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Reply to Liu et al.

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We thank Liu et al. (1) for their thought-provoking letter, in this issue of the American Journal of Physiology-Heart and Circulatory Physiology, to our recent perspectives article (2). Although we and the authors of the letter seem to agree that there is a need for standardized methodological protocols, we differ on our conclusions and ultimate suggestions. In contrast to our suggested standardizations, Liu et al. propose that lower-limb flow-mediated dilation (FMD) assessments should be performed with participants in a seated posture. We appreciate the discourse and believe that these discussions within the literature are a key step toward improving sitting research and moving toward actionable public health policy. The response by Liu et al. predominates on lower-limb artery FMD and makes no mention of pulse wave velocity (PWV) for which we also made recommendations. As such, this response will focus primarily on lower-limb artery FMD.

The arguments of Liu et al. (1) broadly center on using the sitting, rather than supine, posture for lower-limb artery FMD assessments as it demonstrates a more ecologically valid measure when assessing the impact of prolonged sitting that can be used to inform public health messaging. We would counter that there are several pertinent issues associated with performing FMD in said posture. Perhaps the biggest obstacle associated with performing lower-limb FMD in the seated posture is the increased influence of the autonomic nervous system (ANS). It is well established that a seated posture increases ANS activity relative to a supine posture (3, 4). It has also been shown that muscle sympathetic nervous activity (MSNA) increases over time during orthostatic stress (5). This is pertinent to FMD assessments as increased leg MSNA has been shown to increase retrograde shear rate and oscillatory shear index, both of which are likely to detrimentally influence FMD responses (6). Although we concede that performing FMD assessments in the seated posture may reduce methodological confounding, the increased role of the ANS while seated undoubtedly increases measurement error. From a mechanistic standpoint, if we are to put value in seated FMD assessments, we argue that measures of ANS activity are required to add context to what we might be observing. In addition to the above points, the seated position also results in increased hydrostatic pressure in the lower limb (7), increased arterial tortuosity (8), decreased blood flow, and therefore reduced shear stress (9). These additional complexities mean that lower-limb artery FMD performed in a seated posture is not solely measuring endothelial function. By contrast, we are not really sure what we are measuring and draw into question the validity of our measure. However, by performing FMD in a supine posture, we attenuate or eliminate some of these confounding physiological variables and may give a truer reflection of endothelial function in the artery being examined.

A further consideration is the technically challenging nature of FMD as a measure. FMD is an extremely challenging measure to perform well, in even ideal circumstances, e.g., the brachial artery with participants in a supine posture, and is known to yield high within-subject variability (10, 11). Attempting to perform FMD in a seated posture adds an additional layer of difficulty and variability. One source of variability comes from the typical need to partially extend the knee from a ~90^{o} angle at rest to ~20^{o} – 30^{o} for assessment. Small differences in the knee angle at the time of assessment could significantly alter the accuracy of shear rate estimations, and thus the ability to statistically correct for shear is compromised. Furthermore, if the angle differs between assessments, i.e., pre- versus post-sitting or condition 1 versus condition 2, an additional source of error will be introduced. Combined, these issues may prevent the use of lower-limb artery FMD in evaluating the impact of sitting in large epidemiological studies.

Finally, prognostic value is an important consideration from a public health perspective. Liu et al. (1) rightly highlight the need for valid outcomes that can be used to inform sedentary behavior public health guidelines. We would argue, however, that FMD, whether performed seated or supine, is unlikely to directly inform policy, but rather form part of an informed mechanistic model used in the determination of biological plausibility. In the determination of public health policy, bodies such as the United States Preventative Services Task Force consider intermediate outcomes (12). These intermediate outcomes are those that can be assessed in an acute randomized controlled trial setting (e.g., blood pressure and central arterial stiffness) and have a demonstrated, biologically plausible link to long-term health outcomes (e.g., cardiovascular disease). In contrast to measures such as blood pressure or central arterial stiffness, lower-limb artery FMD does not have any established prognostic value, i.e., it has not been shown to be predictive of cardiovascular disease or mortality and thus is unlikely to be considered an intermediate outcome. As such, lower-limb artery FMD, as an indicator of endothelial function, is more likely to form part of biologically plausible model. To that end, it is important that instances of lower-limb artery FMD are assessing endothelial function without the added complications discussed earlier.

In conclusion, although we thank Liu et al. (1) for this discourse, we still maintain that measurements of lower-limb artery FMD should be performed with participants in a supine position following a standardized 10-min post-posture transition rest period to reduce the introduction of additional measurement error from ANS activity, knee angle, hydrostatic pressure, and arterial tortuosity.

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Disclosures
No conflicts of interest, financial or otherwise, are declared by the authors.

Author contributions
C.P. drafted manuscript; C.P., S.H., M.S., K.S., S.F., and L.S. edited and revised manuscript; C.P., S.H., M.S., K.S., S.F., and L.S. approved final version of manuscript.

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