std. Dev. =2.372
N =9
Frequency
ExCCSeqDDown+120minTilt


ExCCSeqDDown+180minTilt
Mean =8.49
Std. Dev. =1.843
N =9
Frequency
ExCCSeqDDown+180minTilt

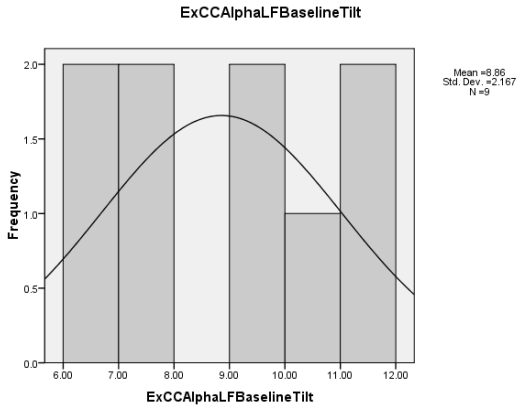

ExCCSeqDDown+24hTilt
Mean =7.30
Std. Dev. =2.086
N =9
Frequency
ExCCSeqDDown+24hTilt

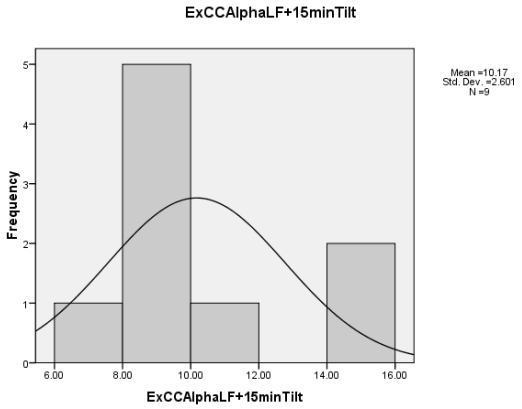
Appendix XVIII (e.xxxv): Control $BRS_{\alpha LF}$ Tilt

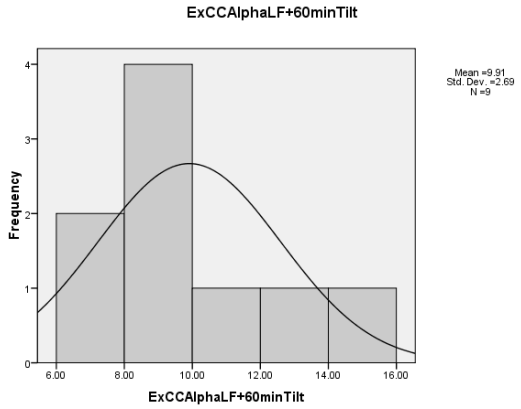
Statistics

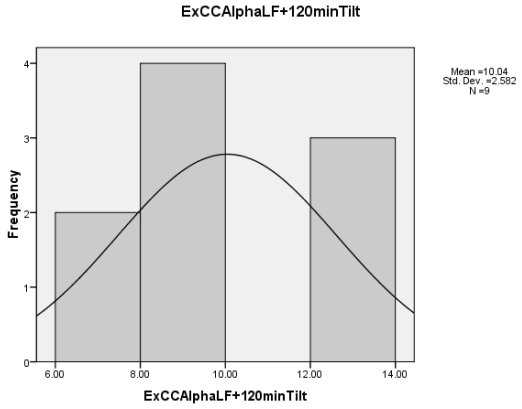
		ExCCAlphaLFBaselineTilt	ExCCAlphaLF+15minTilt	ExCCAlphaLF+60minTilt	ExCCAlphaLF+120minTilt	ExCCAlphaLF+180minTilt	ExCCAlphaLF+24hTilt
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	8.8556	10.1722	9.9111	10.0444	9.9333	8.2333
	Median	9.6000	9.2000	9.3000	9.6000	10.0000	8.4000
	Mode	6.10[a]	14.40	6.70[a]	13.00	7.00	5.10[a]
	Std. Deviation	2.16686	2.60061	2.69000	2.58172	2.43721	2.34254
	Skewness	-.095	1.035	.830	.279	-.118	.123
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-1.944	-.297	-.149	-1.445	-1.539	-1.417
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	6.10	7.40	6.70	6.50	7.00	5.10
	Maximum	11.60	14.40	14.80	13.60	13.30	11.80

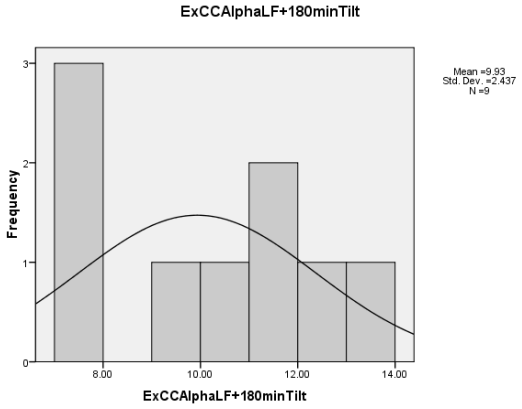
a. Multiple modes exist. The smallest value is shown

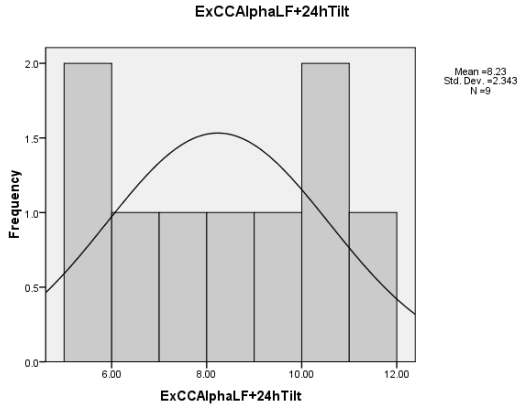

ExCCAlphaLFBaselineTilt
Mean =8.86
Std. Dev. =2.167
N =9
Frequency
ExCCAlphaLFBaselineTilt


ExCCAlphaLF+15minTilt
Mean =10.17
Std. Dev. =2.601
N =9
Frequency
ExCCAlphaLF+15minTilt


ExCCAlphaLF+60minTilt
Mean =9.91
Std. Dev. =2.69
N =9
Frequency
ExCCAlphaLF+60minTilt


ExCCAlphaLF+120minTilt
Mean =10.04
Std. Dev. =2.582
N =9
Frequency
ExCCAlphaLF+120minTilt


ExCCAlphaLF+180minTilt
Mean =9.93
Std. Dev. =2.437
N =9
Frequency
ExCCAlphaLF+180minTilt

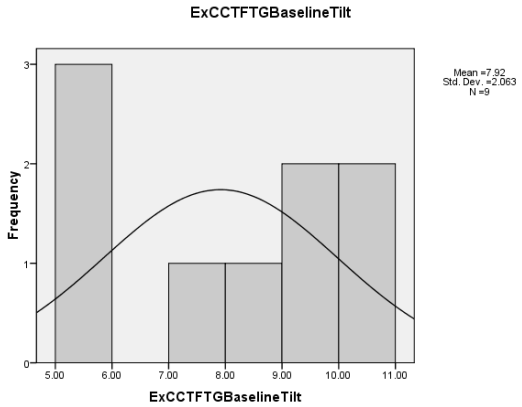

ExCCAlphaLF+24hTilt
Mean =8.23
Std. Dev. =2.343
N =9
Frequency
ExCCAlphaLF+24hTilt

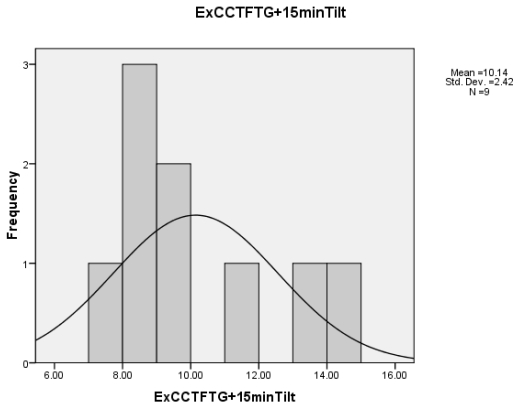
Appendix XVIII (e.xxxvi): Control BRS_{TFTG} Tilt

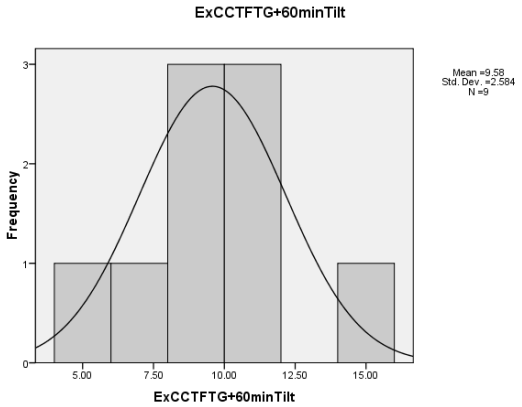
Statistics

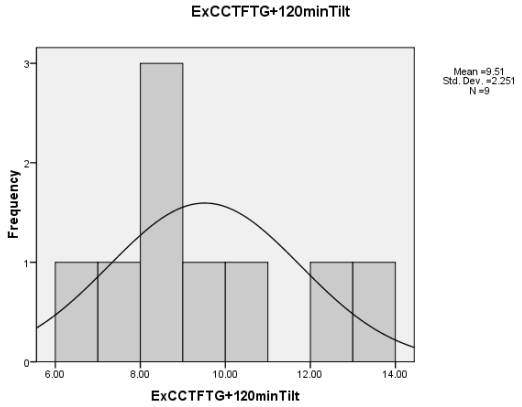
		ExCCTFTGBaselineTilt	ExCCTFTG+15minTilt	ExCCTFTG+60minTilt	ExCCTFTG+120minTilt	ExCCTFTG+180minTilt	ExCCTFTG24hTilt
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	7.9156	10.1428	9.5822	9.5144	9.1533	7.2867
	Median	8.2400	9.5100	9.0800	8.6500	10.0300	6.9000
	Mode	5.23[a]	8.69	5.63[a]	6.44[a]	6.11[a]	4.72[a]
	Std. Deviation	2.06327	2.41971	2.58371	2.25066	1.90713	1.99879
	Skewness	-.063	.826	.209	.529	-.719	.119
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-1.627	-.476	-.136	-.743	-1.411	-1.596
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	5.23	7.13	5.63	6.44	6.11	4.72
	Maximum	10.70	14.00	14.07	13.01	10.96	10.07

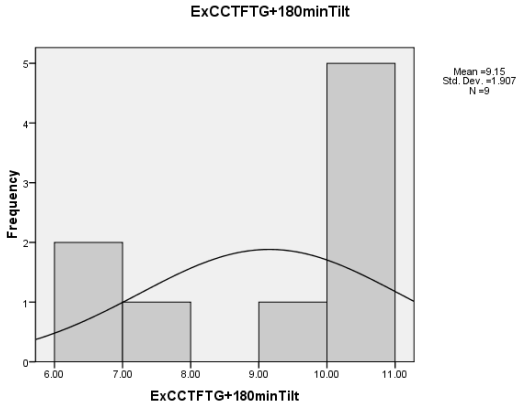
a. Multiple modes exist. The smallest value is shown

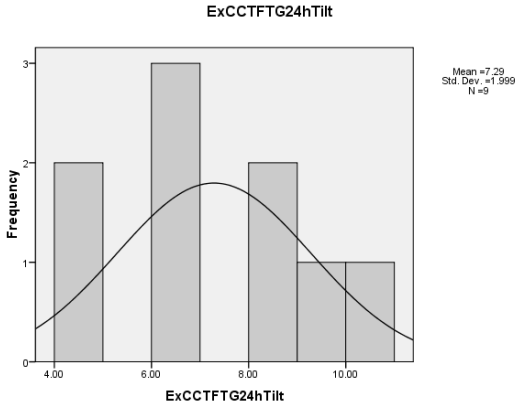

ExCCTFTGBaselineTilt
Mean =7.92
Std. Dev. =2.063
N =9
Frequency
ExCCTFTGBaselineTilt


ExCCTFTG+15minTilt
Mean =10.14
Std. Dev. =2.42
N =9
Frequency
ExCCTFTG+15minTilt


ExCCTFTG+60minTilt
Mean =9.58
Std. Dev. =2.584
N =9
Frequency
ExCCTFTG+60minTilt


ExCCTFTG+120minTilt
Mean =9.51
Std. Dev. =2.251
N =9
Frequency
ExCCTFTG+120minTilt


ExCCTFTG+180minTilt
Mean =9.15
Std. Dev. =1.907
N =9
Frequency
ExCCTFTG+180minTilt

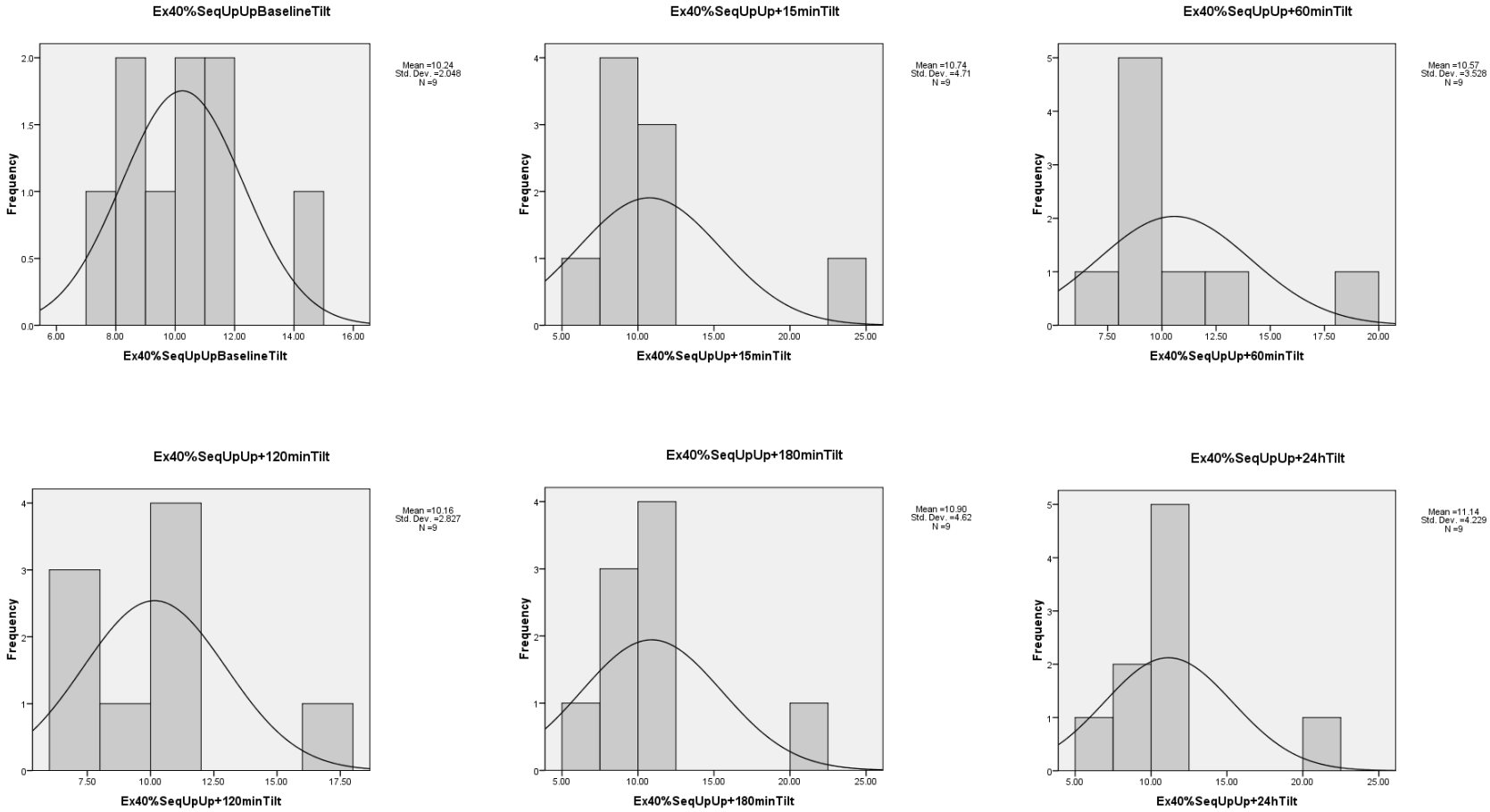

ExCCTFTG24hTilt
Mean =7.29
Std. Dev. =1.999
N =9
Frequency
ExCCTFTG24hTilt

Appendix XVIII (e.xxxvii): 40% BRS_{UpUp} Tilt

Statistics

		Ex40%SeqUpUp BaselineTilt	Ex40%SeqUpUp +15minTilt	Ex40%SeqUpUp +60minTilt	Ex40%SeqUpUp +120minTilt	Ex40%SeqUpUp +180minTilt	Ex40%SeqUpUp +24hTilt
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	10.2444	10.7444	10.5722	10.1556	10.9000	11.1444
	Median	10.6000	9.7000	9.5000	10.0000	10.5000	10.9000
	Mode	7.60[a]	7.10[a]	6.90[a]	11.20	10.50	7.30[a]
	Std. Deviation	2.04824	4.70986	3.52767	2.82671	4.61979	4.22939
	Skewness	.633	2.630	1.724	1.060	1.977	2.110
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	.390	7.461	3.425	1.470	5.236	5.394
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	7.60	7.10	6.90	7.20	5.50	7.30
	Maximum	14.20	22.90	18.70	16.10	22.10	21.50

a. Multiple modes exist. The smallest value is shown

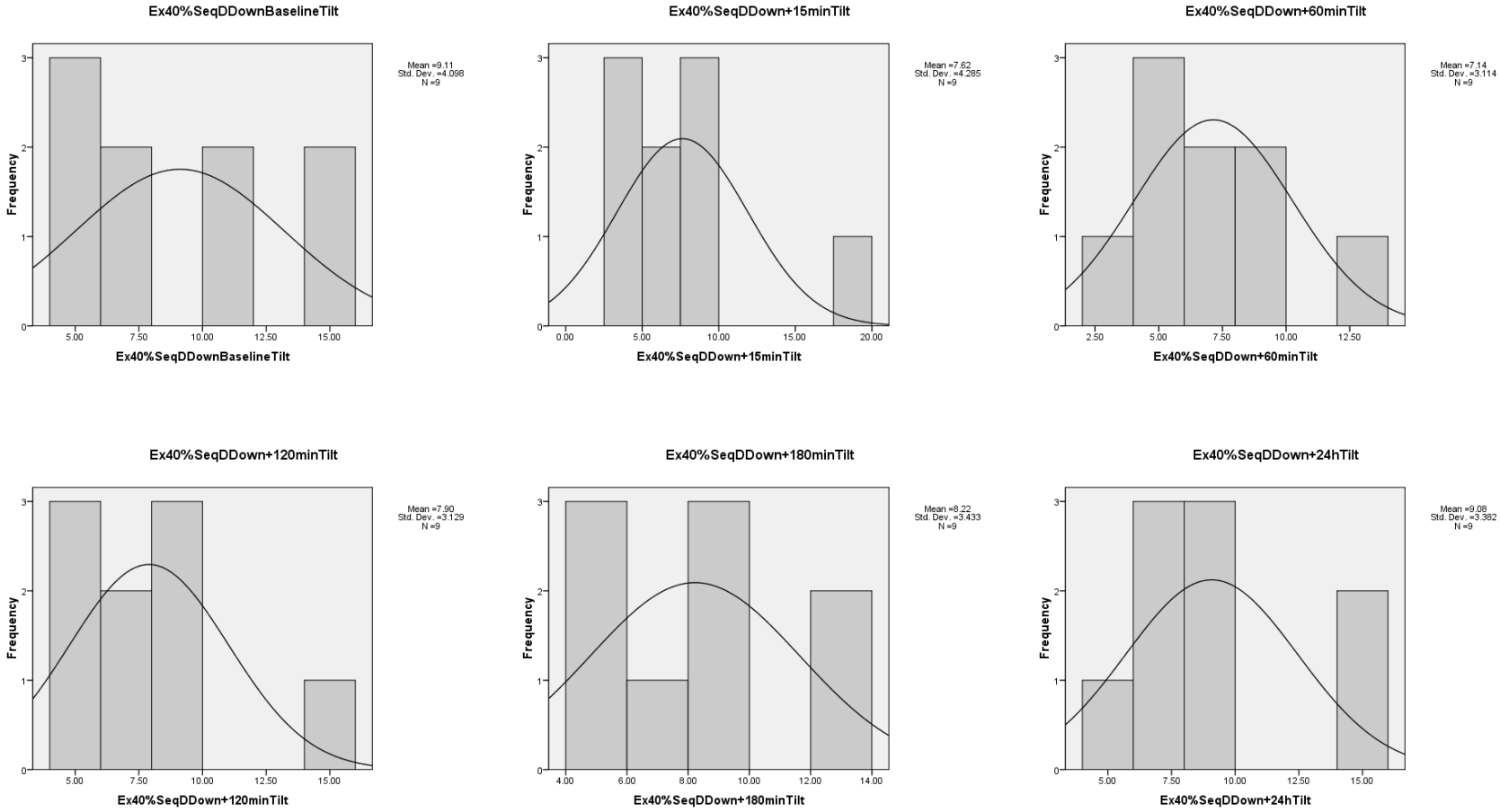

Ex40%SeqUpUpBaselineTilt
Mean =10.24
Std. Dev. =2.048
N =9
Frequency
Ex40%SeqUpUpBaselineTilt
Ex40%SeqUpUp+15minTilt
Mean =10.74
Std. Dev. =4.71
N =9
Frequency
Ex40%SeqUpUp+15minTilt
Ex40%SeqUpUp+60minTilt
Mean =10.57
Std. Dev. =3.528
N =9
Frequency
Ex40%SeqUpUp+60minTilt
Ex40%SeqUpUp+120minTilt
Mean =10.16
Std. Dev. =2.827
N =9
Frequency
Ex40%SeqUpUp+120minTilt
Ex40%SeqUpUp+180minTilt
Mean =10.90
Std. Dev. =4.62
N =9
Frequency
Ex40%SeqUpUp+180minTilt
Ex40%SeqUpUp+24hTilt
Mean =11.14
Std. Dev. =4.229
N =9
Frequency
Ex40%SeqUpUp+24hTilt

Appendix XVIII (e.xxxviii): 40% $BRS_{DownDown}$ Tilt

Statistics

		Ex40%SeqDDownBaselineTilt	Ex40%SeqDDownn+15minTilt	Ex40%SeqDDownn+60minTilt	Ex40%SeqDDownn+120minTilt	Ex40%SeqDDownn+180minTilt	Ex40%SeqDDownn+24hTilt
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	9.1111	7.6222	7.1389	7.9000	8.2222	9.0778
	Median	7.1000	6.9000	7.1000	7.6000	8.1000	8.1000
	Mode	5.60	3.60[a]	3.70[a]	4.50[a]	4.70[a]	4.50[a]
	Std. Deviation	4.09831	4.28538	3.11446	3.12890	3.43285	3.38222
	Skewness	.623	1.937	1.265	1.366	.929	.785
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-1.302	4.696	2.104	2.426	-.315	-.150
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	4.70	3.60	3.70	4.50	4.70	4.50
	Maximum	15.30	17.90	13.90	14.80	13.80	14.50

a. Multiple modes exist. The smallest value is shown

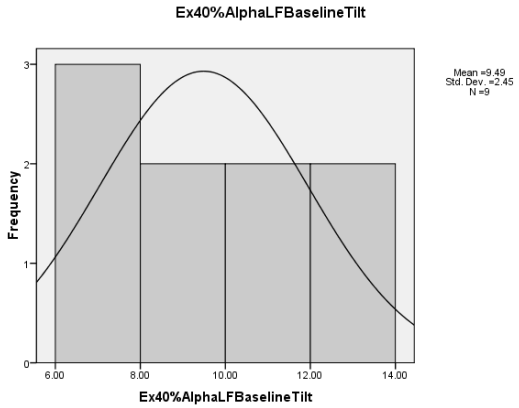

Ex40%SeqDDownBaselineTilt
Mean =9.11
Std. Dev. =4.098
N =9
Frequency
Ex40%SeqDDownBaselineTilt
Ex40%SeqDDown+15minTilt
Mean =7.62
Std. Dev. =4.285
N =9
Frequency
Ex40%SeqDDown+15minTilt
Ex40%SeqDDown+60minTilt
Mean =7.14
Std. Dev. =3.114
N =9
Frequency
Ex40%SeqDDown+60minTilt
Ex40%SeqDDown+120minTilt
Mean =7.90
Std. Dev. =3.129
N =9
Frequency
Ex40%SeqDDown+120minTilt
Ex40%SeqDDown+180minTilt
Mean =8.22
Std. Dev. =3.433
N =9
Frequency
Ex40%SeqDDown+180minTilt
Ex40%SeqDDown+24hTilt
Mean =9.08
Std. Dev. =3.382
N =9
Frequency
Ex40%SeqDDown+24hTilt

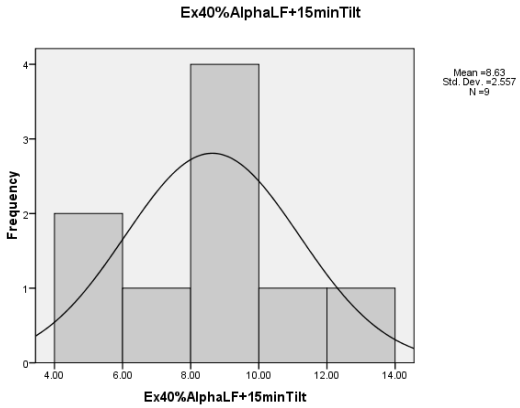
Appendix XVIII (e.xxxix): 40% $BRS_{\alpha LF}$ Tilt

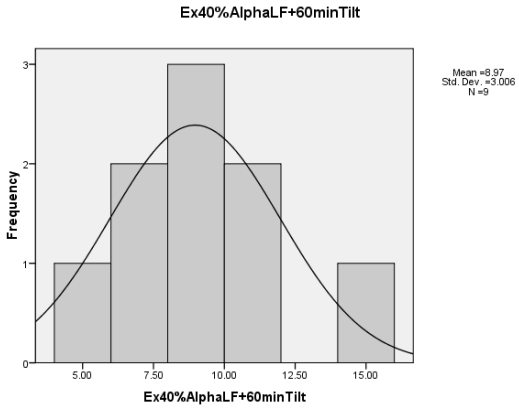
Statistics

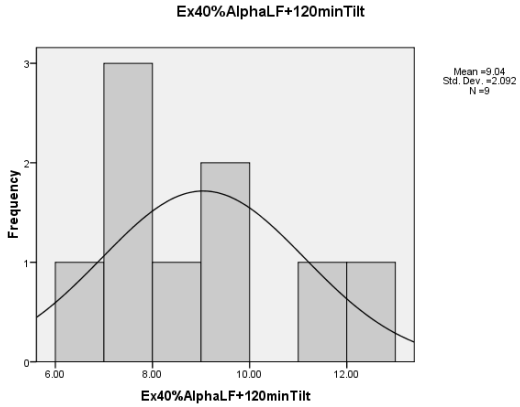
		Ex40%AlphaLFBaselineTilt	Ex40%AlphaLF+15minTilt	Ex40%AlphaLF+60minTilt	Ex40%AlphaLF+120minTilt	Ex40%AlphaLF+180minTilt	Ex40%AlphaLF+24hTilt
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	9.4889	8.6333	8.9667	9.0444	9.6778	10.0111
	Median	9.4000	9.3000	8.2000	8.7000	8.9000	9.1000
	Mode	6.10[a]	9.30	8.20	6.50[a]	6.20[a]	13.80
	Std. Deviation	2.45023	2.55734	3.00624	2.09172	3.11038	3.18255
	Skewness	.318	-.088	.636	.801	1.127	.443
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-.669	-.146	.144	-.135	.289	-1.615
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	6.10	4.90	4.80	6.50	6.20	6.20
	Maximum	13.60	12.90	14.60	12.90	15.50	14.40

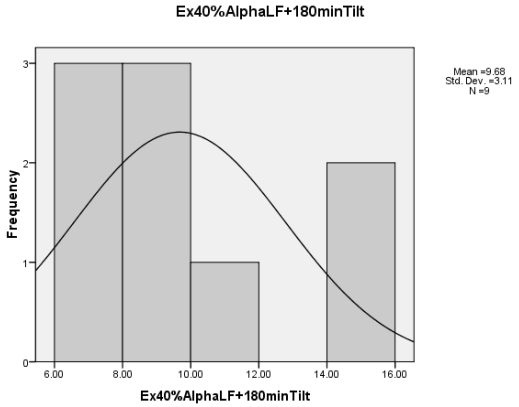
a. Multiple modes exist. The smallest value is shown

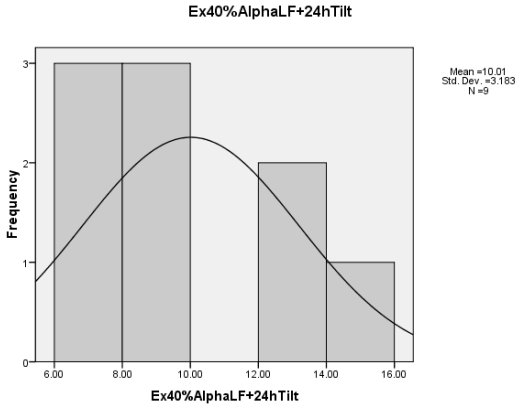

Ex40%AlphaLFBaselineTilt
Mean =9.49
Std. Dev. =2.45
N =9
Frequency
Ex40%AlphaLFBaselineTilt


Ex40%AlphaLF+15minTilt
Mean =8.63
Std. Dev. =2.557
N =9
Frequency
Ex40%AlphaLF+15minTilt


Ex40%AlphaLF+60minTilt
Mean =8.97
Std. Dev. =3.006
N =9
Frequency
Ex40%AlphaLF+60minTilt


Ex40%AlphaLF+120minTilt
Mean =9.04
Std. Dev. =2.092
N =9
Frequency
Ex40%AlphaLF+120minTilt


Ex40%AlphaLF+180minTilt
Mean =9.68
Std. Dev. =3.11
N =9
Frequency
Ex40%AlphaLF+180minTilt

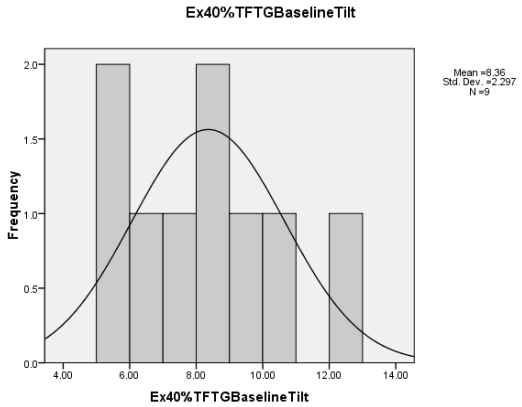

Ex40%AlphaLF+24hTilt
Mean =10.01
Std. Dev. =3.183
N =9
Frequency
Ex40%AlphaLF+24hTilt

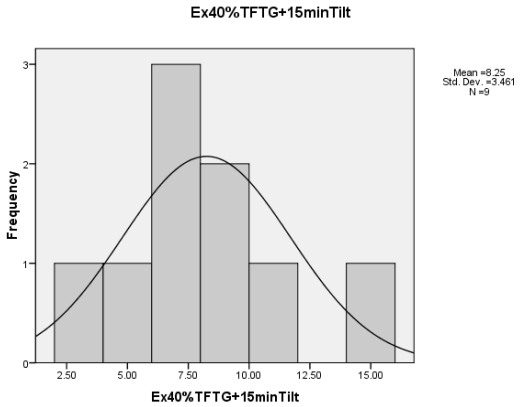
Appendix XVIII (e.xl): 40% BRS_{TFTG} Tilt

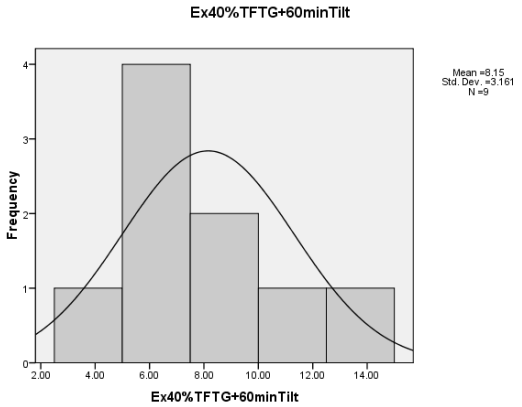
Statistics

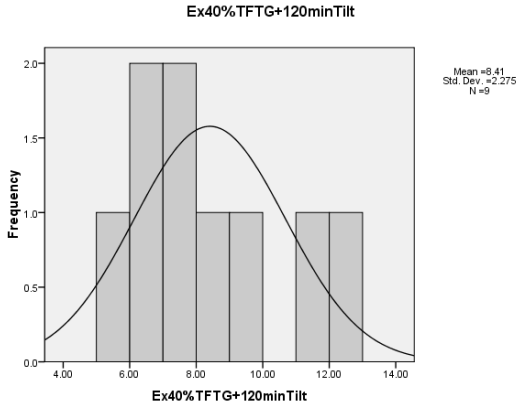
		Ex40%TFTGBaselineTilt	Ex40%TFTG+15minTilt	Ex40%TFTG+60minTilt	Ex40%TFTG+120minTilt	Ex40%TFTG+180minTilt	Ex40%TFTG+24hTilt
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	8.3611	8.2478	8.1544	8.4100	9.2311	9.2556
	Median	8.1800	7.7900	7.4200	7.7200	7.7000	9.3300
	Mode	5.65[a]	3.78[a]	3.71[a]	5.67[a]	5.71[a]	4.70[a]
	Std. Deviation	2.29684	3.46114	3.16082	2.27536	3.48128	2.99585
	Skewness	.487	1.143	.754	.766	1.016	.062
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-.564	2.493	.761	-.425	-.183	-1.249
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	5.65	3.78	3.71	5.67	5.71	4.70
	Maximum	12.44	15.77	14.34	12.39	15.37	13.39

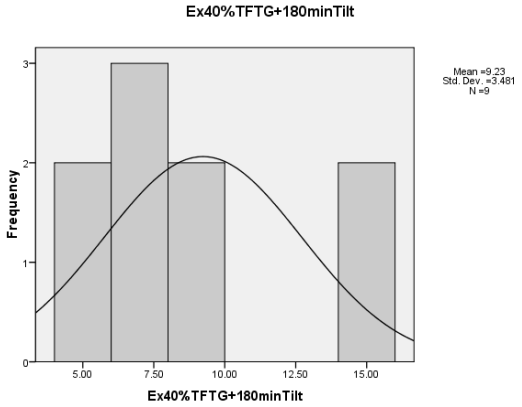
a. Multiple modes exist. The smallest value is shown

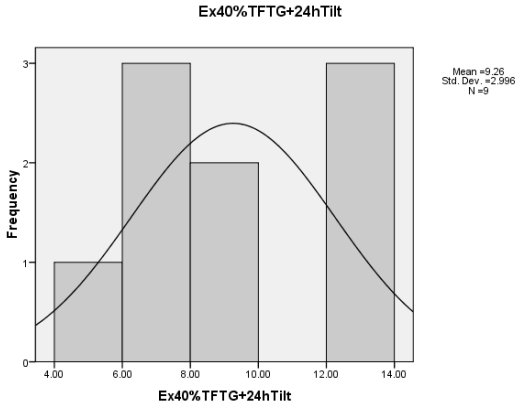

Ex40%TFTGBaselineTilt
Mean =8.36
Std. Dev. =2.297
N =9
Frequency
Ex40%TFTGBaselineTilt


Ex40%TFTG+15minTilt
Mean =8.25
Std. Dev. =3.461
N =9
Frequency
Ex40%TFTG+15minTilt


Ex40%TFTG+60minTilt
Mean =8.15
Std. Dev. =3.161
N =9
Frequency
Ex40%TFTG+60minTilt


Ex40%TFTG+120minTilt
Mean =8.41
Std. Dev. =2.275
N =9
Frequency
Ex40%TFTG+120minTilt


Ex40%TFTG+180minTilt
Mean =9.23
Std. Dev. =3.481
N =9
Frequency
Ex40%TFTG+180minTilt

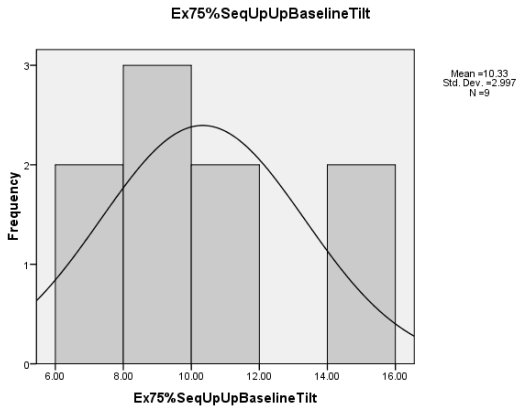

Ex40%TFTG+24hTilt
Mean =9.26
Std. Dev. =2.996
N =9
Frequency
Ex40%TFTG+24hTilt

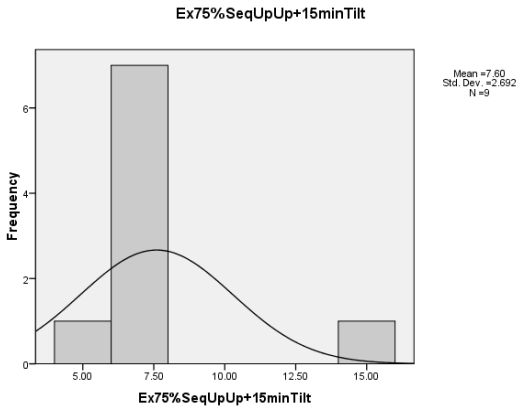
Appendix XVIII (e.xli): 75% BRS_{UpUp} Tilt

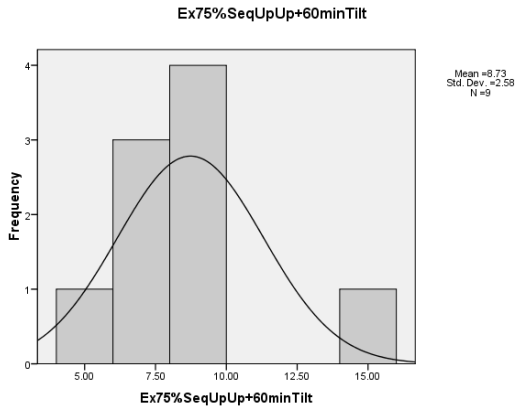
Statistics

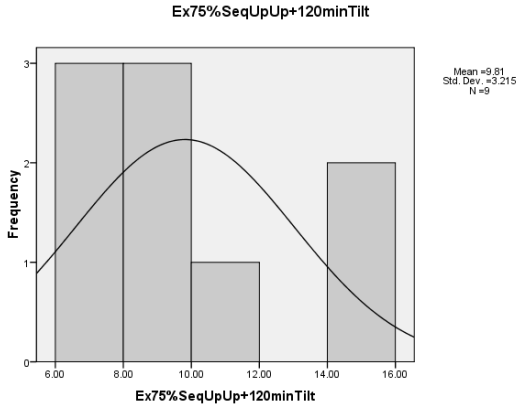
		Ex75%SeqUpUp BaselineTilt	Ex75%SeqUpUp +15minTilt	Ex75%SeqUpUp +60minTilt	Ex75%SeqUpUp +120minTilt	Ex75%SeqUpUp +180minTilt	Ex75%SeqUpUp +24hTilt
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	10.3333	7.6000	8.7333	9.8111	10.6222	11.0444
	Median	9.9000	7.1000	8.6000	8.7000	9.7000	11.3000
	Mode	6.90[a]	5.20[a]	5.80[a]	6.10[a]	6.30[a]	6.60[a]
	Std. Deviation	2.99750	2.69165	2.57973	3.21459	3.72115	3.50646
	Skewness	.918	2.410	1.169	1.005	.810	.392
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-.237	6.571	2.079	-.103	-.407	-.076
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	6.90	5.20	5.80	6.10	6.30	6.60
	Maximum	15.60	14.40	14.30	15.50	17.30	17.50

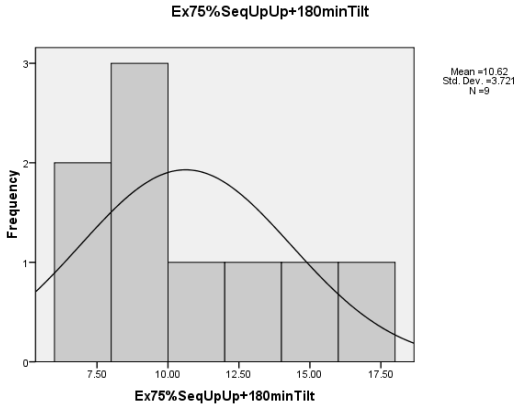
a. Multiple modes exist. The smallest value is shown

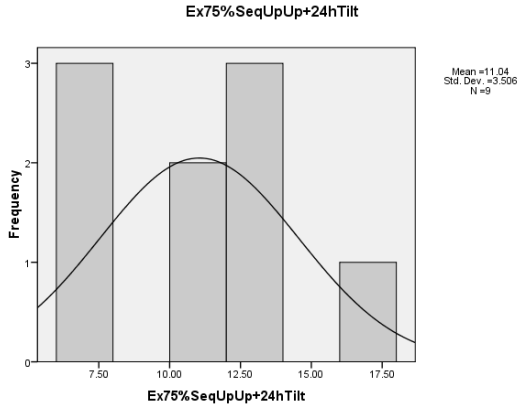

Ex75%SeqUpUpBaselineTilt
Mean =10.33
Std. Dev. =2.997
N =9
Frequency
Ex75%SeqUpUpBaselineTilt


Ex75%SeqUpUp+15minTilt
Mean =7.60
Std. Dev. =2.692
N =9
Frequency
Ex75%SeqUpUp+15minTilt


Ex75%SeqUpUp+60minTilt
Mean =8.73
Std. Dev. =2.58
N =9
Frequency
Ex75%SeqUpUp+60minTilt


Ex75%SeqUpUp+120minTilt
Mean =9.81
Std. Dev. =3.215
N =9
Frequency
Ex75%SeqUpUp+120minTilt


Ex75%SeqUpUp+180minTilt
Mean =10.62
Std. Dev. =3.721
N =9
Frequency
Ex75%SeqUpUp+180minTilt

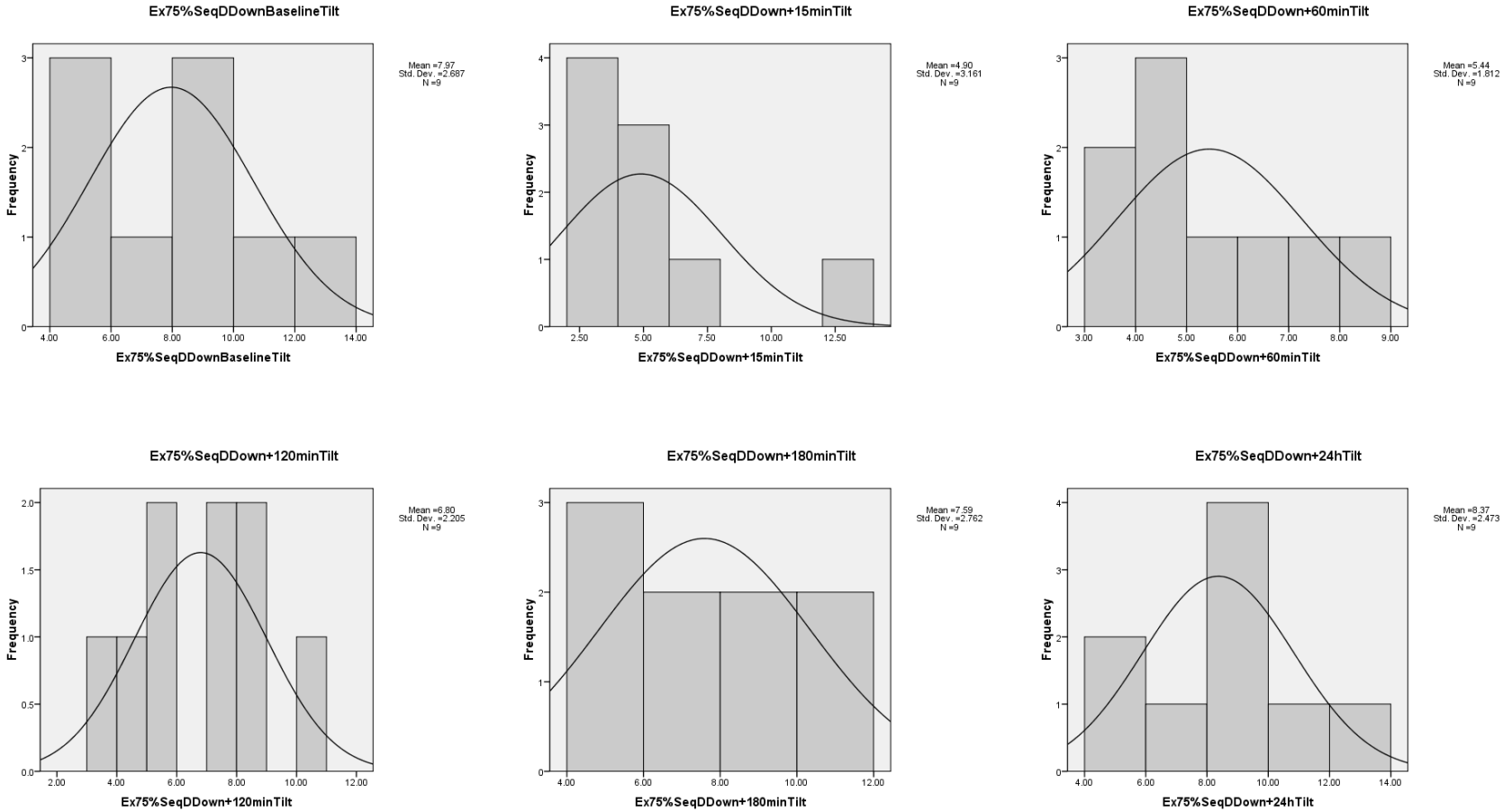

Ex75%SeqUpUp+24hTilt
Mean =11.04
Std. Dev. =3.506
N =9
Frequency
Ex75%SeqUpUp+24hTilt

Appendix XVIII (e.xlii): 75% $BRS_{DownDown}$ Tilt

Statistics

		Ex75%SeqDDownnBaselineTilt	Ex75%SeqDDownn+15minTilt	Ex75%SeqDDownn+60minTilt	Ex75%SeqDDownn+120minTilt	Ex75%SeqDDownn+180minTilt	Ex75%SeqDDownn+24hTilt
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	7.9667	4.9000	5.4444	6.8000	7.5889	8.3667
	Median	8.2000	4.2000	4.6000	7.0000	7.2000	8.5000
	Mode	4.60[a]	2.30[a]	3.60[a]	3.60[a]	9.00	5.10[a]
	Std. Deviation	2.68747	3.16149	1.81184	2.20511	2.76245	2.47285
	Skewness	.283	2.051	.755	.200	.288	.523
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-.745	4.657	-.946	-.686	-1.406	.451
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	4.60	2.30	3.60	3.60	4.20	5.10
	Maximum	12.60	12.50	8.60	10.50	11.70	13.10

a. Multiple modes exist. The smallest value is shown

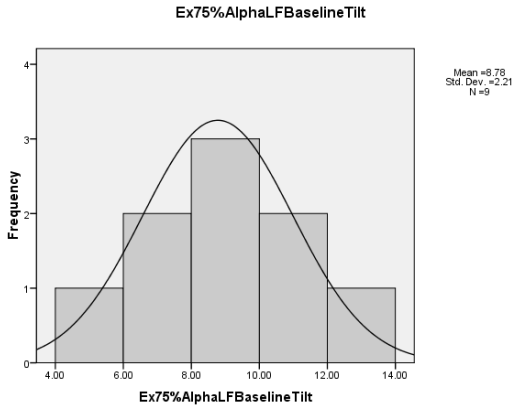

Ex75%SeqDDownBaselineTilt
Mean =7.97
Std. Dev. =2.687
N =9
Frequency
Ex75%SeqDDownBaselineTilt
Ex75%SeqDDown+15minTilt
Mean =4.90
Std. Dev. =3.161
N =9
Frequency
Ex75%SeqDDown+15minTilt
Ex75%SeqDDown+60minTilt
Mean =5.44
Std. Dev. =1.812
N =9
Frequency
Ex75%SeqDDown+60minTilt
Ex75%SeqDDown+120minTilt
Mean =6.80
Std. Dev. =2.205
N =9
Frequency
Ex75%SeqDDown+120minTilt
Ex75%SeqDDown+180minTilt
Mean =7.59
Std. Dev. =2.762
N =9
Frequency
Ex75%SeqDDown+180minTilt
Ex75%SeqDDown+24hTilt
Mean =8.37
Std. Dev. =2.473
N =9
Frequency
Ex75%SeqDDown+24hTilt

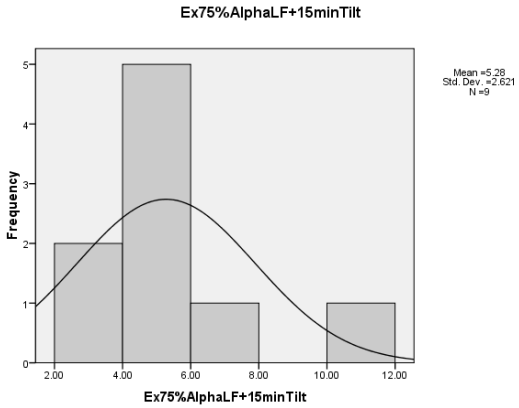
Appendix XVIII (e.xliii): 75% $BRS_{\alpha LF}$ Tilt

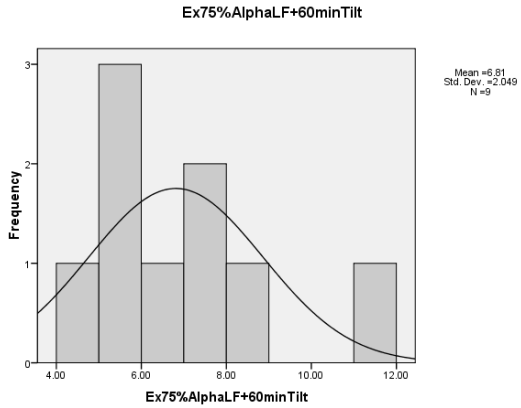
Statistics

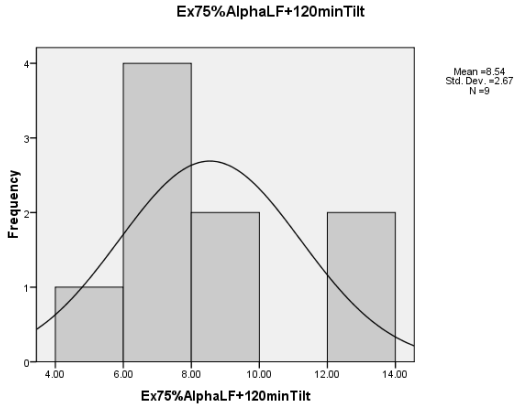
		Ex75%AlphaLFBaselineTilt	Ex75%AlphaLF+15minTilt	Ex75%AlphaLF+60minTilt	Ex75%AlphaLF+120minTilt	Ex75%AlphaLF+180minTilt	Ex75%AlphaLF+24hTilt
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	8.7778	5.2778	6.8111	8.5444	9.4333	9.3889
	Median	8.7000	4.8000	6.6000	7.9000	7.7000	9.5000
	Mode	8.70	2.40[a]	4.90[a]	5.30[a]	7.70	6.40[a]
	Std. Deviation	2.20951	2.62144	2.04905	2.66979	5.00600	2.29098
	Skewness	.278	1.464	1.373	.869	1.696	.973
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-.296	3.118	2.140	-.088	2.275	1.738
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	5.40	2.40	4.90	5.30	4.90	6.40
	Maximum	12.50	11.20	11.30	13.40	20.40	14.20

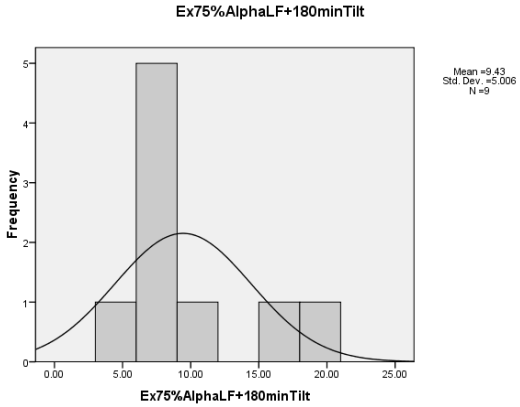
a. Multiple modes exist. The smallest value is shown

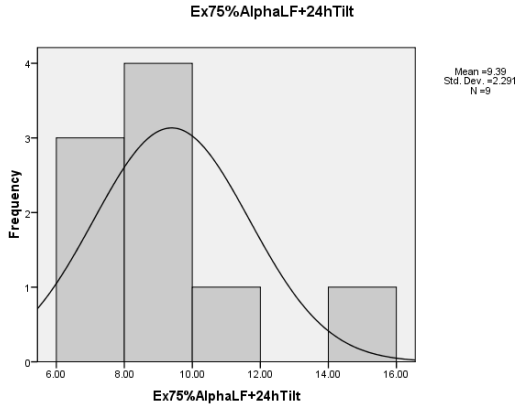

Ex75%AlphaLFBaselineTilt
Mean =8.78
Std. Dev. =2.21
N =9
Frequency
Ex75%AlphaLFBaselineTilt


Ex75%AlphaLF+15minTilt
Mean =5.28
Std. Dev. =2.621
N =9
Frequency
Ex75%AlphaLF+15minTilt


Ex75%AlphaLF+60minTilt
Mean =6.81
Std. Dev. =2.049
N =9
Frequency
Ex75%AlphaLF+60minTilt


Ex75%AlphaLF+120minTilt
Mean =8.54
Std. Dev. =2.67
N =9
Frequency
Ex75%AlphaLF+120minTilt


Ex75%AlphaLF+180minTilt
Mean =9.43
Std. Dev. =5.006
N =9
Frequency
Ex75%AlphaLF+180minTilt

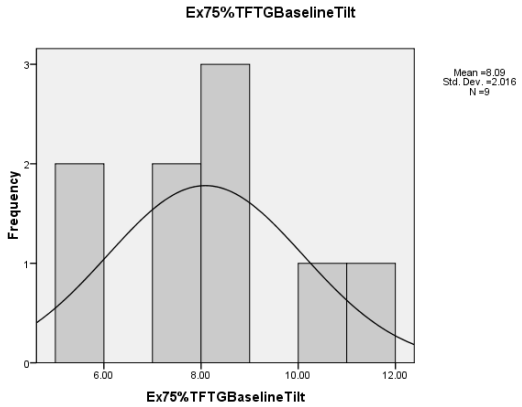

Ex75%AlphaLF+24hTilt
Mean =9.39
Std. Dev. =2.291
N =9
Frequency
Ex75%AlphaLF+24hTilt

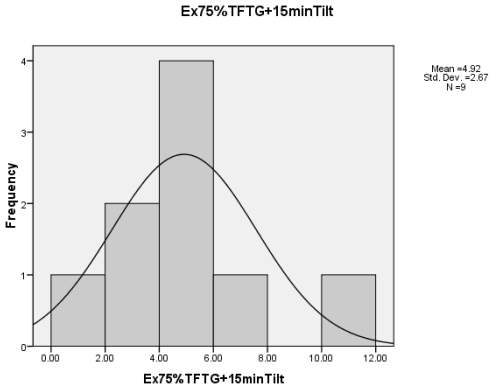
Appendix XVIII (e.xliv): 75% BRS_{TFTG} Tilt

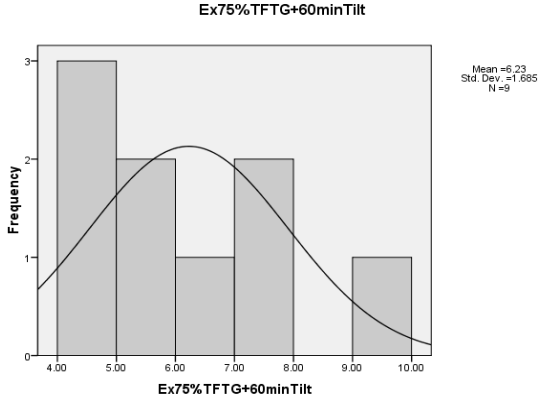
Statistics

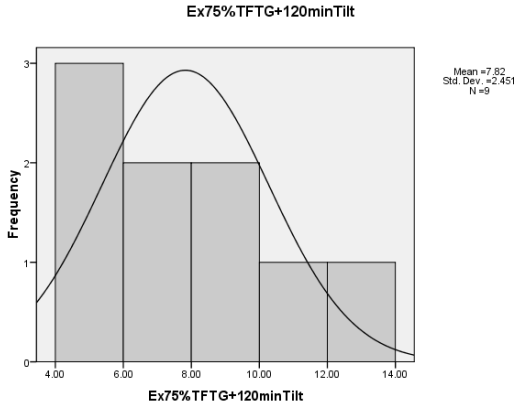
		Ex75%TFTGBaselineTilt	Ex75%TFTG+15minTilt	Ex75%TFTG+60minTilt	Ex75%TFTG+120minTilt	Ex75%TFTG180minTilt	Ex75%TFTG24hTilt
N	Valid	9	9	9	9	9	9
	Missing	0	0	0	0	0	0
	Mean	8.0889	4.9167	6.2267	7.8244	9.1856	8.9444
	Median	8.0800	4.3800	5.8600	7.2800	6.8900	9.0700
	Mode	5.38[a]	1.91[a]	4.32[a]	4.66[a]	5.62[a]	5.66[a]
	Std. Deviation	2.01617	2.67030	1.68516	2.45055	4.52062	2.59288
	Skewness	.536	1.343	1.040	.398	1.607	1.350
	Std. Error of Skewness	.717	.717	.717	.717	.717	.717
	Kurtosis	-.343	2.742	1.002	-.826	1.547	3.306
	Std. Error of Kurtosis	1.400	1.400	1.400	1.400	1.400	1.400
	Minimum	5.38	1.91	4.32	4.66	5.62	5.66
	Maximum	11.52	10.85	9.70	12.00	18.68	14.79

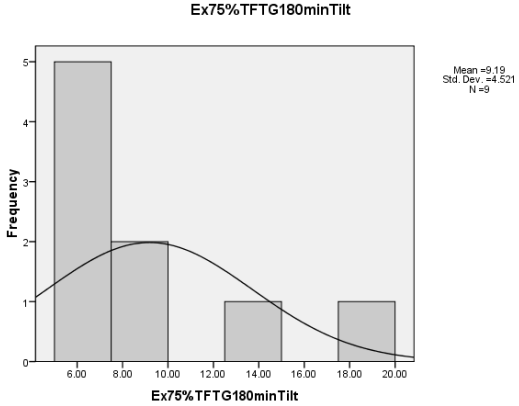
a. Multiple modes exist. The smallest value is shown

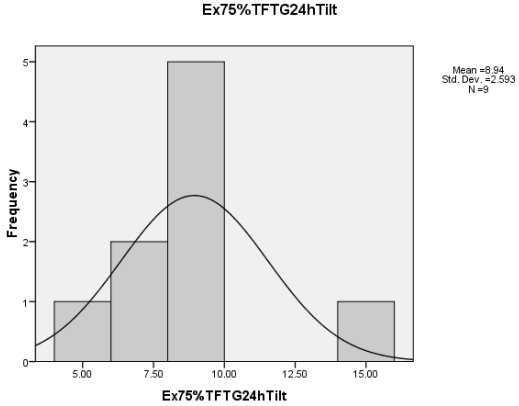

Ex75%TFTGBaselineTilt
Mean =8.09
Std. Dev. =2.016
N =9
Frequency
Ex75%TFTGBaselineTilt


Ex75%TFTG+15minTilt
Mean =4.92
Std. Dev. =2.67
N =9
Frequency
Ex75%TFTG+15minTilt


Ex75%TFTG+60minTilt
Mean =6.23
Std. Dev. =1.685
N =9
Frequency
Ex75%TFTG+60minTilt


Ex75%TFTG+120minTilt
Mean =7.82
Std. Dev. =2.451
N =9
Frequency
Ex75%TFTG+120minTilt


Ex75%TFTG180minTilt
Mean =9.19
Std. Dev. =4.521
N =9
Frequency
Ex75%TFTG180minTilt


Ex75%TFTG24hTilt
Mean =8.94
Std. Dev. =2.593
N =9
Frequency
Ex75%TFTG24hTilt

Appendix XVIII (f): Kolmogorov-Smirnov (KS) tests:

Appendix XVIII (f.i): KS Control BRS_{UpUp} Supine

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
ExCCSeqUpUpBaselineSupine	9	32.1778	14.44894	13.40	55.60
ExCCSeqUpUp+15 minSupine	9	33.9722	13.34801	13.90	50.30
ExCCSeqUpUp+60minSupine	9	30.7111	20.26700	11.80	78.40
ExCCSeqUpUp+120minSupine	9	34.5444	13.32227	15.10	53.80
ExCCSeqUpUp+180minSupine	9	34.6556	11.94823	13.60	50.30
ExCCSeqUpUp+24hSupine	9	23.3000	9.28197	10.40	39.40

One-Sample Kolmogorov-Smirnov Test

		ExCCSeqUp UpBaseline Supine	ExCCSeqUp Up+15 minSupine	ExCCSeqUp Up+60min Supine	ExCCSeqUp Up+120min Supine	ExCCSeqUp Up+180min Supine	ExCCSeqUp Up+24hSupin e
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	32.1778	33.9722	30.7111	34.5444	34.6556	23.3000
	Std. Deviation	14.44894	13.34801	20.26700	13.32227	11.94823	9.28197
Most Extreme Differences	Absolute	.144	.189	.319	.156	.132	.149
	Positive	.144	.111	.319	.155	.132	.149
	Negative	-.144	-.189	-.182	-.156	-.114	-.102
Kolmogorov-Smirnov Z		.432	.568	.956	.467	.397	.448
Asymp. Sig. (2-tailed)		.992	.904	.321	.981	.997	.988

a. Test distribution is Normal.

Appendix XVIII (f.ii): KS Control $BRS_{DownDown}$ Supine

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
ExCCSeqDDownBaselineSupine	9	27.3000	10.32618	16.50	50.80
ExCCSeqDDown+15minSupine	9	30.9333	17.59822	12.60	71.60
ExCCSeqDDown+60minSupine	9	24.6444	5.94393	14.60	35.10
ExCCSeqDDown+120minSupine	9	23.2222	7.30835	11.70	35.00
ExCCSeqDDown+180minSupine	9	25.5333	9.34131	13.60	40.20
ExCCSeqDDown+24hSupine	9	20.3333	6.36475	12.90	29.10

One-Sample Kolmogorov-Smirnov Test

		ExCCSeq DDown Baseline Supine	ExCCSeq DDown+15minSupine	ExCCSeq DDown+60minSupine	ExCCSeq DDown+120minSupine	ExCCSeq DDown+180minSupine	ExCCSeq DDown+24h Supine
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	27.3000	30.9333	24.6444	23.2222	25.5333	20.3333
	Std. Deviation	10.32618	17.59822	5.94393	7.30835	9.34131	6.36475
Most Extreme Differences	Absolute	.251	.210	.116	.158	.202	.206
	Positive	.251	.210	.116	.120	.202	.206
	Negative	-.148	-.149	-.104	-.158	-.133	-.193
Kolmogorov-Smirnov Z		.752	.631	.347	.475	.607	.619
Asymp. Sig. (2-tailed)		.623	.820	1.000	.978	.855	.838

a. Test distribution is Normal.

Appendix XVIII (f.iii): KS Control $BRS_{\alpha LF}$ Supine

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
ExCCAlphaLFBaselineSupine	9	13.8778	6.42471	5.40	22.20
ExCCAlphaLF+15minSupine	9	23.1000	8.48591	10.85	41.90
ExCCAlphaLF+60minSupine	9	21.0444	4.00846	12.30	25.10
ExCCAlphaLF+120minSupine	9	19.3222	7.83801	10.30	37.30
ExCCAlphaLF+180minSupine	9	19.7111	4.75932	13.40	28.10
ExCCAlphaLF+24hSupine	9	16.2333	6.93488	7.00	30.10

One-Sample Kolmogorov-Smirnov Test

		ExCCAlpha LFBaseline Supine	ExCCAlpha LF+15min Supine	ExCCAlpha LF+60min Supine	ExCCAlpha LF+120min Supine	ExCCAlpha LF+180min Supine	ExCCAlpha LF+24hSupine
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	13.8778	23.1000	21.0444	19.3222	19.7111	16.2333
	Std. Deviation	6.42471	8.48591	4.00846	7.83801	4.75932	6.93488
Most Extreme Differences	Absolute	.256	.251	.214	.250	.201	.177
	Positive	.256	.251	.156	.250	.201	.177
	Negative	-.213	-.126	-.214	-.125	-.122	-.117
Kolmogorov-Smirnov Z		.768	.752	.642	.751	.603	.532
Asymp. Sig. (2-tailed)		.597	.623	.805	.625	.860	.940

a. Test distribution is Normal.

Appendix XVIII (f.iv): KS Control BRS_{TFTG} Supine

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
ExCCTFTGBaselineSupine	9	15.0656	5.47849	7.58	23.52
ExCCTFTG+15minSupine	9	24.6533	8.66932	12.79	37.85
ExCCTFTG+60minSupine	9	20.1700	5.72606	12.00	30.71
ExCCTFTG+120minSupine	9	19.1011	6.42219	10.56	31.75
ExCCTFTG+180minSupine	9	19.3589	5.07145	12.21	26.93
ExCCTFTG+24hSupine	9	15.2300	5.98371	9.02	26.54

One-Sample Kolmogorov-Smirnov Test

		Ex CCTFTGBaselineSupine	ExCCTFTG+15minSupine	ExCCTFTG+60minSupine	Ex CCTFTG+120 minSupine	Ex CCTFTG+180 minSupine	Ex CCTFTG+24h Supine
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	15.0656	24.6533	20.1700	19.1011	19.3589	15.2300
	Std. Deviation	5.47849	8.66932	5.72606	6.42219	5.07145	5.98371
Most Extreme Differences	Absolute	.198	.184	.255	.175	.189	.168
	Positive	.198	.184	.255	.175	.189	.168
	Negative	-.155	-.161	-.130	-.134	-.125	-.150
Kolmogorov-Smirnov Z		.594	.551	.765	.526	.566	.504
Asymp. Sig. (2-tailed)		.872	.922	.601	.945	.906	.961

a. Test distribution is Normal.

Appendix XVIII (f.v): KS 40% BRS_{UpUp} Supine

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex40%SeqUpUpBaselineSupine	9	25.2333	11.43624	8.30	44.60
Ex40%SeqUpUp+15minSupine	9	21.4889	7.69033	12.00	34.40
Ex40%SeqUpUp+60minSupine	9	25.8556	12.42277	12.00	46.20
Ex40%SeqUpUp+120minSupine	9	24.7111	14.56369	6.80	52.80
Ex40%SeqUpUp+180minSupine	9	25.0444	9.72138	9.90	37.80
Ex40%SeqUpUp+24hSupine	9	30.1667	14.53418	10.40	56.90

One-Sample Kolmogorov-Smirnov Test

		Ex40% SeqUpUp Baseline Supine	Ex40%SeqUp Up+15min Supine	Ex40%SeqUp Up+60min Supine	Ex40%SeqUp Up+120min Supine	Ex40%SeqUp Up+180min Supine	Ex40%SeqUp Up+24hSupine
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	25.2333	21.4889	25.8556	24.7111	25.0444	30.1667
	Std. Deviation	11.43624	7.69033	12.42277	14.56369	9.72138	14.53418
Most Extreme Differences	Absolute	.149	.205	.190	.200	.201	.164
	Positive	.149	.205	.190	.200	.175	.164
	Negative	-.116	-.144	-.132	-.110	-.201	-.088
Kolmogorov-Smirnov Z		.446	.615	.569	.601	.604	.493
Asymp. Sig. (2-tailed)		.989	.844	.903	.863	.859	.968

a. Test distribution is Normal.

Appendix XVIII (f.vi): KS 40% $BRS_{DownDown}$ Supine

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex40%SeqDDownBaselineSupine	9	23.0778	10.63823	11.80	39.40
Ex40%SeqDDown+15minSupine	9	20.4111	7.59711	10.20	32.20
Ex40%SeqDDown+60minSupine	9	23.5111	7.77262	13.90	37.10
Ex40%SeqDDown+120minSupine	9	22.5667	8.04161	12.40	38.30
Ex40%SeqDDown+180minSupine	9	21.0889	7.11994	11.80	33.20
Ex40%SeqDDown+24hSupine	9	23.2056	8.13751	11.80	33.70

One-Sample Kolmogorov-Smirnov Test

		Ex40% SeqDDown Baseline Supine	Ex40%Seq DDown+15min Supine	Ex40%Seq DDown+60min Supine	Ex40%Seq DDown+120 minSupine	Ex40%Seq DDown+180 minSupine	Ex40%Seq DDown+24h Supine
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	23.0778	20.4111	23.5111	22.5667	21.0889	23.2056
	Std. Deviation	10.63823	7.59711	7.77262	8.04161	7.11994	8.13751
Most Extreme Differences	Absolute	.170	.148	.182	.271	.190	.187
	Positive	.170	.148	.182	.271	.156	.177
	Negative	-.145	-.128	-.108	-.174	-.190	-.187
Kolmogorov-Smirnov Z		.509	.445	.547	.813	.571	.560
Asymp. Sig. (2-tailed)		.958	.989	.926	.522	.900	.912

a. Test distribution is Normal.

Appendix XVIII (f.vii): KS40% $BRS_{\alpha LF}$ Supine

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex40%AlphLFBaselineSupine	9	15.0889	5.95954	9.10	25.10
Ex40%AlphaLF+15minSupine	9	15.8222	6.10630	8.20	26.10
Ex40%AlphLF+60minSupine	9	13.9000	5.50976	5.20	23.50
Ex40%AlphaLF+120minSupine	9	18.1778	8.69882	7.20	32.40
Ex40%AlphaLF+180minSupine	9	18.8111	7.14431	9.80	29.90
Ex40%AlphaLF+24hSupine	9	15.9722	6.10589	7.50	24.80

One-Sample Kolmogorov-Smirnov Test

		Ex40%Alph LFBaseline Supine	Ex40%Alpha LF+15min Supine	Ex40%Alph LF+60min Supine	Ex40%Alpha LF+120min Supine	Ex40%Alpha LF+180min Supine	Ex40% AlphaLF+24h Supine
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	15.0889	15.8222	13.9000	18.1778	18.8111	15.9722
	Std. Deviation	5.95954	6.10630	5.50976	8.69882	7.14431	6.10589
Most Extreme Differences	Absolute	.197	.216	.123	.198	.224	.143
	Positive	.197	.216	.123	.198	.224	.138
	Negative	-.157	-.160	-.116	-.144	-.137	-.143
Kolmogorov-Smirnov Z		.592	.647	.368	.593	.672	.430
Asymp. Sig. (2-tailed)		.875	.796	.999	.873	.757	.993

a. Test distribution is Normal.

Appendix XVIII (f.viii): KS 40% BRS_{TFTG} Supine

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex40%TFTGBaselineSupine	9	16.0011	5.82167	7.58	25.86
Ex40%TFTG+15minSupine	9	14.4289	5.72707	7.46	25.87
Ex40%TFTG60minSupine	9	17.6644	7.60083	4.25	27.90
Ex40%TFTG120minSupine	9	16.3022	7.03789	7.02	27.23
Ex40%TFTG180minSupine	9	17.9589	7.27542	9.93	33.42
Ex40%TFTG24hSupine	9	17.6678	5.70816	9.55	26.56

One-Sample Kolmogorov-Smirnov Test

		Ex40% TFTGBaselineSupine	Ex40% TFTG+15min Supine	Ex40% TFTG60min Supine	Ex40% TFTG120min Supine	Ex40% TFTG180min Supine	Ex40% TFTG24h Supine
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	16.0011	14.4289	17.6644	16.3022	17.9589	17.6678
	Std. Deviation	5.82167	5.72707	7.60083	7.03789	7.27542	5.70816
Most Extreme Differences	Absolute	.243	.206	.171	.201	.151	.205
	Positive	.243	.206	.123	.201	.151	.205
	Negative	-.176	-.126	-.171	-.161	-.135	-.178
Kolmogorov-Smirnov Z		.728	.619	.514	.602	.452	.614
Asymp. Sig. (2-tailed)		.664	.839	.955	.861	.987	.845

a. Test distribution is Normal.

Appendix XVIII (f.ix): KS 75% BRS_{UpUp} Supine

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex75%SeqUpUpBaselineSupine	9	25.5000	10.37123	12.10	44.70
Ex75%SeqUpUp+15minSupine	9	11.5000	9.74256	4.20	33.30
Ex75%SeqUpUp+60minSupine	9	21.0889	14.24495	5.90	44.90
Ex75%SeqUpUp+120minSupine	9	23.4444	12.20114	8.00	47.50
Ex75%SeqUpUp+180minSupine	9	24.5000	8.10262	9.90	36.90
Ex75%SeqUpUp+24hSupine	9	28.8889	13.51929	10.50	51.20

One-Sample Kolmogorov-Smirnov Test

		Ex75% SeqUpUp Baseline Supine	Ex75%SeqUp Up+15min Supine	Ex75%SeqUp Up+60min Supine	Ex75%SeqUp Up+120min Supine	Ex75%SeqUp Up+180min Supine	Ex75%SeqUp Up+24hSupine
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	25.5000	11.5000	21.0889	23.4444	24.5000	28.8889
	Std. Deviation	10.37123	9.74256	14.24495	12.20114	8.10262	13.51929
Most Extreme Differences	Absolute	.236	.339	.227	.168	.143	.245
	Positive	.236	.339	.227	.168	.133	.245
	Negative	-.135	-.227	-.164	-.117	-.143	-.156
Kolmogorov-Smirnov Z		.707	1.017	.682	.503	.428	.736
Asymp. Sig. (2-tailed)		.700	.252	.742	.962	.993	.650

a. Test distribution is Normal.

Appendix XVIII (f.x): KS 75% $BRS_{DownDown}$ Supine

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex75%SeqDDownBaselineSupine	9	24.0111	9.78768	14.90	44.70
Ex75%SeqDDown+15minSupine	9	11.3778	10.01022	3.70	33.60
Ex75%SeqDDown+60minSupine	9	18.9056	7.40213	8.25	28.70
Ex75%SeqDDown+120minSupine	9	21.9778	14.23796	8.60	49.10
Ex75%SeqDDown+180minSupine	9	21.3778	7.91656	12.40	34.00
Ex75%SeqDDown+24hSupine	9	23.7778	6.55129	13.80	31.50

One-Sample Kolmogorov-Smirnov Test

		Ex75% SeqDDown Baseline Supine	Ex75%Seq DDown+15mi nSupine	Ex75%Seq DDown+60mi nSupine	Ex75%Seq DDown+120 minSupine	Ex75%Seq DDown+180 minSupine	Ex75%Seq DDown+24h Supine
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	24.0111	11.3778	18.9056	21.9778	21.3778	23.7778
	Std. Deviation	9.78768	10.01022	7.40213	14.23796	7.91656	6.55129
Most Extreme Differences	Absolute	.176	.291	.184	.293	.274	.218
	Positive	.172	.291	.117	.293	.274	.168
	Negative	-.176	-.222	-.184	-.174	-.184	-.218
Kolmogorov-Smirnov Z		.528	.874	.552	.878	.822	.655
Asymp. Sig. (2-tailed)		.943	.430	.921	.423	.509	.785

a. Test distribution is Normal.

Appendix XVIII (f.xi): KS 75% $BRS_{\alpha LF}$ Supine

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex75%AlphaLFBaselineSupine	9	16.3444	8.91783	6.30	30.40
Ex75%AlphaLF+15minSupine	9	7.3667	6.42223	2.10	23.70
Ex75%AlphaLF+60Supine	9	12.0500	5.09117	3.90	20.90
Ex75%AlphaLF+120Supine	9	16.9444	6.04258	5.80	28.10
Ex75%AlphaLF+180Supine	9	18.1000	7.98984	8.00	30.80
Ex75%AlphaLF+24hSupine	9	17.9889	8.77147	9.60	32.60

One-Sample Kolmogorov-Smirnov Test

		Ex75%Alpha LFBaseline Supine	Ex75%Alpha LF+15min Supine	Ex75%Alpha LF+60Supine	Ex75%Alpha LF+120Supin e	Ex75%Alpha LF+180Supin e	Ex75% AlphaLF+24h Supine
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	16.3444	7.3667	12.0500	16.9444	18.1000	17.9889
	Std. Deviation	8.91783	6.42223	5.09117	6.04258	7.98984	8.77147
Most Extreme Differences	Absolute	.202	.362	.205	.173	.226	.221
	Positive	.202	.362	.205	.145	.226	.221
	Negative	-.161	-.206	-.105	-.173	-.184	-.172
Kolmogorov-Smirnov Z		.605	1.086	.614	.520	.679	.662
Asymp. Sig. (2-tailed)		.857	.189	.845	.950	.746	.774

a. Test distribution is Normal.

Appendix XVIII (f.xii): KS 75% BRS_{TFTG} Supine

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex75%TFTGBaselineSupine	9	17.2556	6.51385	8.77	28.79
Ex75%TFTG+15minSupine	9	6.9556	5.37901	1.73	20.38
Ex75%TFTG+60minSupine	9	12.1189	6.05534	2.36	20.78
Ex75%TFTG+120minSupine	9	16.2889	5.94696	4.92	26.76
Ex75%TFTG+180minSupine	9	16.8800	7.22387	6.29	27.73
Ex75%TFTG+24hSupine	9	16.7956	6.53185	9.76	28.45

One-Sample Kolmogorov-Smirnov Test

		Ex75% TFTGBaselineSupine	Ex75% TFTG+15min Supine	Ex75% TFTG+60min Supine	Ex75% TFTG+120minSupine	Ex75% TFTG+180minSupine	Ex75% TFTG+24h Supine
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	17.2556	6.9556	12.1189	16.2889	16.8800	16.7956
	Std. Deviation	6.51385	5.37901	6.05534	5.94696	7.22387	6.53185
Most Extreme Differences	Absolute	.190	.321	.146	.202	.187	.216
	Positive	.190	.321	.146	.159	.187	.216
	Negative	-.114	-.166	-.142	-.202	-.117	-.141
Kolmogorov-Smirnov Z		.571	.962	.439	.607	.562	.649
Asymp. Sig. (2-tailed)		.900	.313	.990	.854	.910	.793

a. Test distribution is Normal.

Appendix XVIII (f.xiii): KS Control BRS_{UpUp} Tilt

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
ExCCSeqUpUpBaselineTilt	9	9.8333	2.52834	5.00	13.20
ExCCSeqUpUp+15minTilt	9	11.5278	3.89817	7.00	18.20
ExCCSeqUpUp+60minTilt	9	12.1000	3.98967	8.20	19.80
ExCCSeqUpUp+120minTilt	9	10.4556	3.56970	6.40	17.50
ExCCSeqUpUp+180minTilt	9	10.1222	2.08613	7.60	13.40
ExCCSeqUpUp+24hTilt	9	9.6111	2.65775	6.70	14.80

One-Sample Kolmogorov-Smirnov Test

		ExCCSeqUp UpBaselineTilt	ExCCSeqUp Up+15minTilt	ExCCSeqUp Up+60minTilt	ExCCSeqUp Up+120minTilt	ExCCSeqUp Up+180minTilt	ExCCSeqUp Up+24hTilt
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	9.8333	11.5278	12.1000	10.4556	10.1222	9.6111
	Std. Deviation	2.52834	3.89817	3.98967	3.56970	2.08613	2.65775
Most Extreme Differences	Absolute	.257	.233	.240	.207	.220	.249
	Positive	.109	.233	.240	.207	.191	.249
	Negative	-.257	-.156	-.164	-.128	-.220	-.137
Kolmogorov-Smirnov Z		.770	.700	.721	.622	.659	.748
Asymp. Sig. (2-tailed)		.593	.712	.676	.834	.778	.630

a. Test distribution is Normal.

Appendix XVIII (f.xiv): KS Control $BRS_{DownDown}$ Tilt

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
ExCCSeqDDownBaselineTilt	9	8.1333	2.75590	4.20	11.70
ExCCSeqDDown+15minTilt	9	10.0000	3.55739	5.20	16.70
ExCCSeqDDown+60minTilt	9	9.0778	3.73523	4.80	15.20
ExCCSeqDDown+120minTilt	9	8.9111	2.37247	5.60	12.00
ExCCSeqDDown+180minTilt	9	8.4889	1.84285	5.60	12.10
ExCCSeqDDown+24hTilt	9	7.3000	2.08567	4.40	10.50

One-Sample Kolmogorov-Smirnov Test

		ExCCSeq DDown BaselineTilt	ExCCSeq DDown+15minTilt	ExCCSeq DDown+60minTilt	ExCCSeq DDown+120minTilt	ExCCSeq DDown+180minTilt	ExCCSeq DDown+24hTilt
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	8.1333	10.0000	9.0778	8.9111	8.4889	7.3000
	Std. Deviation	2.75590	3.55739	3.73523	2.37247	1.84285	2.08567
Most Extreme Differences	Absolute	.151	.148	.276	.209	.239	.145
	Positive	.145	.148	.276	.209	.239	.145
	Negative	-.151	-.100	-.141	-.170	-.215	-.145
Kolmogorov-Smirnov Z		.453	.444	.827	.627	.716	.436
Asymp. Sig. (2-tailed)		.986	.989	.501	.826	.684	.991

a. Test distribution is Normal.

Appendix XVIII (f.xv): KS Control $BRS_{\alpha LF}$ Tilt

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
ExCCAlphaLFBaselineTilt	9	8.8556	2.16686	6.10	11.60
ExCCAlphaLF+15minTilt	9	10.1722	2.60061	7.40	14.40
ExCCAlphaLF+60minTilt	9	9.9111	2.69000	6.70	14.80
ExCCAlphaLF+120minTilt	9	10.0444	2.58172	6.50	13.60
ExCCAlphaLF+180minTilt	9	9.9333	2.43721	7.00	13.30
ExCCAlphaLF+24hTilt	9	8.2333	2.34254	5.10	11.80

One-Sample Kolmogorov-Smirnov Test

		ExCCAlpha LFBaselineTil t	ExCCAlpha LF+15minTilt	ExCCAlpha LF+60minTilt	ExCCAlpha LF+120minTil t	ExCCAlpha LF+180minTil t	ExCCAlpha LF+24hTilt
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	8.8556	10.1722	9.9111	10.0444	9.9333	8.2333
	Std. Deviation	2.16686	2.60061	2.69000	2.58172	2.43721	2.34254
Most Extreme Differences	Absolute	.194	.246	.227	.207	.211	.145
	Positive	.194	.246	.227	.204	.211	.145
	Negative	-.190	-.170	-.118	-.207	-.145	-.133
Kolmogorov-Smirnov Z		.581	.739	.682	.622	.632	.436
Asymp. Sig. (2-tailed)		.889	.646	.741	.835	.819	.991

a. Test distribution is Normal.

Appendix XVIII (f.xvi): KS Control BRS_{TFTG} Tilt

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
ExCCTFTGBaselineTilt	9	7.9156	2.06327	5.23	10.70
ExCCTFTG+15minTilt	9	10.1428	2.41971	7.13	14.00
ExCCTFTG+60minTilt	9	9.5822	2.58371	5.63	14.07
ExCCTFTG+120minTilt	9	9.5144	2.25066	6.44	13.01
ExCCTFTG+180minTilt	9	9.1533	1.90713	6.11	10.96
ExCCTFTG24hTilt	9	7.2867	1.99879	4.72	10.07

One-Sample Kolmogorov-Smirnov Test

		Ex CCTFTGBaselineTilt	ExCCTFTG+15minTilt	ExCCTFTG+60minTilt	Ex CCTFTG+120 minTilt	Ex CCTFTG+180 minTilt	ExCCTFTG24 hTilt
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	7.9156	10.1428	9.5822	9.5144	9.1533	7.2867
	Std. Deviation	2.06327	2.41971	2.58371	2.25066	1.90713	1.99879
Most Extreme Differences	Absolute	.189	.220	.133	.205	.235	.166
	Positive	.189	.220	.133	.205	.189	.166
	Negative	-.148	-.162	-.096	-.145	-.235	-.147
Kolmogorov-Smirnov Z		.566	.659	.398	.615	.704	.499
Asymp. Sig. (2-tailed)		.906	.778	.997	.843	.705	.964

a. Test distribution is Normal.

Appendix XVIII (f.xvii): KS 40% BRS_{UpUp} Tilt

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex40%SeqUpUpBaselineTilt	9	10.2444	2.04824	7.60	14.20
Ex40%SeqUpUp+15minTilt	9	10.7444	4.70986	7.10	22.90
Ex40%SeqUpUp+60minTilt	9	10.5722	3.52767	6.90	18.70
Ex40%SeqUpUp+120minTilt	9	10.1556	2.82671	7.20	16.10
Ex40%SeqUpUp+180minTilt	9	10.9000	4.61979	5.50	22.10
Ex40%SeqUpUp+24hTilt	9	11.1444	4.22939	7.30	21.50

One-Sample Kolmogorov-Smirnov Test

		Ex40% SeqUpUp BaselineTilt	Ex40%SeqUp Up+15minTilt	Ex40%SeqUp Up+60minTilt	Ex40%SeqUp Up+120minTil t	Ex40%SeqUp Up+180minTil t	Ex40%SeqUp Up+24hTilt
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	10.2444	10.7444	10.5722	10.1556	10.9000	11.1444
	Std. Deviation	2.04824	4.70986	3.52767	2.82671	4.61979	4.22939
Most Extreme Differences	Absolute	.149	.401	.264	.194	.295	.327
	Positive	.149	.401	.264	.194	.295	.327
	Negative	-.124	-.220	-.149	-.148	-.161	-.182
Kolmogorov-Smirnov Z		.448	1.203	.793	.581	.884	.982
Asymp. Sig. (2-tailed)		.988	.110	.556	.889	.415	.290

a. Test distribution is Normal.

Appendix XVIII (f.xviii): KS 40% $BRS_{DownDown}$ Tilt

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex40%SeqDDownBaselineTilt	9	9.1111	4.09831	4.70	15.30
Ex40%SeqDDown+15minTilt	9	7.6222	4.28538	3.60	17.90
Ex40%SeqDDown+60minTilt	9	7.1389	3.11446	3.70	13.90
Ex40%SeqDDown+120minTilt	9	7.9000	3.12890	4.50	14.80
Ex40%SeqDDown+180minTilt	9	8.2222	3.43285	4.70	13.80
Ex40%SeqDDown+24hTilt	9	9.0778	3.38222	4.50	14.50

One-Sample Kolmogorov-Smirnov Test

		Ex40% SeqDDown BaselineTilt	Ex40%Seq DDown+15minTilt	Ex40%Seq DDown+60minTilt	Ex40%Seq DDown+120 minTilt	Ex40%Seq DDown+180 minTilt	Ex40%Seq DDown+24h Tilt
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	9.1111	7.6222	7.1389	7.9000	8.2222	9.0778
	Std. Deviation	4.09831	4.28538	3.11446	3.12890	3.43285	3.38222
Most Extreme Differences	Absolute	.244	.281	.169	.171	.257	.216
	Positive	.244	.281	.169	.171	.257	.216
	Negative	-.147	-.174	-.135	-.139	-.167	-.164
Kolmogorov-Smirnov Z		.731	.842	.508	.514	.771	.649
Asymp. Sig. (2-tailed)		.659	.478	.959	.954	.591	.793

a. Test distribution is Normal.

Appendix XVIII (f.xix): KS 40% $BRS_{\alpha LF}$ Tilt

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex40%AlphaLFBaselineTilt	9	9.4889	2.45023	6.10	13.60
Ex40%AlphaLF+15minTilt	9	8.6333	2.55734	4.90	12.90
Ex40%AlphaLF+60minTilt	9	8.9667	3.00624	4.80	14.60
Ex40%AlphaLF+120minTilt	9	9.0444	2.09172	6.50	12.90
Ex40%AlphaLF+180minTilt	9	9.6778	3.11038	6.20	15.50
Ex40%AlphaLF+24hTilt	9	10.0111	3.18255	6.20	14.40

One-Sample Kolmogorov-Smirnov Test

		Ex40%Alpha LFBaselineTil t	Ex40%Alpha LF+15minTilt	Ex40%Alpha LF+60minTilt	Ex40%Alpha LF+120minTil t	Ex40%Alpha LF+180minTil t	Ex40% AlphaLF+24h Tilt
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	9.4889	8.6333	8.9667	9.0444	9.6778	10.0111
	Std. Deviation	2.45023	2.55734	3.00624	2.09172	3.11038	3.18255
Most Extreme Differences	Absolute	.136	.161	.189	.169	.240	.230
	Positive	.136	.160	.189	.169	.240	.230
	Negative	-.088	-.161	-.105	-.112	-.140	-.216
Kolmogorov-Smirnov Z		.409	.484	.566	.506	.721	.691
Asymp. Sig. (2-tailed)		.996	.973	.906	.960	.676	.726

a. Test distribution is Normal.

Appendix XVIII (f.xx): KS 40% BRS_{TFTG} Tilt

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex40%TFTGBaselineTilt	9	8.3611	2.29684	5.65	12.44
Ex40%TFTG+15minTilt	9	8.2478	3.46114	3.78	15.77
Ex40%TFTG+60minTilt	9	8.1544	3.16082	3.71	14.34
Ex40%TFTG+120minTilt	9	8.4100	2.27536	5.67	12.39
Ex40%TFTG+180minTilt	9	9.2311	3.48128	5.71	15.37
Ex40%TFTG+24hTilt	9	9.2556	2.99585	4.70	13.39

One-Sample Kolmogorov-Smirnov Test

		Ex40% TFTGBaselineTilt	Ex40% TFTG+15min Tilt	Ex40% TFTG+60min Tilt	Ex40% TFTG+120minTilt	Ex40% TFTG+180minTilt	Ex40% TFTG+24hTilt
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	8.3611	8.2478	8.1544	8.4100	9.2311	9.2556
	Std. Deviation	2.29684	3.46114	3.16082	2.27536	3.48128	2.99585
Most Extreme Differences	Absolute	.167	.208	.157	.175	.226	.169
	Positive	.167	.208	.157	.175	.226	.160
	Negative	-.119	-.134	-.086	-.129	-.156	-.169
Kolmogorov-Smirnov Z		.500	.623	.471	.524	.677	.507
Asymp. Sig. (2-tailed)		.964	.833	.979	.946	.750	.960

a. Test distribution is Normal.

Appendix XVIII (f.xxi): KS 75% BRS_{UpUp} Tilt

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex75%SeqUpUpBaselineTilt	9	10.3333	2.99750	6.90	15.60
Ex75%SeqUpUp+15minTilt	9	7.6000	2.69165	5.20	14.40
Ex75%SeqUpUp+60minTilt	9	8.7333	2.57973	5.80	14.30
Ex75%SeqUpUp+120minTilt	9	9.8111	3.21459	6.10	15.50
Ex75%SeqUpUp+180minTilt	9	10.6222	3.72115	6.30	17.30
Ex75%SeqUpUp+24hTilt	9	11.0444	3.50646	6.60	17.50

One-Sample Kolmogorov-Smirnov Test

		Ex75% SeqUpUp BaselineTilt	Ex75%SeqUp Up+15minTilt	Ex75%SeqUp Up+60minTilt	Ex75%SeqUp Up+120minTil t	Ex75%SeqUp Up+180minTil t	Ex75%SeqUp Up+24hTilt
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	10.3333	7.6000	8.7333	9.8111	10.6222	11.0444
	Std. Deviation	2.99750	2.69165	2.57973	3.21459	3.72115	3.50646
Most Extreme Differences	Absolute	.190	.345	.214	.193	.201	.149
	Positive	.190	.345	.214	.193	.201	.149
	Negative	-.145	-.186	-.128	-.150	-.123	-.116
Kolmogorov-Smirnov Z		.569	1.034	.643	.579	.604	.447
Asymp. Sig. (2-tailed)		.902	.236	.802	.891	.860	.988

a. Test distribution is Normal.

Appendix XVIII (f.xxii): KS 75% $BRS_{DownDown}$ Tilt

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex75%SeqDDownBaselineTilt	9	7.9667	2.68747	4.60	12.60
Ex75%SeqDDown+15minTilt	9	4.9000	3.16149	2.30	12.50
Ex75%SeqDDown+60minTilt	9	5.4444	1.81184	3.60	8.60
Ex75%SeqDDown+120minTilt	9	6.8000	2.20511	3.60	10.50
Ex75%SeqDDown+180minTilt	9	7.5889	2.76245	4.20	11.70
Ex75%SeqDDown+24hTilt	9	8.3667	2.47285	5.10	13.10

One-Sample Kolmogorov-Smirnov Test

		Ex75% SeqDDown BaselineTilt	Ex75%Seq DDown+15minTilt	Ex75%Seq DDown+60minTilt	Ex75%Seq DDown+120 minTilt	Ex75%Seq DDown+180 minTilt	Ex75%Seq DDown+24h Tilt
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	7.9667	4.9000	5.4444	6.8000	7.5889	8.3667
	Std. Deviation	2.68747	3.16149	1.81184	2.20511	2.76245	2.47285
Most Extreme Differences	Absolute	.123	.265	.235	.119	.150	.161
	Positive	.123	.265	.235	.119	.150	.161
	Negative	-.108	-.205	-.154	-.099	-.140	-.156
Kolmogorov-Smirnov Z		.370	.795	.705	.358	.449	.484
Asymp. Sig. (2-tailed)		.999	.552	.703	1.000	.988	.974

a. Test distribution is Normal.

Appendix XVIII (f.xxiii): KS 75% $BRS_{\alpha LF}$ Tilt

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex75%AlphaLFBaselineTilt	9	8.7778	2.20951	5.40	12.50
Ex75%AlphaLF+15minTilt	9	5.2778	2.62144	2.40	11.20
Ex75%AlphaLF+60minTilt	9	6.8111	2.04905	4.90	11.30
Ex75%AlphaLF+120minTilt	9	8.5444	2.66979	5.30	13.40
Ex75%AlphaLF+180minTilt	9	9.4333	5.00600	4.90	20.40
Ex75%AlphaLF+24hTilt	9	9.3889	2.29098	6.40	14.20

One-Sample Kolmogorov-Smirnov Test

		Ex75%Alpha LFBaselineTilt	Ex75%Alpha LF+15minTilt	Ex75%Alpha LF+60minTilt	Ex75%Alpha LF+120minTilt	Ex75%Alpha LF+180minTilt	Ex75% AlphaLF+24h Tilt
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	8.7778	5.2778	6.8111	8.5444	9.4333	9.3889
	Std. Deviation	2.20951	2.62144	2.04905	2.66979	5.00600	2.29098
Most Extreme Differences	Absolute	.181	.209	.199	.218	.312	.190
	Positive	.181	.209	.199	.218	.312	.190
	Negative	-.086	-.136	-.175	-.124	-.183	-.134
Kolmogorov-Smirnov Z		.542	.628	.597	.654	.937	.569
Asymp. Sig. (2-tailed)		.931	.825	.869	.786	.344	.903

a. Test distribution is Normal.

Appendix XVIII (f.xxiv): KS 75% BRS_{TFTG} Tilt

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum
Ex75%TFTGBaselineTilt	9	8.0889	2.01617	5.38	11.52
Ex75%TFTG+15minTilt	9	4.9167	2.67030	1.91	10.85
Ex75%TFTG+60minTilt	9	6.2267	1.68516	4.32	9.70
Ex75%TFTG+120minTilt	9	7.8244	2.45055	4.66	12.00
Ex75%TFTG180minTilt	9	9.1856	4.52062	5.62	18.68
Ex75%TFTG24hTilt	9	8.9444	2.59288	5.66	14.79

One-Sample Kolmogorov-Smirnov Test

		Ex75% TFTGBaselineTilt	Ex75% TFTG+15min Tilt	Ex75% TFTG+60min Tilt	Ex75% TFTG+120minTilt	Ex75% TFTG180min Tilt	Ex75% TFTG24hTilt
N		9	9	9	9	9	9
Normal Parameters[a]	Mean	8.0889	4.9167	6.2267	7.8244	9.1856	8.9444
	Std. Deviation	2.01617	2.67030	1.68516	2.45055	4.52062	2.59288
Most Extreme Differences	Absolute	.161	.218	.211	.143	.292	.292
	Positive	.161	.218	.211	.143	.292	.292
	Negative	-.125	-.130	-.129	-.129	-.215	-.127
Kolmogorov-Smirnov Z		.482	.653	.633	.430	.877	.876
Asymp. Sig. (2-tailed)		.974	.787	.817	.993	.425	.426

a. Test distribution is Normal.