**Letter to the editor**

The recent study investigating the effect of passive heat stress on vascular structure and function published by Brunt and co-workers (Brunt *et al.*, 2016*a*) in the December issue of *The Journal of Physiology* provides compelling evidence for the ability of heat therapy to exert improvements in multiple subclinical markers of cardiovascular disease, and has rightly received much positive interest in recent months. While the study appears carefully carried out and a number of measures of vascular function show physiologically plausible improvements, we have reservations over the rapid improvements reported in carotid intima-media thickness (cIMT) following treatment.

The tests employed in the study included a wide range of arterial measures assessing structural changes (cIMT), functional changes (flow-mediated dilation; FMD), and composites of both (pulse-wave velocity; PWV). It is well known that changes in FMD and, to a lesser extent, PWV are largely determined by improvements in endothelial function, and numerous studies have previously shown the ability of numerous interventions (including heat stress) to induce rapid improvements in these responses. The haemodynamic changes accompanying these effects have also been investigated by a number of researchers – including ourselves – and a mechanistic basis for these adaptations therefore seems plausible (Tinken *et al.*, 2009; Green *et al.*, 2010; Carter *et al.*, 2013; Chiesa *et al.*, 2016). In contrast to FMD and PWV, however, changes in cIMT represent structural changes within the arterial wall which may occur in the intima, media, or both. Analysis of Fig. 4 from the current study suggests a remarkable decrease in cIMT from ~0.43mm to ~0.38mm following 8 weeks of heat therapy, yet no observable change in femoral intima-media thickness (fIMT) over the same time. We feel that this substantial change in cIMT may be unlikely for a number of reasons.

Firstly, while it could be postulated that the decrease in cIMT observed here is due to atherosclerotic regression within the intimal layer, the use of young and healthy (albeit sedentary) participants in the study makes it unlikely that participants had any significant atherosclerotic burden to regress, as evidenced by cIMT values which are comparable to those from our laboratory in over 400 healthy young adults recruited from the Avon Longitudinal Study of Parents and Children (ALSPAC) (unpublished). Even in individuals with significant atherosclerotic burden and intimal thickening, such as those seen in heterozygous familial hypercholesterolaemia, regression of cIMT appears extremely difficult to achieve, as shown by a recent meta-analysis in which various high-dose statin treatments administered over periods of months reported a mean decrease in cIMT of only ~ 0.025 mm (Masoura et al., 2011); that is, half of that observed by Brunt and co-workers. While intimal thickening in this population is unlikely, another component of the arterial wall that may respond to intervention is the underlying medial layer. Previously, the use of traditional ultrasound techniques has prevented the distinction between intimal and medial layers due to insufficient image resolution (~12MHz) resulting from limits in operating frequency. Using a very-high resolution ultrasound scanner (VHRUS) operating at frequencies of up to 50MHz, our group have recently investigated the determinants of intimal and medial thickening in a subset of 170 participants from the ALSPAC cohort, and have reported increases in IMT that appear to result from changes in the medial layer alone, with these changes related with increases in blood pressure and unrelated to serum lipid levels (Dangardt et al., 2016). While we note that a small decrease in blood pressure was observed in the current study, the extent and duration of this change seem insufficient for smooth muscle remodelling to occur.

Secondly, previous research surrounding arterial adaptations to heat therapy have commonly focused on heat-induced increases in endothelial shear stress as the putative mechanisms underlying improvements in arterial function. We have previously shown that leg blood

flow and shear rates during heating of the lower body are significantly increased (0.3 to 0.8 L/min), with pro-atherogenic shear profiles decreased or even abolished (Chiesa *et al.*, 2016). In contrast, increases in common carotid artery blood flow during moderate heat stress are minimal (Ogoh *et al.*, 2013), with increases in skin blood flow partially offset by decreases in brain perfusion (Ogoh *et al.*, 2013; Trangmar *et al.*, 2017). With this in mind, it could be expected that greater vascular responses should have been observed in the lower limbs due to the greater stimulus, and encouragingly, with regards to beta-stiffness index this appears to be the case. However, despite these substantial improvements in compliance in this vessel, no effect was observed in fIMT, while in the carotid artery the opposite was true.

There are a number of methodological considerations to consider when assessing whether the observed changes in cIMT over such a short time-span may simply be an anomalous result. Firstly, the use of simple point-to-point caliper measurements – as appear to be have been used in the present study – are not recommended in cIMT guidelines (Stein *et al.*, 2008), and where possible, semi-automated wall-tracking software covering a 1cm portion of the vessel wall should be used to improve reproducibility. We appreciate that not all laboratories have access to this software, however, and while we note that the researchers have perhaps used an average of multiple wall measurements in order to overcome this, this analysis technique may have impacted upon results. Secondly, it is not clear from the methodology of the article whether the authors were blinded during analyses of cIMT, although it is again encouraging to note that this was the case for PWV analyses (Brunt *et al.*, 2016*b*). Nevertheless, it should be emphasised for future studies that this is especially important if measurements are carried out manually, as unconscious analyser bias - while clearly inadvertent - remains a risk with this technique.

In conclusion, we commend the authors on a well-conducted and insightful study that provides the first compelling evidence of heat therapy's ability to simultaneously improve numerous measures of arterial function at multiple sites. The rapid changes observed in endothelial function and arterial stiffness are extremely promising, and may partially explain heat-induced improvements in symptoms and status previously documented in patients with peripheral arterial disease (Tei *et al.*, 2007; Shinsato *et al.*, 2010). However, until changes in cIMT reported here are reproduced in follow-up studies using gold-standard measurement techniques as recommended in official guidelines, we urge caution in reporting short-term heat therapy as a viable mechanism for arterial structural changes.

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