



This is a peer-reviewed, post-print (final draft post-refereeing) version of the following published document and is licensed under All Rights Reserved license:

**MartinezAguirre-Betolaza, Aitor, Mujika, Iñigo, Fryer, Simon M
ORCID logoORCID: <https://orcid.org/0000-0003-0376-0104>,
Corres, Pablo, Gorostegi-Anduaga, Ilargi, Arratibel-Imaz,
Iñaki, Pérez-Asenjo, Javier and Maldonado-Martin, Sara (2020)
Effects of different aerobic exercise programs on cardiac
autonomic modulation and hemodynamics in hypertension:
data from EXERDIET-HTA randomized trial. *Journal of Human
Hypertension*, 34 (10). pp. 709-718. doi:10.1038/s41371-020-
0298-4**

Official URL: <https://doi.org/10.1038/s41371-020-0298-4>
DOI: <http://dx.doi.org/10.1038/s41371-020-0298-4>
EPrint URI: <https://eprints.glos.ac.uk/id/eprint/7911>

Disclaimer

The University of Gloucestershire has obtained warranties from all depositors as to their title in the material deposited and as to their right to deposit such material.

The University of Gloucestershire makes no representation or warranties of commercial utility, title, or fitness for a particular purpose or any other warranty, express or implied in respect of any material deposited.

The University of Gloucestershire makes no representation that the use of the materials will not infringe any patent, copyright, trademark or other property or proprietary rights.

The University of Gloucestershire accepts no liability for any infringement of intellectual property rights in any material deposited but will remove such material from public view pending investigation in the event of an allegation of any such infringement.

PLEASE SCROLL DOWN FOR TEXT.

Effects of different aerobic exercise programs on cardiac autonomic modulation and hemodynamics in hypertension: data from EXERDIET-HTA randomized trial

Running title: Aerobic exercise training in hypertension

Authors of the manuscript:

Aitor MartinezAguirre-Betolaza, MS¹, Iñigo Mujika, PhD^{2,3}; Simon M. Fryer, Ph.D⁴; Pablo Corres, MS¹, Ilargi Gorostegi-Anduaga, PhD¹; Iñaki Arratibel-Imaz, PhD¹; Javier Pérez-Asenjo, MD⁵; Sara Maldonado-Martín, PhD¹,

¹ Department of Physical Education and Sport. Faculty of Education and Sport-Physical Activity and Sport Sciences Section. University of the Basque Country (UPV/EHU). Vitoria-Gasteiz. Araba/Álava. Basque Country, Spain

² Department of Physiology. Faculty of Medicine and Nursing. University of the Basque Country (UPV/EHU). Leioa. Basque Country, Spain

³ Exercise Science Laboratory, School of Kinesiology, Faculty of Medicine, Universidad Finis Terrae, Santiago, Chile.

⁴ University of Gloucestershire, School of Sport and Exercise. Oxstalls Campus. Gloucester, GL2 9HW, UK.

⁵ Cardiology Unit. Igualatorio Médico Quirúrgico (IMQ-América). Vitoria-Gasteiz. Araba/Álava. Basque Country, Spain

Corresponding author: Sara Maldonado-Martín. Department of Physical Education and Sport. Faculty of Education and Sport. Physical Activity and Sport Sciences Section. University of the Basque Country (UPV/EHU). Portal de Lasarte, 71. 01007 Vitoria-Gasteiz (Araba/Alava)-Basque Country, Spain.

Phone: +34 945013534. Fax: +34 945013501. E-mail: sara.maldonado@ehu.eus

Authorship: all authors have seen and approved the manuscript.

Abstract

The aims of the present study were to analyze the effects of 16 weeks of different aerobic exercise training (ExT) programs with diet on cardiac autonomic modulation and hemodynamics in non-physically active and overweight/obese adults ($n=249$, 53.7 ± 8.0 years) with primary hypertension, and the possible differences among ExT programs and their effects on heart rate (HR), blood pressure (BP), and long-term BP variability (BPV). Participants were randomly assigned into an attention control (AC) group (physical activity recommendations) or one of three supervised ExT groups: high-volume of moderate-intensity continuous training, high-volume and high-intensity interval training (HIIT), and low volume-HIIT. 24 h ambulatory BP monitoring was used to analyze systolic and diastolic BP, HR and BPV. A cardiopulmonary exercise test was performed to determine peak oxygen uptake (VO_{2peak}). Following intervention, resting and submaximal exercise (HR, SBP and DBP), along with diurnal and nocturnal SBP and DBP values decreased ($P<0.05$) in all groups with no differences between groups. When the ExT groups were combined, submaximal SBP ($P=0.048$) and DBP ($P=0.004$), VO_{2peak} ($P=0.014$) and HR reserve ($P=0.030$) were significantly improved compared to AC. Intervention did not have significant effects on BPV. In the present study better improvements in the autonomic nervous system were seen when the aerobic ExT was individually designed and supervised with *pari passu* effects irrespective of exercise intensity and volume. Low volume-HIIT ExT combined with a healthy diet should be considered as a time efficient and safe mechanism for reducing the cardiovascular risk in hypertensive individuals.

Introduction

Primary hypertension (HTN) is associated with dysfunctional autonomic cardiovascular control (*i.e.* inappropriate activation of the sympathetic and reduction of the parasympathetic divisions), both at rest and in response to exercise (1). This dysfunction is mainly due to neural factors such as an enhanced pressor reflex, decreased baroreflex sensitivity and impaired functional sympatholysis, leading to a progressively greater decrease in blood flow to the working muscles during exercise (2). Hence, compared to normotensive individuals, those with HTN show a significant increase in heart rate (HR), blood pressure (BP), and BP variability (BPV, *i.e.*, the variation of BP over time) (1). Current HTN guidelines highlight the risk associated with high BPV, since it represents an additional risk factor for cardiovascular complications (3) and is an independent predictor of the incidence of cardiovascular disease and mortality (4,5).

The aforementioned abnormal cardiovascular response to exercise in those individuals with HTN may induce untoward events. However, a single session of aerobic exercise yields a reduced sympathetic outflow, which is associated with a sustained postexercise vasodilation in the exercising muscle, and this contributes to the fall in arterial BP; through adaptation this can lead to potential benefits to the individual (6). Likewise, a recent study assessing the acute effects of a single bout of three different exercise modalities (*i.e.*, moderate-intensity continuous training, MICT; high-intensity interval training, HIIT, or combined training including MICT and resistance training) found different changes on BPV favoring the combined training (7). Regular aerobic exercise training (ExT), carefully designed and supervised by exercise specialists and a healthy diet are known to be an excellent non-pharmacological treatment against HTN-

caused disturbances. As such ExT is strongly recommended by current European and American HTN guidelines (8,9).

Whilst there is a lack of consistency between studies regarding exercise intensity and duration (10), previous it has been demonstrated that ExT induces positive changes in hemodynamic, autonomic and cardiac adaptations in individuals with HTN (11-13). Previously, aerobic ExT programs in individuals with HTN have included MICT and different volumes of HIIT of which all showed a significant reduction in BP with no between group differences (14). Nevertheless, to the best of our knowledge, there are no investigations analyzing the impact of aerobic ExT programs which differ in intensity and volume on resting, submaximal exercise, peak and recovery autonomic modulation, and long-term BPV (*i.e.* visit-to-visit measures spaced by months) in overweight/obese adults suffering from HTN. Given the clinical relevance of autonomic cardiovascular control, the aim of the present investigation was to study the effects of 16 weeks of different aerobic ExT programs with a hypocaloric diet on cardiac autonomic modulation and hemodynamics in overweight/obese adults with HTN. The secondary objective was to analyze the possible differences in HR, BP, and long-term BPV variables between different ExT programs.

Methods

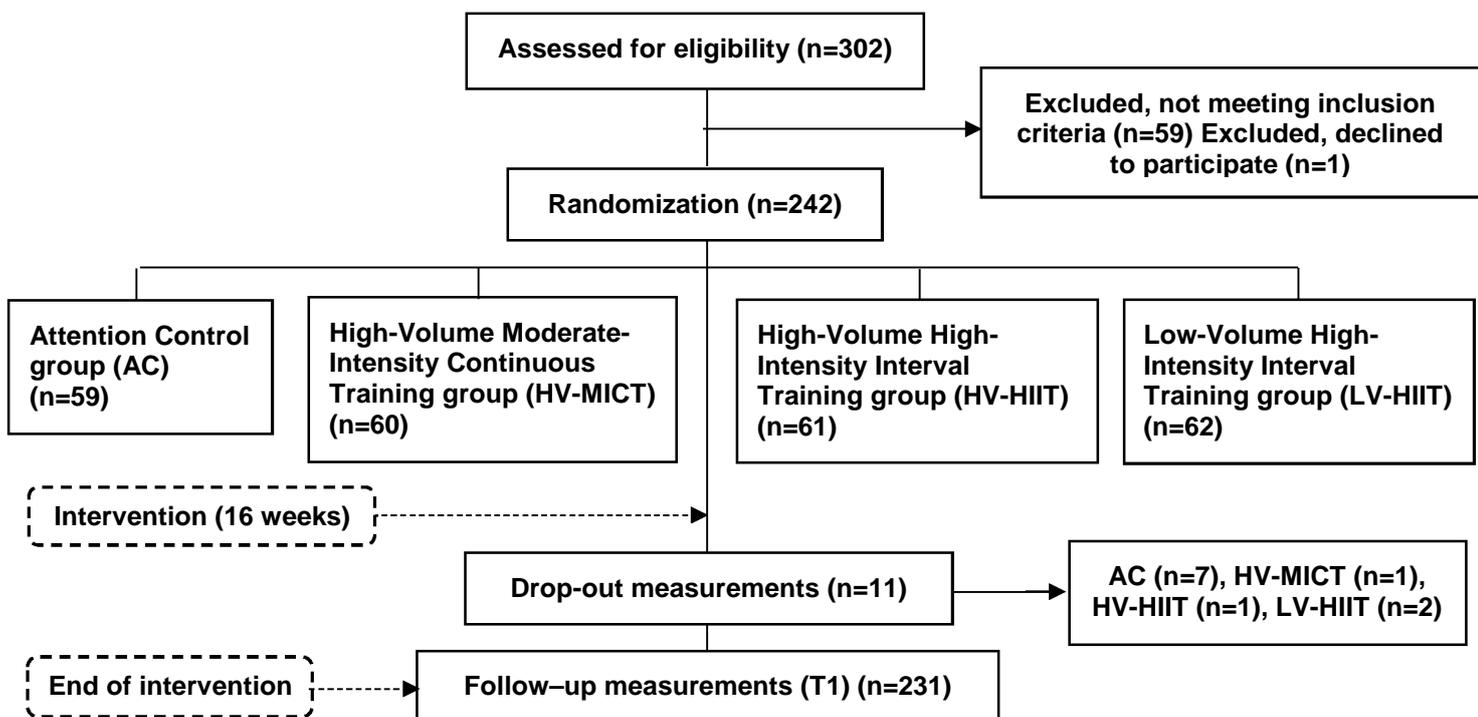
Study design

The EXERDIET-HTA study is a multi-arm parallel, randomized, single-blind controlled experimental trial comparing the effects of different 16-week aerobic ExT programs (performed 2 days/week), in overweight/obese participants with HTN (www.clinicaltrials.gov, number NCT02283047). The study protocol was approved by

the ethics committees of the University of the Basque Country (CEISH UPV/EHU, 279/2014, 229/2018) and clinical investigation of Araba University Hospital (2015-030). Medical staff were blinded to the participant randomization process. The design, selection criteria and procedures for the EXERDIET-HTA study have been detailed previously (15).

Participants

Non-Hispanic white EXERDIET-HTA participants (n=249, 158 men [63.5%] and 91 women [36.5%]) took part in the present study. All participants provided written informed consent before any data collection. Figure 1 presents a flow diagram of the study process for this sample. On the other hand, a HEALTHY sample (n=30) was recruited from the community and excluded if they had any chronic medical illness, were taking any daily prescription medications, had current medical symptoms, had abnormal findings on physical examination (including BP \geq 140/90 mmHg, or overweight \geq 25 kg/m²), or had abnormal results on screening test (rest and exercise electrocardiogram).



Measurements

The measurements for the current study were taken pre (T0) and post a 16-week intervention period (T1). The HEALTHY sample only performed baseline measurements with no intervention procedures.

Blood pressure

Participants wore an ambulatory blood pressure monitor (ABPM) over a 24-h period using an oscillometric ABPM 6100 (Welch Allyn, New York City, NY, USA) device to evaluate BP in line with the European guidelines (5). Values of ABPM are shown as the mean of global (24 h), day and night hours for systolic BP (SBP) and diastolic BP (DBP). Blood pressure variability, expressed as coefficient of variation (CV), was calculated by the standard deviation (SD) of the BP values over a defined period of the 24h and by the day and night hour period respectively (13,16). Resting HR was assessed as the mean global of the 24 h measurements.

Cardiorespiratory fitness (CRF)

A cardiopulmonary exercise test was used to determine peak oxygen uptake (VO_{2peak}) and ventilatory thresholds (VT). The cardiopulmonary exercise test was performed on an electronically braked Lode Excalibur Sport cycle ergometer (Groningen, The Netherlands). The test protocol started at 40W for HTN individuals and at 70W for the HEALTHY group (~70 rpm), with gradual increments of 10W being applied every minute until volitional exhaustion occurred. Continuous electrocardiogram monitoring was conducted throughout each test. Expired gas was analyzed using a commercially available metabolic cart (Ergo CardMedi-soft S.S, Belgium; Ref. USM001 V1.0). Achievement of VO_{2peak} criteria have previously been defined (17). Submaximal BP and HR were obtained at the fourth minute of the test and peak values were taken from the

peak at maximal effort. Ventilatory thresholds (VT1 and VT2) were assessed using standardized methods using the ventilatory equivalents (17). After completion of the test, participants remained seated on the bike for five minutes of recovery to assess electrocardiogram, HR and BP. Heart rate variables during the recovery period were calculated from the cardiopulmonary exercise test as follows: heart rate reserve (HRR), difference between HR_{peak} during exercise and pre-exercise HR_{rest} ; HR_{rec1} , HR at one minute recovery; and HR_{rec} , difference between HR_{peak} and HR_{rec1} . Blood pressure recovery variables (SBP and DBP) were obtained at minute three of the recovery period. Based on VT1 and VT2, the three exercise intensity domains (*i.e.* R1, light to moderate, $HR < VT1$; R2, moderate to high, HR between VT1 and VT2; R3, high to severe $HR > VT2$ to HR_{peak}) were determined (17).

Medication

In the EXERDIET-HTA sample, prescribed medications were recorded and classified into the following groups: betablockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers, diuretics, and other antihypertensive drugs. Medical staff controlled and prescribed all necessary changes to medication before intervention. Pharmacological treatment was not changed during the intervention.

Intervention

All participants from the EXERDIET-HTA sample underwent a hypocaloric and controlled sodium diet (3-6 g/d) (14). Following baseline data collection, participants were randomly allocated to one of the four intervention groups: the attention control (AC) group (only received general physical activity recommendations in one face-to-face session, with no supervised exercise), or the three supervised ExT groups: high-volume

(HV) MICT, HV-HIIT, or low-volume (LV) HIIT. Each group was stratified by sex, SBP, body mass index (BMI) and age (14,15).

The three ExT groups trained two non-consecutive days per week under the supervision of exercise specialists. All sessions started and finished with BP monitoring, and training intensity was dictated by individual HR responses (Polar Electro, Kempele, Finland) and the rate of perceived exertion (Borg's 6–20 point scale). Each session included a 5–10-min warm-up and a 10-min cool-down. The core part of each training session consisted of a range of aerobic exercises, *i.e.* one day of the week on the treadmill, and the second one on the bike (BH Fitness equipment, Vitoria-Gasteiz, Spain). The HV-MICT group performed 45 min aerobic exercise (*i.e.* continuous steady training at R2), the HV- and LV-HIIT groups performed 45 and 20 minutes, respectively. The intensity in HIIT groups was individually tailored to each participant's HR at moderate (R2) or vigorous (R3) intensities, adjusting the speed and/or incline of the treadmill or the power and speed on the exercise bike. Supervised exercise training protocols have previously been explained in detail (14,15).

As participants were overweight/obese the combined use of stationary exercise bike and treadmill was used to avoid the osteoarticular impact of two weekly treadmill sessions.

Statistical analysis

Descriptive statistics were calculated for all variables. Comparison between HEALTHY vs. HTN groups was conducted using the Student *t*-test for independent samples. Analysis of variance was used to determine if there were significant pre-intervention between-group differences. The comparison of frequencies in categorical variables among groups was performed using the chi-square test. A two sample paired *t*-test was used to

determine whether there was a significant difference in the recorded data between T0 and T1 within each group. Analysis of covariance was used to examine the delta (Δ) score for each group (AC, HV-MICT, HV-HIIT, LV-HIIT), adjusting for age, sex, body mass and the initial value of each of the dependent variables. Helmert contrasts were performed to analyze the difference between the three ExT groups pooled together and the AC group. Bonferroni correction was used to determine the significance when a significant main effect was found. The required sample size was determined for the primary outcome variable (SBP). It was identified that adequate power (0.80) to evaluate differences in our design consisting of four experimental groups would be achieved with 164 people (41 each group, $\alpha=0.05$, effect size $f=0.27$) based on the pilot study with an SD of 9 mmHg. Data were analyzed according to the intention-to-treat principle. Statistical significance was set at $P<0.05$. All statistical analyses were performed with SPSS version 24.0.

Results

The characteristics of the HTN population and HEALTHY group are presented in Table 1. At baseline, mean BMI in all HTN groups was above 30 kg/m², which is considered obesity, and waist circumference was >100 cm, which is considered a cardiovascular risk factor (18). No significant between-group differences were found in any variable for the groups with HTN.

Comparing the entire HTN sample with the HEALTHY group, significant differences were found in all baseline variables ($P<0.001$). Body mass index, waist circumference, rest BP, and HR_{rest} values were significantly higher in the HTN group compared to the HEALTHY group. However, HR_{peak} and VO_{2peak} were significantly lower (Table 1).

Table 1. Baseline characteristics for each group of participants.

	HTN GROUPS							
	HEALTHY (N = 30)	HTN (N = 259)	P-value HEALTHY vs. HTN	AC (N = 59)	HV-MICT (N = 60)	HV-HIIT (N = 61)	LV-HIIT (N = 62)	P-value Intergroups HTN
Sex (men/women)	13/17	163/96	<0.001	33/26	38/22	40/21	41/21	0.642
Age (years)	40.5±8.7	53.7±8.0	<0.001	52.9±8.5	54.2±7.2	53.1±8.6	54.4±7.2	0.650
BMI (kg/m ²)	23.1±2.7	32.1±4.2	<0.001	32.4±4.6	32.1±4.3	31.6±3.7	32.0±4.2	0.751
Waist perimeter (cm)	75.1±8.0	103.1±11.1	<0.001	102.9±10.6	104.1±12.4	101.2±11.0	104.1±10.6	0.449
Rest SBP (mmHg)	114.1±6.7	136.5±12.6	<0.001	138.5±14.0	135.4±11.5	134.8±11.8	137.2±13.3	0.353
Rest DBP (mmHg)	68.3±7.2	78.2±8.4	<0.001	78.2±8.8	76.7±8.0	78.8±7.9	79.0±8.2	0.392
HR _{rest} (bpm)	58.2±6.9	71.2±10.1	<0.001	70.4±9.2	72.9±10.7	70.3±9.9	72.1±11.1	0.396
HR _{peak} (bpm)	178.7±9.7	154.5±16.8	<0.001	150.2±17.6	154.9±16.5	156.2±15.7	158.3±15.7	0.052
HR _{rec} (bpm)	35.3±11.1	26.8±10.9	<0.001	26.0±8.8	27.5±11.7	27.3±12.6	26.2±10.6	0.814
VO _{2peak} (mL·kg ⁻¹ ·min ⁻¹)	48.1±9.0	22.6±5.5	<0.001	22.1±5.5	22.0±5.2	22.7±4.8	22.7±5.4	0.816
Concomitant diseases								
DM (%)				3.5	6.7	4.9	8.1	0.732

Smoking (%)	4.2	9.9	18.7	9.4	0.076
<i>Antypertensive medication</i>					
Medication (%)	87.9	91.7	83.6	88.7	0.594
Number antihypertensive drugs	1.6±1.0	1.8±1.2	1.5±1.1	1.6±1.1	0.492
Beta-blockers (%)	10.5	8.3	6.6	4.8	0.678
ACEI (%)	43.9	38.3	42.6	27.4	0.229
ARB (%)	45.6	43.3	29.5	50.0	0.119
Calcium channel blocker (%)	7.0	20	13.1	14.5	0.242
Diuretic (%)	36.8	43.3	41.0	35.5	0.801
Other antihypertensive drugs (%)	3.9	5.3	3.3	5.8	0.617

Values are mean±SD, percentage (%) or number. HTN: hypertension; AC: attention control group; HV: high volume; LV: low volume; MICT: moderate-intensity continuous training group; HIIT: high-intensity interval training group; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR_{rest}: resting heart rate; HR_{peak}: peak heart rate; HR_{rec}: difference between HR_{peak} and HR after recovery's first minute; VO_{2peak}: peak oxygen uptake; DM: diabetes mellitus; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers. Blood pressure (BP) values show the mean BP calculated by 24-hour ambulatory blood pressure monitoring. *P*<0.05

Regarding pharmacological therapy, 87.1% of HTN participants were taking regular medication. The percentage of participants who took one, two, three, four or more medications was 38.7%, 29%, 13.7% and 5.6%, respectively. Regarding medication type, 7.3% of participants took beta-blockers, 37.7% angiotensin converting enzyme inhibitors, 41.7% angiotensin II receptor blockers, 13.8% calcium channel blockers, 38.5% diuretics and 4.6% other antihypertensive drugs. With respect to other concomitant diseases, 6.1% had diabetes mellitus and 10.6% were smokers. No significant differences were found among HTN groups for any baseline variable.

Following the 16-week intervention period, resting and submaximal HR, SBP and DBP decreased ($P<0.05$) in all groups (Table 2), except AC group's submaximal SBP. Furthermore, peak DBP decreased in the HV-HIIT group ($\Delta = -9.9\%$, $P<0.001$) only.

Table 2. Heart rate and blood pressure responses before and after 16-weeks intervention.

	AC (N=52)	HV-MICT (N=59)	HV-HIIT (N=60)	LV-HIIT (N=60)	P-value AC vs. ExT	P-value Intergroups	F-value	Effect size
Rest								
HR _{rest} (bpm)								
T0	70.1±9.2	72.8±10.1	69.9±10.3	72.3±11.3				
T1	66.3±8.8*	67.4±9.1*	63.6±8.3*	66.1±10.7*	0.054	0.331	1.148	0.016
Global SBP (mmHg)								
T0	138.6±13.9	135.0±11.4	134.5±11.9	136.9±13.5				
T1	133.7±14.5*	130.2±10.4*	130.3±11.3*	130.5±11.7*	0.905	0.777	0.366	0.005
Global DBP (mmHg)								
T0	78.5±8.1	76.2±7.9	78.5±8.0	79.1±8.3				
T1	75.5±8.9*	73.6±7.8*	74.5±7.0*	75.4±7.7*	0.661	0.700	0.475	0.007
Submaximal								
HR _{submax} (bpm)								
T0	121.6±16.8	126.8±18.5	123.7±23.0	123.2±16.8				
T1	115.3±15.5*	116.5±17.9*	110.9±13.3*	114.6±16.8*	0.109	0.239	1.418	0.019
SBP (mmHg)								
T0	178.9±35.8	182.8±34.9	177.8±23.3	173.6±24.3				
T1	169.8±25.3	164.7±30.4*	158.5±23.1*	155.0±25.0*	0.048	0.395	0.997	0.014
DBP (mmHg)								
T0	96.0±13.6	97.8±15.2	99.6±15.6	97.6±14.7				
T1	92.1±12.9*	90.1±15.2*	87.0±12.2* ^x	88.9±11.9*	0.004	0.027	3.106	0.042
Peak								
HR _{peak} (bpm)								
T0	151.5±17.7	155.0±16.8	155.7±16.0	157.6±15.7				
T1	152.5±15.6	157.0±16.4	157.4±13.0	158.7±13.0	0.748	0.978	0.067	0.001
SBP (mmHg)								
T0	218.5±25.6	214.8±27.9	207.3±27.6	209.5±26.1				
T1	216.7±21.8	210.0±28.0	205.9±26.1	208.3±23.4	0.425	0.722	0.444	0.006
DBP (mmHg)								
T0	102.1±24.1	99.9±15.0	100.9±14.7	102.0±16.6				
T1	98.6±17.4	99.1±14.7	95.1±14.5*	99.0±17.3	0.930	0.574	0.666	0.009
VO _{2peak} (mL·kg ⁻¹ ·min ⁻¹)								
T0	22.3±5.6	22.0±5.2	22.7±4.9	22.7±5.3				
T1	22.8±8.0	24.3±8.8*	28.1±9.7* ^x	26.7±11.3*	0.014	0.046	2.708	0.036
Recovery								
HRR (bpm)								
T0	80.2±20.3	81.6±16.8	85.8±16.5	85.6±17.6				
T1	79.9±27.8	92.6±28.2*	93.4±34.1	92.2±20.5*	0.030	0.274	1.304	0.017
HR _{rec1} (bpm)								
T0	125.5±20.2	127.8±19.4	128.6±19.7	131.6±17.1				
T1	126.8±15.7	130.1±20.6	129.2±15.9	129.0±15.9	0.608	0.353	1.092	0.015
HR _{rec} (bpm)								
T0	26.3±8.3	27.0±11.2	27.2±12.7	25.9±10.6				
T1	26.2±17.3	26.5±10.7	26.8±11.7	29.3±9.3*	0.698	0.350	1.099	0.014
SBP _{rec3} (mmHg)								
T0	155.4±24.7	154.3±20.1	147.0±23.6	152.7±22.4				
T1	150.5±22.1	147.1±28.1	141.3±22.1	142.3±18.7*	0.829	0.771	0.375	0.005
DBP _{rec3} (mmHg)								
T0	85.7±12.8	84.3±10.6	88.7±10.7	86.1±12.7				
T1	82.6±11.9	79.4±12.4*	79.1±10.7* ^x	81.6±10.9*	0.141	0.039	2.833	0.039

Mean±SD. HRR: heart rate reserve (peak HR-rest HR); HR_{rec1}: heart rate after recovery's first minute; HR_{rec}: difference between HR_{peak} and HR_{rec1}; SBP: systolic blood pressure; DBP: diastolic blood pressure; VO_{2peak}: peak oxygen uptake; AC: attention control group; ExT: exercise training group; HV: high volume; LV: low volume; MICT: moderate-intensity continuous training group; HIIT: high-intensity interval training group. *P value<0.05 from T0. ^xP value<0.05 from the AC.

Cardiorespiratory fitness expressed as VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) increased in all ExT groups (HV-MICT $\Delta = 10.5\%$, $P = 0.025$; HV-HIIT $\Delta = 23.8\%$, $P < 0.001$, and LV-HIIT $\Delta = 17.6\%$; $P = 0.005$). In addition, HV-MICT and LV-HIIT showed an increase in HRR ($\Delta = 13.5\%$, $P = 0.004$ and $\Delta = 7.7\%$, $P = 0.017$, respectively), and only LV-HIIT group decreased SBP after 3 min of recovery ($\Delta = -4.4\%$, $P = 0.001$). On the other hand, DPB at 3 min of recovery was reduced in all ExT groups (HV-MICT $\Delta = -5.8\%$, $P = 0.013$; HV-HIIT $\Delta = -10.8\%$ and LV-HIIT $\Delta = -5.2\%$, $P < 0.001$) after the intervention period. Only LV-HIIT group showed an increased number of beats between HR_{peak} and the HR_{rec1} ($\Delta = 13.1\%$, $P = 0.015$). Following Bonferroni correction, there were no significant between-group differences in any resting variable. However, AC showed a smaller reduction compared to HV-HIIT group in submaximal DBP ($P = 0.017$) mean difference 8.319, 95% confidence interval (CI) 0.968-15.671 mmHg; VO_{2peak} ($P = 0.049$) mean difference -4.564, 95% (CI) -9.126-0.002 $mL \cdot kg^{-1} \cdot min^{-1}$; and DBP_{rec3} ($P = 0.041$) mean difference 6.498, 95% (CI) 0.166-12.830 mmHg. Furthermore, there were significant differences between all ExT groups as a whole and AC group in submaximal SBP ($P = 0.048$), DBP ($P = 0.004$), VO_{2peak} ($P = 0.014$) and HRR ($P = 0.030$).

After the 16-week intervention, diurnal and nocturnal SBP and DBP significantly ($P < 0.05$) decreased in all groups (Table 3), with no between-group differences. However, the intervention did not have significant effects on any of the BPV variables (*i.e.*, CV of BP). Taking into account all ExT groups together, a significant decrease was found in day-time DBP's CV ($\Delta = -4.4\%$, $P = 0.023$).

Discussion

To our knowledge, this is the first intervention investigating the effects of different volume (HV vs. LV) and intensity (MICT vs. HIIT) aerobic ExT programs on hemodynamics and cardiac autonomic modulation in hypertensive and overweight/obese individuals. The present investigation confirms that a dual treatment with aerobic ExT and diet is helpful to reduce resting and submaximal HR, together with global, day and night BP values. Further, ExT groups showed a greater improvement in CRF, HRR and submaximal BP compared to the AC group. Nevertheless, 16-weeks of aerobic ExT and diet intervention did not reduce BPV. Importantly, the lack of post-intervention difference between-ExT groups in most of the studied variables suggested that the most effective method was ExT using the LV-HIIT protocol.

The lower VO_{2peak} seen in HTN group compared to HEALTHY group (22.6 ± 5.5 mL·kg⁻¹·min⁻¹ vs. 48.1 ± 9.0 mL·kg⁻¹·min⁻¹, Table 1) (19) at baseline may be the result of both reduced peak cardiac output, secondary to impaired resting, peak and reserve HR, or arterial-venous oxygen content difference, secondary to an impaired sympatholysis with high BP values (2,20). These alterations are presented as a result of sustained sympatho-excitation and reduced vagal activity, which explains the likely association of HR and HTN, facilitating further body fat gain and progression of associated co-morbidities (20,21). Therefore, autonomic modulation through diet (caloric restriction) and aerobic exercise is currently the recommended approach (8). Findings from the current study support this as we report a decrease in resting (AC=-5.4%, HV-MICT=-7.4%, HV-HIIT=-9%, LV-HIIT=-8.6%) and submaximal HR (AC=-5.2%, HV-MICT=-8.1%, HV-HIIT=-10.3%, LV-HIIT=-7.0%). Further, it was found an average net reduction of 5 mmHg in resting SBP and 3-4 mmHg in resting DBP, with no between-group differences. Although

one session of HIIT seems to promote a greater post-exercise hypotension compared to isocaloric MICT (22), in the present study long-term physical activity and ExT improved cardiovascular autonomic function by shifting the balance towards vagal dominance and decreased sympathetic activity, independent of FITT principle (*i.e.*, Frequency, Intensity, Time, Type of exercise). Thus, the diet intervention along with hypertensive medication in the study population might have induced a similar effect regardless of physical activity program (unsupervised or supervised). Hence, it could be suggested that ExT provided no additional benefit to cardiovascular health than caloric restriction in lowering HR and BP (23). However, consistent with previous studies (12,24), the lower submaximal SBP and DBP, and higher VO_{2peak} and HRR found in the supervised ExT groups (Table 2) highlights the additional beneficial effects of supervised ExT. Adding to that, although peak HR remained unchanged in the present study, the higher VO_{2peak} and HRR together with a lower submaximal HR and a reduction in resting HR are independent risk factors for the reduction of coronary heart disease and cardiovascular disease morbidity and mortality (25). Further, previous studies have shown that a higher CRF is associated with lower SBP responses during submaximal exercise in hypertensive population, leading to an important reduction in the risk of left ventricular hypertrophy (26). Thus, a lower ambulatory and exercise BP, secondary to aerobic ExT, is driven by a reduction in systemic vascular resistance and is included as a behavioral intervention, since even the smallest reduction (1 mmHg) in SBP is associated with lower cardiovascular risk (27). The underlying mechanisms suggested to be responsible for the aforementioned benefits of ExT have previously been explored (2), *i.e.*, a decrease of the enhanced exercise pressor reflex, including mechano- and metaboreflex, and an improvement of the impaired functional sympatholysis, leading to a greater muscle blood flow to the active muscles

during exercise and normal cardiovascular response. Therefore, although in the present study the autonomic function was non-directly assessed, the changes observed in HR and BP could be considered the mirror of an improved autonomic function taking into account that in HTN the parasympathetic impairment is not only related to the heart or cardiovascular system, but also to all para-sympathetically dependent functions (1).

fig

Table 3. Changes of ambulatory blood pressure and blood pressure variability after 16-weeks intervention period.

	AC (N=52)	HV-MICT (N=59)	HV-HIIT (N=60)	LV-HIIT (N=60)	P-value AC vs. ExT	P-value Intergroups	F-value	Size effect
Day-time SBP (mmHg)								
T0	141.9±14.0	138.0±11.6	138.4±12.1	140.3±14.0				
T1	137.1±14.4*	133.2±11.0*	133.0±11.2*	134.1±12.0*	0.589	0.921	0.163	0.002
Day-time DBP (mmHg)								
T0	81.3±8.6	78.7±8.4	82.0±7.9	81.8±9.0				
T1	78.1±9.3*	76.2±8.5*	77.2±7.0*	78.1±8.0*	0.701	0.431	0.922	0.013
Night-time SBP (mmHg)								
T0	127.9±17.9	123.5±13.6	121.8±14.8	122.9±15.2				
T1	121.8±18.0*	118.4±13.5*	118.5±15.2*	116.6±13.9*	0.766	0.507	0.678	0.007
Night-time DBP (mmHg)								
T0	68.4±8.8	66.6±8.5	68.5±7.2	67.7±8.2				
T1	65.3±9.3*	62.4±7.2*	65.7±7.1*	63.3±11.2*	0.553	0.700	0.475	0.007
CV of global SBP (%)								
T0	10.4±2.8	10.6±2.0	10.6±2.6	11.1±2.6				
T1	10.8±2.8	10.3±2.5	10.4±2.5	10.7±2.1	0.098	0.450	0.884	0.012
CV of global DBP (%)								
T0	14.0±3.3	14.4±2.5	13.8±3.0	14.3±3.1				
T1	14.1±3.7	14.1±3.3	13.3±3.1	13.6±2.9	0.277	0.723	0.442	0.006
CV of day-time SBP (%)								
T0	8.8±2.2	9.1±1.9	8.8±2.4	9.2±2.5				
T1	9.0±2.5	8.6±2.8	9.0±2.3	8.8±2.0	0.283	0.317	1.182	0.016
CV of day-time DBP (%)								
T0	11.1±3.4	12.1±2.9	11.0±3.0	11.4±3.6				
T1	11.7±3.4	11.4±3.5	11.1±3.0	10.7±3.0	0.023	0.072	2.364	0.032
CV of night-time SBP (%)								
T0	10.1±3.9	10.5±6.8	9.1±3.6	10.1±4.0				
T1	9.6±3.4	10.2±5.4	9.0±4.0	9.9±3.4	0.733	0.974	0.073	0.001
CV of night-time DBP (%)								
T0	14.1±5.6	13.1±5.6	12.8±5.1	13.9±5.9				
T1	13.1±4.5	12.9±5.4	12.5±4.7	13.6±4.9	0.395	0.854	0.261	0.004

Mean±SD.

SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: coefficient of variation; AC: attention control group; ExT: exercise training group; HV: high volume; LV: low volume; MICT: moderate-intensity continuous training group; HIIT: high-intensity interval training group.

*P value<0.05 from T0.

An increased BPV may carry some additional risk for higher incidence and faster progression of cardiovascular disease (28). Previous literature has suggested that BPV is highly related to 24-hour mean BP (quantified as the SD of the 24-hour, day and night mean values) and is found to be an independent predictor of the incidence of cardiovascular events (4). In the present study (Table 3) all groups significantly decreased day- and night-time SBP and DBP. However, after the intervention visit-to-visit long-term BPV (expressed as CV, Table 3) was not significantly changed which is similar to previous studies (13). Previously, it has been observed that in individuals with a SD of daytime SBP lower than 16 mmHg, the rate of cardiovascular mortality was significantly less than in those with an SD equal to or above 16 mmHg (29). In the current study, following the 16-week intervention, the SD was less than 16 mmHg in all ExT groups, but not in AC group's nocturnal SBP. As such, it seems likely that the current 16-week intervention decreases the development of cardiovascular risk events. Further, daytime DBP showed lower values in ExT groups compared to AC group, further suggesting positive cardiovascular benefits to all ExT groups. The exact reasons for the lack of effect of ExT on BPV remain elusive (13). Previous reports have highlighted that the level of the 24 h BP and not BPV should remain the primary BP-related risk factor to account for in clinical practice (30).

All the aforementioned results and discussion confirm that ExT *pari passu* improves hemodynamics and autonomic responses in overweight/obese and hypertensive population, irrespective of intensity and volume. The current study adds further evidence to the argument that LV-HIIT (twice a week) is an efficient ExT alternative for this population due to: 1) time efficiency (less time to get similar results)

(14,31), and 2) lower stress of autonomic modulation (31). These findings are relevant for both practitioners and clinicians alike.

Study limitations

Despite the novelty of our results providing clear evidence for the benefits of aerobic exercise on hemodynamics and cardiac autonomic modulation in overweight/obese population with HTN, we should acknowledge a few limitations of our study. First, physical activity performed by participants in the AC group could not be controlled. Second, other BPV quantifying methods, such as the calculation of the “residual BPV” or the average of the absolute differences between consecutive measurements (*i.e.*, “average real variability”) have been proposed by other authors (3), and the comparability between results obtained in by different techniques is limited.

Acknowledgments

Our special thanks to G. Rodrigo Aispuru, the medical doctor who has taken part in this project with medical assessment. Also thanks to the Department of Physical Education and Sport and Faculty of Physical Education and Sport-Physical Activity and Sport Sciences Section (University of the Basque Country, UPV/EHU) for believing in our project and providing the material and facilities to carry it out. Also thanks to Exercycle S.L. (BH Fitness Company) for the machines donated to conduct the exercise intervention. Last but not least to all undergraduate and postgraduate students who collaborated in this project (2011-2017 academic years).

Conflict of interest

The authors declare that they have no conflict of interest.

Funding: This work was supported by the University of the Basque Country (EHU14/08, PPGA18/15) and the Government of the Basque Country supported PC, AMAB, and IGA with predoctoral grants.

References

(1) Mancia G, Grassi G. The autonomic nervous system and hypertension. *Circ Res* 2014;114(11):1804-1814.

(2) Mitchell JH. Abnormal cardiovascular response to exercise in hypertension: contribution of neural factors. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 2017;312(6):R851-R863.

(3) Schillaci G, Bilo G, Pucci G, Laurent S, Macquin-Mavier I, Boutouyrie P, et al. Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from 2 large databases. *Hypertension* 2012 Aug;60(2):369-377.

(4) Mancia G. Short-and long-term blood pressure variability: present and future. *Hypertension* 2012;60(2):512-517.

(5) Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013 Jul;31(7):1281-1357.

- (6) Halliwill JR, Buck TM, Lacewell AN, Romero SA. Postexercise hypotension and sustained postexercise vasodilatation: what happens after we exercise? *Exp Physiol* 2013 Jan;98(1):7-18.
- (7) Caminiti G, Mancuso A, Raposo AF, Fossati C, Selli S, Volterrani M. Different exercise modalities exert opposite acute effects on short-term blood pressure variability in male patients with hypertension. *European journal of preventive cardiology* 2019:2047487318819529.
- (8) Cuspidi C, Tadic M, Grassi G, Mancia G. Treatment of hypertension: The ESH/ESC guidelines recommendations. *Pharmacol Res* 2018 Feb;128:315-321.
- (9) Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;71(19):e127-e248.
- (10) Anunciação PG, Polito MD. A review on post-exercise hypotension in hypertensive individuals. *Arq Bras Cardiol* 2011;96(5):425-426.
- (11) Cardoso CG,Jr, Gomides RS, Queiroz AC, Pinto LG, da Silveira Lobo F, Tinucci T, et al. Acute and chronic effects of aerobic and resistance exercise on ambulatory blood pressure. *Clinics (Sao Paulo)* 2010 Mar;65(3):317-325.
- (12) Edwards KM, Wilson KL, Sadjja J, Ziegler MG, Mills PJ. Effects on blood pressure and autonomic nervous system function of a 12-week exercise or exercise plus DASH-diet intervention in individuals with elevated blood pressure. *Acta Physiologica* 2011;203(3):343-350.

- (13) Pagonas N, Dimeo F, Bauer F, Seibert F, Kiziler F, Zidek W, et al. The impact of aerobic exercise on blood pressure variability. *J Hum Hypertens* 2014 Jun;28(6):367-371.
- (14) Gorostegi-Anduaga I, Corres P, MartinezAguirre-Betolaza A, Perez-Asenjo J, Aispuru GR, Fryer SM, et al. Effects of different aerobic exercise programmes with nutritional intervention in sedentary adults with overweight/obesity and hypertension: EXERDIET-HTA study. *Eur J Prev Cardiol* 2018 Mar;25(4):343-353.
- (15) Maldonado-Martín S, Gorostegi-Anduaga I, Aispuru G, Illera-Villas M, Jurio-Iriarte B. Effects of Different Aerobic Exercise Programs with Nutritional Intervention in Primary Hypertensive and Overweight/Obese Adults: EXERDIET-HTA Controlled Trial. *J Clin Trials* 2016;6(252):2167-0870.1000252.
- (16) Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. *Nat Rev Cardiol* 2013 Mar;10(3):143-155.
- (17) Mezzani A, Hamm LF, Jones AM, McBride PE, Moholdt T, Stone JA, et al. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation. *Eur J Prev Cardiol* 2013 Jun;20(3):442-467.
- (18) Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk--a review of the literature. *Eur J Clin Nutr* 2010 Jan;64(1):16-22.
- (19) Kaminsky LA, Imboden MT, Arena R, Myers J. Reference Standards for Cardiorespiratory Fitness Measured With Cardiopulmonary Exercise Testing Using Cycle Ergometry: Data From the

Fitness Registry and the Importance of Exercise National Database (FRIEND) Registry. *Mayo Clin Proc* 2017 Feb;92(2):228-233.

(20) Prasad VK, Hand GA, Sui X, Shrestha D, Lee DC, Lavie CJ, et al. Association of exercise heart rate response and incidence of hypertension in men. *Mayo Clin Proc* 2014 Aug;89(8):1101-1107.

(21) Carnagarin R, Gregory C, Azzam O, Hillis GS, Schultz C, Watts GF, et al. The Role of Sympatho-Inhibition in Combination Treatment of Obesity-Related Hypertension. *Curr Hypertens Rep* 2017;19(12):99.

(22) Pimenta FC, Montrezol FT, Dourado VZ, da Silva LFM, Borba GA, de Oliveira Vieira W, et al. High-intensity interval exercise promotes post-exercise hypotension of greater magnitude compared to moderate-intensity continuous exercise. *Eur J Appl Physiol* 2019:1-9.

(23) Nicoll R, Henein M. Caloric restriction and its effect on blood pressure, heart rate variability and arterial stiffness and dilatation: a review of the evidence. *International journal of molecular sciences* 2018;19(3):751.

(24) Blumenthal JA, Babyak MA, Hinderliter A, Watkins LL, Craighead L, Lin P, et al. Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. *Arch Intern Med* 2010;170(2):126-135.

(25) Molmen-Hansen HE, Stolen T, Tjonna AE, Aamot IL, Ekeberg IS, Tyldum GA, et al. Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients. *Eur J Prev Cardiol* 2012 Apr;19(2):151-160.

(26) Kokkinos P, Pittaras A, Narayan P, Faselis C, Singh S, Manolis A. Exercise capacity and blood pressure associations with left ventricular mass in prehypertensive individuals. *Hypertension* 2007;49(1):55-61.

(27) Nystoriak MA, Bhatnagar A. Cardiovascular effects and benefits of exercise. *Frontiers in cardiovascular medicine* 2018;5:135.

(28) Marrone O, Bonsignore MR. Blood-pressure variability in patients with obstructive sleep apnea: current perspectives. *Nat Sci Sleep* 2018 Aug 21;10:229-242.

(29) Kikuya M, Ohkubo T, Metoki H, Asayama K, Hara A, Obara T, et al. Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis: the Ohasama study. *Hypertension* 2008 Dec;52(6):1045-1050.

(30) Asayama K, Schutte R, Li Y, Hansen TW, Staessen JA. Blood pressure variability in risk stratification: What does it add? *Clinical and Experimental Pharmacology and Physiology* 2014;41(1):1-8.

(31) Castrillón CIM, Miranda RAT, Cabral-Santos C, Vanzella LM, Rodrigues B, Vanderlei LCM, et al. High-Intensity Intermittent Exercise and Autonomic Modulation: Effects of Different Volume Sessions. *Int J Sports Med* 2017;38(06):468-472.

Summary Table

What is known about topic

- Hypertension is associated with an inappropriate activation of the sympathetic and reduction of the parasympathetic divisions at rest and in response to exercise.
- Regular aerobic exercise training is an excellent non-pharmacological treatment against hypertension-caused disturbances.

What this study adds

- Supervised aerobic physical activity and healthy diet may have produced a significant improvement in the autonomic nervous system functioning (reducing heart rate and blood pressure).
 - Low volume-HIIT exercise training combined with a hypocaloric diet should be considered as a time efficient and safe mechanism for reducing the cardiovascular risk in hypertensive individuals.
 - The better improvements seen when the exercise training was individually designed and supervised in overweight/obese individuals with hypertension empowers the existing professional exercise recommendations.
-