Passive leg movement: a novel method to assess vascular function during passive leg heating?

Nuno Koch Esteves[1], Scott T. Chiesa[2]

[1]*Centre for Human Performance, Exercise and Rehabilitation, College of Health, Medicine and Life Sciences, Brunel University London, Uxbridge, UK*

[2]*Vascular Physiology Unit, Institute of Cardiovascular Science, University College London, London, UK*

Correspondence to:

Nuno Koch Esteves

Centre for Human Performance, Exercise and Rehabilitation

College of Health, Medicine and Life Sciences

Brunel University London

Kingston Lane, Uxbridge UB8 3PH, UK

E-mail: nuno.kochesteves@brunel.ac.uk

Over the last decade, passive leg movement (PLM) has emerged as an increasingly popular alternative to flow-mediated dilation (FMD) for the non-invasive assessment of vascular endothelial function. PLM involves continuously measuring common femoral artery (CFA) blood flow (BF) by Doppler ultrasound as the participant's leg is passively extended and flexed at a fixed rate (60 movements per minute) for 1–2 min. The assessment is based on the notion that the mechanical deformation of vessels caused by the movement stimulates a predominantly nitric oxide (NO)-mediated vasodilatory response (Mortensen *et al.*, 2012), the magnitude of which is believed to be indicative of vascular endothelial function. Despite a growing appreciation of the many potential benefits of this new easy-to-administer and non-invasive technique, many questions remain unanswered regarding the optimisation of the method and the interpretation of the results.

In October's issue of *Experimental Physiology*, Shields *et al.* (2021) employed local passive leg heating to investigate the extent to which differences in baseline BF may impact estimates of vascular function measured during PLM. While the authors are to be commended for a well-planned and carefully executed study, their paper—as is often the case in newly burgeoning fields of research—introduced as many exciting new research questions as it answered. As far as their primary aim was concerned, their results are clear: at high levels of baseline BF—in this case almost double normal resting values—PLM responses are affected, with the overall peak BF response found to be greater (~100 ml·min^{-1}), but relative changes from baseline ($BF_{\Delta peak}$) smaller. Thus, they reasonably conclude that taking care to obtain *true* baseline BF values prior to conducting PLM is paramount to the reliability of this technique. A welcome bonus to using a local passive heating model to manipulate baseline BF in the current study, however, is that Shields *et al.* (2021) also provide the first data to our knowledge in

which vascular responsiveness to local hyperthermia has been reported using PLM. Whilst not the primary aim of this study, these novel data are interesting and—at times—somewhat surprising and warrant further scrutiny.

Previous studies using the current gold-standard non-invasive test of vascular function (FMD) have generally demonstrated unchanged or even improved vascular function during acute passive heating (Romero *et al.*, 2017). Given the agreeability between FMD and PLM outcomes, one may therefore have expected the reactive hyperaemic response to be enhanced following upper or lower leg heating, and in absolute terms (i.e., BF_{peak}), this was true. However, as pointed out by the authors in their paper, the relative change from baseline when combining heating and PLM was, in fact, lower than that observed during normothermic conditions, suggesting that acute heating may, in fact, attenuate—rather than augment—vascular responsiveness. Given the ever-growing interest in passive heating as a potential therapeutic intervention to *improve* vascular function, this finding raises several questions regarding both the intervention itself and the applicability of PLM to assess its response.

Firstly, could the timing of the measurement explain these apparently discrepant results? In the current study, passive heating was used solely as a tool to manipulate baseline BF and, as a result, the authors rightly initiated PLM during (or immediately after) heating when ‘resting’ BF levels were at their peak (approximately double baseline values). An interesting and clinically relevant area of future research may be to assess PLM responses following a post-heating return to true resting values, thereby assessing whether the sustained exposure to increased shear stress during heating may improve longer-term endothelial function in the resting state. Secondly, how to interpret the observation of higher absolute but lower relative BF changes demonstrated here? While the greater absolute BF_{peak} is likely the consequence of a

greater dual stimulus to both skin and muscle—i.e., the combination of skin and muscle-directed hyperthermic hyperaemia and muscle-directed mechanical hyperaemia—the finding of a reduced relative increase in profunda/deep femoral artery (DFA) BF during heating, in fact, suggests a reduction in skeletal muscle vascular responsiveness. Given skeletal muscle's extraordinary capacity for vasodilation, this finding seems surprising and certainly warrants further investigation. Although only speculative, one potential explanation may lie in the method by which DFA BF has been quantified here, with the authors opting to estimate the value as the difference between CFA BF and superficial femoral artery (SFA) BF. This technique is understandable and likely unavoidable due to the extreme difficulty, if not impossibility, of measuring DFA during PLM. Nonetheless, it should be noted that this method has been shown by both ourselves and others to overestimate DFA BF in comparison to direct measures (Chiesa *et al.*, 2016; Koch Esteves *et al.*, 2021). Indeed, the finding of a significantly higher DFA than SFA during baseline measures in this study (DFA: 213 ± 89 ml·min^{-1}; SFA: 135 ± 63 ml·min^{-1}) is the exact opposite to what we and others have observed with direct measures (DFA: ~130 ml·min^{-1}; SFA: ~170 ml·min^{-1}) (Hussain, 1997; Chiesa *et al.*, 2016; Koch Esteves *et al.*, 2021). Given the obvious importance of baseline values in calculating subsequent $BF_{\Delta peak}$, demonstrated by the authors themselves here in their primary aim, an overestimated DFA BF at baseline may at least partially explain why the relative $BF_{\Delta peak}$ was attenuated. Further research using pharmaceutical interventions to independently manipulate BF (e.g., sodium nitroprusside infusion) may help to further clarify these answers.

In summary, Shields *et al.* (2021) demonstrate that obtaining a true baseline is vital for the interpretation of vascular function using PLM. Furthermore, whilst the present study was not centred around the effects of acute passive heating, their findings

provide exciting future directions for research assessing the applicability of PLM to assess vascular function in conditions where ‘baseline’ BF is elevated (e.g., heat stress/exercise). PLM remains a promising tool for vascular research, but further research is required to establish a robust protocol that can be used in various conditions.

Competing interests

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

Funding

This study was completed without external funding.

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