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Substantive hemodynamic and thermal strain upon completing lower-limb hot-water immersion; comparisons with treadmill running

Kate N. Thomas[a,b], André M. van Rij[a], Samuel J.E. Lucas[c,d], Andrew R. Gray[e], and James D. Cotter[b]

[a]Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand; [b]School of Physical Education, Sport and Exercise Sciences, University of Otago, Dunedin, New Zealand; [c]Department of Physiology, University of Otago, Dunedin, New Zealand; [d]School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK; [e]Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand

ABSTRACT

Exercise induces arterial flow patterns that promote functional and structural adaptations, improving functional capacity and reducing cardiovascular risk. While heat is produced by exercise, local and whole-body passive heating have recently been shown to generate favorable flow profiles and associated vascular adaptations in the upper limb. Flow responses to acute heating in the lower limbs have not yet been assessed, or directly compared to exercise, and other cardiovascular effects of lower-limb heating have not been fully characterized. Lower-limb heating by hot-water immersion (30 min at 42°C, to the waist) was compared to matched-duration treadmill running (65-75% age-predicted heart rate maximum) in 10 healthy, young adult volunteers. Superficial femoral artery shear rate assessed immediately upon completion was increased to a greater extent following immersion (mean ± SD: immersion +252 ± 137% vs. exercise +155 ± 69%, interaction: $p = 0.032$), while superficial femoral artery flow-mediated dilation was unchanged in either intervention. Immersion increased heart rate to a lower peak than during exercise (immersion +38 ± 3 beats·min^{-1} vs. exercise +87 ± 3 beats·min^{-1}, interaction: $p < 0.001$), whereas only immersion reduced mean arterial pressure after exposure (−8 ± 3 mmHg, $p = 0.012$). Core temperature increased twice as much during immersion as exercise (+1.3 ± 0.4°C vs. +0.6 ± 0.4°C, $p < 0.001$). These data indicate that acute lower-limb hot-water immersion has potential to induce favorable shear stress patterns and cardiovascular responses within vessels prone to atherosclerosis. Whether repetition of lower-limb heating has long-term beneficial effects in such vasculature remains unexplored.

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acute exercise; immersion; lower-limb heating; passive heat; shear stress

Introduction

Limb blood flow is affected by the temperature of local tissue, the limb and the body as a whole. Both the profile and the magnitude of arterial flow within limbs have important effects on that limb's arteries and potentially on downstream vessels, as well as on remote vasculature. Shear stress, the mechanical force of blood flow on the walls of arteries[1] provides the stimulus for both acute[2,3] and adaptive effects.[4] Specifically, an increase in forward-directional (antegrade) shear acutely promotes vasodilation.[5] Chronic exposure to increased antegrade shear (over several weeks), as in during repetitive bouts of exercise training, is known to improve endothelial function[6] (responsiveness to shear stress) within the first 4 weeks, after which structural remodeling becomes evident (and thereby structurally normalizes shear stress within 6 to 8 weeks).[7,8]

Shear stress can be manipulated using various thermal and non-thermal interventions, including exercise, terrestrial heat exposure and hot-water immersion.[5,9–12] Hot-water immersion can acutely increase antegrade shear in the arteries of immersed limbs[9] as well as in remote limbs.[12] Chronically, favorable adaptations in endothelial function[10,12] and microvascular vasodilation[13] have been demonstrated following repeated local heating in healthy individuals. Systemically-applied heat via sauna bathing has also been reported to improve endothelial function in patients with coronary risk factors[14] and heart failure.[15] Again, the suggested mechanism for these effects has been increased peripheral artery blood flow

CONTACT James D. Cotter jim.cotter@otago.ac.nz School of Physical Education, Sport and Exercise Sciences University of Otago, PO Box 56 Dunedin 9054, New Zealand.

(+68% following 15 min of sauna[14]), although a causal relationship has not always been expounded in such studies. In support of the shear stress hypothesis, repeated sauna therapy (4-5 weeks) upregulates endothelial nitric oxide synthesis expression in animal models.[16,17] Therefore, heat therapy, applied in various ways, appears to have potential as a stimulus for increasing blood flow and antegrade shear stress,[12] in a manner similar to exercise.[7,8]

Heat is also implicated in other exercise-induced cardiovascular adaptations, which occur as a result of, or are amplified by, increased core and tissue temperature. Examples include blood volume expansion,[18,19] muscle growth[20,21] and glucose uptake,[22] and a heightened cellular stress response conferring increased resilience to stress.[23-25] Isolated heat stress also causes several other significant physiological responses similar to those induced by exercise (which is also heat stressful[26]). These include elevations in cutaneous and muscle blood flow, heart rate and sympathetic activity.[27,28] Furthermore, repetitive heat exposure, independent of exercise, can improve cardiac function,[15,29–31] reduce blood pressure[32] and induce cardiac preconditioning,[33] and is associated with reduced risk of cardiovascular and all-cause mortality.[34]

Despite this background, much remains unknown about the acute hemodynamic effects of heat and how these compare with traditional exercise, especially in the lower limbs. Therefore, the aim of this study was to directly compare the lower-limb artery shear rate pattern induced by an acute bout of lower-limb heating to that induced by running (i.e., the ubiquitous mode of exercise) – within the same young, healthy individuals. The duration of exposure was matched between interventions. Importantly, the novelty of this study was in the assessment of the lower-limb arterial response, as most investigations on arterial responses to exercise (acute and chronic) focus on the brachial artery and infer that this reflects global arterial responses. However, in cases where more than one anatomical location has been assessed, upper- and lower-limb arteries often show little resemblance in their respective flow profiles.[35] It follows that upper-limb responses are unlikely to reflect local effects of lower-limb-specific interventions. Thus far, the superficial femoral artery (SFA) has not been studied in relation to acute hot-water immersion, and much also remains unknown about the acute vascular effects of exercise, especially in the lower limb.[36] Assessing the hemodynamics in lower-limb arteries is important for 2 reasons: 1) to understand the response in the limbs involved in heat and exercise administration, and 2) atherosclerotic disease is far more prevalent in the lower than upper limbs,[37] so understanding their shear profiles is important for considering future therapeutic prospects, particularly for people with a limited exercise capacity and concomitant high cardiovascular risk. Of secondary interest were systemic cardiovascular responses to the acute lower-limb heating protocol. There is a growing body of literature examining isolated stressors (e.g., heat) for their potential to induce beneficial cardiovascular and thermoregulatory strain. Understanding the complex acute effects of any such approach is therefore warranted to understand their potential as an alternative or complement to an exercise-training stimulus.

Participants and methods

Participant characteristics

Ten young, healthy individuals volunteered for this study (8 male and 2 female; age 27 ± 5 y, height 181 ± 8 cm, mass 81 ± 8 kg, BMI 24.4 ± 1.5 $kg \cdot m^{-2}$). Participants were not taking any medications or supplements, all were non-smokers, and all were recreationally active, typically engaging in moderate-intensity aerobic exercise (e.g. jogging) and resistance training (≥3 d per week). Written informed consent was obtained before participation. The study was approved by the University of Otago Human Ethics Committee, and conformed to the standards set by the *Declaration of Helsinki*.

Experimental procedures

This cross-over study involved 2 experimental interventions, namely exercise and water immersion, which were performed in a randomized and balanced order. Upon arrival to the laboratory, participants rested supine for 15 min before initial baseline data collection. They then completed the assigned intervention (exercise or immersion), with measures recorded during and immediately afterward as outlined below. The interventions were matched for parameters of stress

rather than strain; i.e., 30-min duration of exposure; being realistic/tolerable for both interventions as well as meeting the current health-related exercise guidelines.[38] Similarly, intensities were chosen to be strenuous but tolerable. Neither intervention provides an exclusively lower-limb or whole-body stimulus per se, so the intent was for interventions to be somewhat matched for the extent of tissue exposed to the stimulus provided. ***Exercise*** consisted of 30-min treadmill running at 65-75% age-predicted heart rate maximum. Running speeds ranged from 9.5 to 12 $km \cdot h^{-1}$ with an average of 10 $km \cdot h^{-1}$. Exercise was performed in a temperature-controlled environment at 22-23°C. ***Water Immersion*** consisted of 30-min seated, immersed to the waist in hot water (42.0 ± 0.4°C). Water temperature was checked continually and adjusted throughout the 30-min immersion. This temperature was chosen as 'a tolerable maximum' based on pilot experiments.

Each session was performed at the same time of day (>10 :00 h because of the known early-morning attenuation of endothelial function),[39] and 3-7 d apart, sufficient to ensure wash-out. All participants were instructed to abstain from exercise[36] and alcohol[40] for 24 h prior to the test, and to avoid caffeine on the morning of testing.[41] Participants were also instructed to maintain their normal diet during the study period. Female participants were tested in days 1 – 7 of the menstrual cycle.[42]

Experimental measures

Temperature measurements

Core body temperature (T_c) was measured using a thermistor in the esophagus at a depth 48% of sitting height, minus 4.44 cm.[43] Muscle temperature (T_m) of the medial gastrocnemius was measured using a needle thermocouple (YSI 525, Yellow Springs Instruments, Yellow Springs, OH, USA) at a depth of 2 cm below the skin surface. Muscle temperature was measured throughout the water immersion protocol, and after exercise (<5 min post-exercise). All temperatures were recorded at 30-s intervals using portable, battery-operated loggers (Squirrel SQ2010, Grant Instruments, Cambridge, UK). Perceived ratings of body temperature and thermal discomfort were ascertained from a 13- and 5-point scale respectively (extended from Gagge[44]), at baseline and at 10, 20 and 30 min through the intervention.

Superficial femoral artery hemodynamics

Superficial femoral artery (SFA) diameter and blood velocity were measured using ultrasound (Aplio XG, Toshiba, Nasu, Japan) with a 7 MHz linear array transducer (bandwidth 4-11 MHz) by simultaneously recording a longitudinal section B-mode image and a spectral Doppler trace of blood velocity. The Doppler angle of insonation was maintained at 60°. Participants were supine during this procedure. Measurements were made 2-3 cm distal to the bifurcation of the common femoral artery. The location of the transducer was recorded and marked on the skin using indelible ink and reused for the repeat test. Ultrasound settings (depth, focus position and gain) were optimized for each participant, and reused for the repeat test. All ultrasound scans were performed by the same vascular sonographer (K.T.). Video clips were recorded using a VGA to USB screen capture device at 21 Hz (VGA2USB LR, Epiphan Systems Inc., Palo Alto, California, USA). Analysis of diameter and velocity, and the calculation of shear rate (SR = 4* velocity / diameter)[45] were performed using wall-tracking software (Cardiovascular Suite UE v 2.5, Quipu, Pisa, Italy),[46,47] which reduces investigator bias. Our test-retest reliability using this software for measures of diameter and velocity were 0.4% and 2.1% respectively (n = 10).

Flow-mediated dilation (FMD)

FMD is predominantly an endothelium-dependent measure of vascular function based on the ability of the vessel to respond to transient ischemia with reactive hyperemia. The resting hemodynamics (diameter, velocity, shear rate) and FMD of the SFA were assessed before and 5-10 min after the intervention, following 2-min baseline recording, according to international guidelines.[48] To perform the FMD, arterial flow was blocked at the distal thigh using a 17-cm contoured cuff inflated to 200 mmHg within 2 seconds (CC17 contoured leg cuff, E20 Rapid Cuff Inflator and AG101 Cuff Inflator Air Source, Hokanson, Bellevue WA, USA). Occlusion was maintained for 5 min. Recording resumed for the final 30 s of occlusion and continued for 3 min following rapid release of the cuff (<2 s).

Systemic hemodynamics

Heart rate (HR) was obtained continuously using detection of the R-R wave of ventricular

depolarization frequency (Polar S810i, Polar, Finland). Blood pressure (BP) was measured using finger photoplethysmography (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands). Stroke volume (SV) and cardiac output ($\dot{Q}$) were calculated using the Modelflow method, which incorporates sex, age, height and mass (BeatScope 1.0 software, Finapres Medical Systems, Amsterdam, The Netherlands). Continuous recording of the above variables was obtained at 200 Hz using an analog-to-digital converter (Powerlab/16SP, ADInstruments, Dunedin, New Zealand) and later analyzed using Chart software (LabChart Pro v 7.2.5, ADInstruments). Baseline data were collected over 5 min before each intervention, and post-intervention recording began within 5 min of finishing exercise or exiting the water.

Data analysis

Calculations: Core temperature (T_c) was calculated as the maximum change from baseline during the intervention (ΔT), while muscle temperature (T_m) was calculated as either the maximum change from baseline during immersion, or immediately post-exercise (ΔT). Heat impulse was calculated using ΔT * time at that temperature for both T_c and T_m[49], to approximate the volume of heat strain and thus a unitary but admittedly simplistic index of the thermal stimulus for adaptation.

Mean arterial blood pressure (MAP) was calculated as one-third systolic (SBP) plus two-thirds diastolic blood pressure (DBP). Baseline blood pressure, HR, SV and $\dot{Q}$ data were obtained as an average of a 5-min period. MAP, SBP, DBP, SV and $\dot{Q}$ are presented as pre vs. post-intervention (within 5 min of completion); HR is presented as pre vs. peak HR attained during intervention.

Baseline diameter (D_{base}), blood flow velocity (v) and shear rate (SR) were calculated as the mean of the last minute of the baseline period, pre-cuff inflation. Peak diameter post-deflation was determined automatically using the edge-detection software. FMD was calculated as the percentage increase (FMD%) in diameter from the baseline (FMD = (D_{peak} − D_{base}) / D_{base} * 100). Recent publications[50,51] have highlighted the biased nature of using the FMD% due to its reliance on D_{base} and the known negative correlation between FMD% and D_{base}.[51] We therefore followed guidelines[51,52] utilizing allometric scaling to adjust for D_{base} with a covariate-controlled approach. These results are presented as "D_{base}-adjusted FMD%."

Statistics: All descriptives are reported as mean ± SD and all estimates are presented as mean ± SE unless stated otherwise. The cardiovascular and shear stress responses to the 2 interventions were analyzed using mixed models with random effects at the participant and participant-intervention levels, with an intervention-time interaction used to identify differences between intervention effects. Within-intervention changes are presented to assist interpretation of between intervention tests. Mixed models were used to compare between-intervention changes in FMD in 3 ways: using the raw data, FMD adjusted for baseline FMD, and FMD adjusted for D_{base}. Period effects (first or second) were included in all mixed models and a lack of carryover was assumed based on the study design rather than being formally tested for. Analyses were performed using Graphpad Prism 6 (Graphpad Software, Inc., La Jolla, California, USA), SPSS (v 19.0, SPSS Inc., Chicago, Illinois, USA), and Stata (v 13.1, StataCorp, College Station, Texas, USA) statistical software. All statistical tests were performed at the 2-sided 0.05 level with no adjustment for multiple comparisons.

Results

All participants completed both conditions. All data are of n = 10 for all variables except post-exercise T_m, for which n = 8.

Temperature

The increase in T_c during 30 min of water immersion was approximately twice as much as during 30 min of exercise ($p < 0.001$; Table 1 and Fig. 1). Peak T_m,

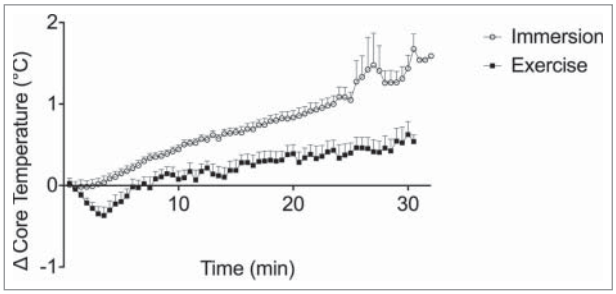

Figure 1. Change in core temperature from baseline throughout exercise and water immersion measured at 30-s intervals. Data points represent the group mean and error bars are SD.

Table 1. Thermoregulatory and systemic cardiovascular variables at baseline and immediately post-intervention (<5 min). Data are mean ± SD for baseline and post values, and mean ± SE for change scores. Baseline and post-intervention data were averaged over 5 min. T_c, core temperature; T_m, muscle temperature; SV, stroke volume; $\dot{Q}$, cardiac output; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.[a] HR post is peak HR reached during intervention.

	Baseline		Post		Change	
Variable	Exercise	Immersion	Exercise	Immersion	Exercise	Immersion
T_c (°C)	36.3 ± 0.5	36.5 ± 0.3	37.0 ± 0.7	37.7 ± 0.6 *†	+0.6 ± 0.4	+1.3 ± 0.4
T_m (°C)	–	33.7 ± 0.7	38.1 ± 0.4	38.5 ± 0.4 ‡	–	+4.7 ± 0.9
SV (mL·min^{-1})	89 ± 22	109 ± 24	89 ± 16	98 ± 38	+1 ± 9	−10 ± 9
$\dot{Q}$ (L·min^{-1})	4.8 ± 1.6	5.6 ± 1.5	6.9 ± 2.0 †	6.6 ± 1.1	+2.1 ± 0.5	+1.0 ± 0.5
MAP (mm Hg)	88 ± 7	89 ± 9	88 ± 11	82 ± 12 †	0 ± 3	−8 ± 3
SBP (mm Hg)	119 ± 11	125 ± 11	120 ± 13	116 ± 16 †	+1 ± 4	−10 ± 4
DBP (mm Hg)	72 ± 6	71 ± 9	72 ± 10	65 ± 11 †	0 ± 3	−6 ± 3
HR (beats·min^{-1})[a]	54 ± 7	54 ± 7	141 ± 12 †*	93 ± 8 †	+87 ± 3	+38 ± 3

*interaction: intervention x time ($p < 0.05$)
†different from baseline ($p < 0.05$)
‡different from post-exercise ($p < 0.05$).

measured as soon as possible (<5 min) following exercise and at the equivalent time following immersion, was higher following immersion (mean ± SD: 38.5 ± 0.4 vs. 38.1 ± 0.4°C, $p = 0.007$). The T_m at this time post-immersion was within 0.2 ± 0.3°C of the peak recorded for the entire immersion trial. Consequently, the heat impulse generated for both T_c and T_m was larger for water immersion than exercise (T_c, as calculated from the entire trial: 19.0 ± 2.2 vs. 6.0 ± 2.2°C·min, $p < 0.001$; T_m, as calculated from 10 min of recovery: 44.1 ± 1.8 vs. 30.4 ± 2.0°C·min, $p < 0.001$). Perceived body temperature was "hot" (i.e., 10 on the 13-point sensation scale) at completion of both interventions, which was rated as 'slightly uncomfortable' (2/5) for exercise and 'slightly uncomfortable'-to-'uncomfortable' (2.5) for water immersion on the discomfort scale.

Shear rate patterns

Total shear rate was increased to a greater extent after immersion than exercise (measured 5-10 min following cessation of intervention; immersion: +181 s^{-1} ± 23 s^{-1}; exercise: +104 s^{-1} ± 23 s^{-1}, both $p<0.001$, interaction $p = 0.032$, see Table 2 and Fig. 2). This represents an increase of ~250% following immersion and ~150% following exercise. Similarly, antegrade shear rate was increased differentially between interventions (immersion: +157 s^{-1} ± 22 s^{-1}; exercise: +85 s^{-1} ± 22 s^{-1}, both $p < 0.001$, interaction $p=0.004$). Retrograde shear rate was attenuated by 24 s^{-1} ± 4 s^{-1} following both interventions (both $p < 0.001$) but not differentially so ($p = 0.862$).

Flow-mediated dilation

Baseline diameter (D_{base}, i.e., before FMD) was increased following exercise (+0.40 ± 0.11 mm, $p <$ 0.001, see Table 2 and Fig. 3), but did not change following immersion (−0.04 ± 0.11 mm, $p = 0.713$, interaction: $p = 0.005$, Fig. 3). The FMD was unrelated to D_{base} before or after either intervention (all $p \geq 0.256$). Irrespective of analyses used, FMD was not reliably affected between interventions (all $p \geq 0.640$) or across time (all $p \geq 0.584$), and showed large individual variability (Fig. 4). FMD results are presented as D_{base}-adjusted FMD% based on the methods suggested by Atkinson and Batterham.[51,52]

Systemic cardiovascular responses

The stress-induced rise in HR was approximately twice as large during exercise than immersion (interaction $p < 0.001$; Table 1). $\dot{Q}$ was elevated following

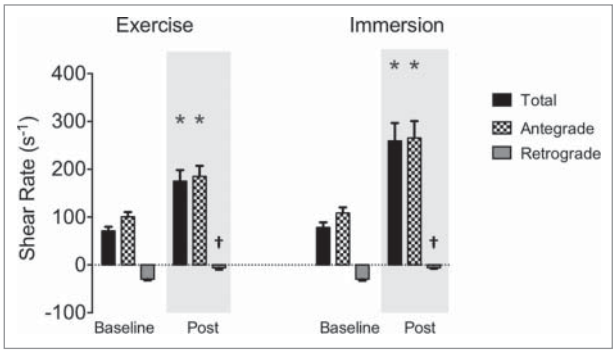

Figure 2. Superficial femoral artery total (black bars), antegrade (checked bars) and retrograde (gray bars) shear rate at baseline and post-intervention. Bars represent group mean, error bars are SE. * interaction: intervention x time ($p<0.05$); † different from baseline ($p<0.05$).

Table 2. Superficial femoral artery (SFA) hemodynamic responses at baseline and post-intervention (< 10 min). D_{base}, baseline diameter; SR, shear rate; D_{peak}, peak diameter; D_{diff}, change in diameter; FMD, flow-mediated dilation. Data are mean ± SD for baseline and post values, except for adjusted FMD, which are mean ± SE. Change scores are mean ± SE.

	Baseline		Post		Change	
Variable	**Exercise**	**Immersion**	**Exercise**	**Immersion**	**Exercise**	**Immersion**
D_{base} (mm)	6.6 ± 0.8	6.8 ± 0.9	7.0 ± 0.9 †	6.7 ± 1.0	+0.4 ± 0.1	−0.0 ± 0.1
Total SR (s^{-1})	71 ± 28	78 ± 34	175 ± 74 †	259 ± 118 *†	+104 ± 23	+181 ± 23
Antegrade SR (s^{-1})	101 ± 32	108 ± 38	185 ± 70 †	265 ± 112 *†	+85 ± 22	+157 ± 22
Retrograde SR (s^{-1})	−30 ± 9	−30 ± 10	−6 ± 12 †	−6 ± 7 †	+24 ± 4	+24 ± 4
D_{peak} (mm)	6.9 ± 0.9	7.1 ± 0.9	7.3 ± 1.0 †	7.0 ± 1.0	+0.4 ± 0.1	−0.1 ± 0.1
D_{diff} (mm)	0.3 ± 0.2	0.3 ± 0.1	0.3 ± 0.2	0.3 ± 0.2	−0.0 ± 0.1	−0.0 ± 0.1
D_{base}-adjusted FMD (%)	4.75 ± 0.83	4.69 ± 0.83	4.31 ± 0.83	4.71 ± 0.83	−0.41 ± 1.11	+0.01 ± 1.10

* interaction: intervention x time ($p<0.05$)
† different from baseline ($p<0.05$).

exercise (+2.1 ± 0.5 L·min^{-1}, $p < 0.001$) but the changes post-immersion did not reach statistical significance (+1.0 ± 0.5 L·min^{-1}, $p = 0.056$). For SV, there was no differential response following each intervention (interaction: $p = 0.400$), nor an effect of intervention per se ($p \geq 0.275$). The MAP tended to show a hypotensive response following immersion only (interaction: $p = 0.068$, immersion MAP: −8 ± 3 mmHg, $p = 0.012$; exercise: 0 ± 3 mmHg, $p = 0.944$), with 9 out of 10 participants having a reduction in MAP following immersion. The SBP was reduced by ~10 ± 4 mmHg following immersion ($p = 0.008$) but was unchanged following exercise (1 ± 4 mmHg; interaction: $p = 0.041$). The DBP responses to interventions were unclear (interaction: $p = 0.134$).

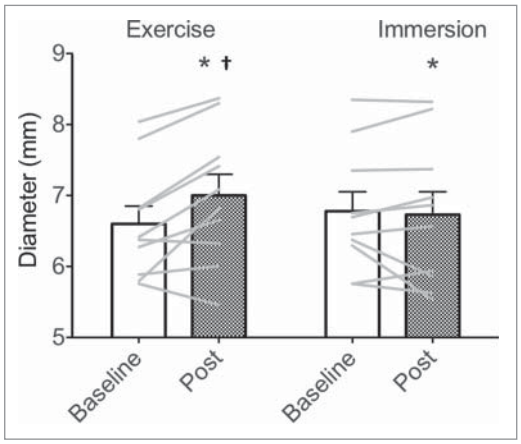

Figure 3. Absolute superficial femoral artery diameter (mm) at baseline and in response to exercise and water immersion. Bars represent group mean, error bars are SE, gray lines are individual data. * interaction: intervention x time ($p < 0.05$); † different from baseline ($p < 0.05$).

Discussion

Shear stress is a principal determinant of arteries' acute responses and adaptive remodeling (reviewed in Laughlin[4] and Newcomer[53]). The shear stress effects of heating and exercise have been studied mostly in the upper limb yet the lower limb is susceptible to arterial disease,[37] so we examined SFA shear rate responses to acute lower-limb heating via hot-water immersion, and also relative to a typical bout of predominantly lower-limb exercise. Understanding the acute responses during and/or following transient stress such as heat or exercise is important for at least 3 reasons. First, heat is part of exercise, so delineating effects of heat within or apart from exercise has mechanistic value. Second, acute responses mediate long-term adaptation, so understanding these responses improves knowledge of adaptation. Third, a major portion of the health-related benefits of regular bouts of stress is attributable to the recovery period itself, (e.g., prolonged post-exercise hypotension is likely more important in cardiovascular risk reduction than

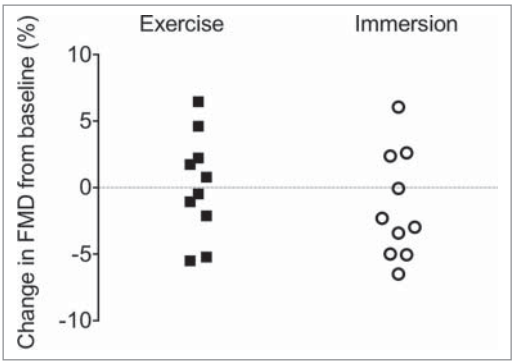

Figure 4. Individual absolute change in superficial femoral artery flow-mediated dilation (FMD, %) in response to exercise and water immersion.

is the small adaptive reduction in resting blood pressure induced by exercise training). We were interested also in systemic cardiovascular responses because the potential for lower-limb heating to provide therapeutic benefit is largely unknown as this intervention has not been comprehensively described or directly compared to exercise.

Our main findings were that: 1) antegrade shear rate in the SFA increased at least 2-fold following each of the stressors, and to a greater extent following hot-water immersion than exercise; 2) core and muscle temperatures were also higher after immersion; and 3) acute endothelium-dependent vasodilation in the SFA was not consistently altered by either intervention.

Shear rate

Increased antegrade shear rate is an important driver in vascular adaptation. To our knowledge, this is the first time that SFA shear rate has been assessed and demonstrated to be increased substantially in response to lower-limb heating. The peak SFA shear rate induced by lower-limb heating in this study (265 s^{-1}, 95%CI: 196 to 335 s^{-1}) was within the range of brachial shear rates that have been associated with acute and chronic improvements in FMD (~200 s^{-1} during handgrip exercise[7] and forearm heating,[5] ~230 s^{-1} during cycling[5]), but lower than others (~350 s^{-1} during forearm heating,[10] ~450 s^{-1} during cycling[8]). However, in the literature there is considerable variation in brachial shear rate between very similar forearm heating protocols (~200 s^{-1}[5] vs. ~350 s^{-1}[10]). Contextualising the shear changes demonstrated here is therefore challenging, as comparative data in the lower-limb vessels are scarce – the lower-limb arteries appear to be persistently overlooked in studies of shear rate manipulation. However, a human MRI study found smaller mean and peak shear rates for the SFA than brachial artery, by ~33% and ~20%, respectively,[54] so the lower SFA shear rates found in our study than in some studies on the brachial artery may be anticipated.

It remains unknown whether a threshold exists above which shear rate must be increased to induce adaptation, and if so, whether it differs between limbs or in healthy versus diseased vessels. Until such evidence is available in humans, the implications of our shear stress findings (Table 2) are difficult to quantify or comment on. Importantly though, *in vitro* studies on animal models indicate that endothelial nitric oxide synthase upregulation in endothelial cells responds to shear stress in a dose-dependent manner.[55] Therefore, *any* increase in antegrade shear rate may induce some adaptation, if repeated appropriately.

The lesser increase in shear rate when measured after exercise than after immersion possibly reflects a methodological bias. The peak of the exercise induced-shear response was likely to have been missed by our protocol because the largely-metabolic stimulus was already decaying following exercise, whereas the heat stimulus following lower-limb heating was still mostly present. However, the range of shear rates reported in this study for both immersion and exercise were not dissimilar to those exhibited in other studies manipulating shear in conduit vessels,[5,7] as mentioned above. The lower shear rate after exercise could also be partly due to the increased D_{base} induced by the exercise. Furthermore, the difference in T_c and/or T_m could contribute to the shear rates generated, as the immersion protocol resulted in higher temperatures in both the core and muscle; however a matched-temperature study design would be required to resolve this, and is a possible future research direction. Regardless of the comparison between interventions however, the finding of an elevated shear rate, in particular antegrade, following lower-limb heating is significant due to the important role of repetitive antegrade shear stress in promoting vascular adaptation.

Systemic cardiovascular strain

Knowledge of the MAP-lowering effects of hot-water immersion alone, regardless of the comparison with exercise, is valuable because post-stress hypotension is important in its own right and for mediating cardiovascular adaptations, as mentioned above and described below. The heating protocol was effective in inducing a hypotensive effect in recovery whereas exercise was not in this study. The average MAP reduction post-immersion of 8 mmHg (95%CI: −3 to −12 mmHg) was similar to that found previously following passive heating.[24] Whether repetitive heating (e.g., a 6-week conditioning intervention) would lower baseline blood pressure is unknown.

As hypotension appears necessary for expanding plasma volume,[56] heat stress may be a useful such

stimulus. Convertino et al.[19] demonstrated that thermal effects alone accounted for 40% of the exercise-induced plasma volume expansion. Larger blood volume, even via the plasma alone, improves cardiovascular function at rest and across the range of cardiovascular capacity, by increasing stroke volume,[57] lowering heart rate and increasing aerobic capacity.[58,59] The significant reductions in MAP demonstrated here may be important in this role, although the dose-response relations of acute hypotensive duration and magnitude required to provoke this hypervolemia effect are not yet fully known.

Hot-water immersion additionally increased heart rate and tended to increase cardiac output, as occurs with various forms of passive heat stress.[24,28] Increased heart rate and cardiac output with a concomitant, albeit non-significant, reduction in blood pressure would indicate the heat stimulus provides an attenuated increase in cardiac workload compared to that for an equivalent increase in heart rate during exercise.[27] This increased cardiac work plus the increased heart temperature as discussed below, could be interpreted as a gentler but perhaps appropriate stressor for those with contraindications to exercise, i.e., increased cardiac work pertaining to volume and temperature changes rather than pressure changes. Overall, these results indicate that hot-water immersion may have potential to induce at least some of the acute hemodynamic and cardiovascular effects associated with exercise.

Temperature

Core and muscle temperature increased significantly, and to a greater extent upon completing immersion than exercise. As mentioned above, this difference may have impacted on the shear rate generated following interventions, but regardless of the temperature-dependence of the shear rate response, heating of the heart and skeletal muscle can mediate other beneficial adaptations including muscle growth and stress response proficiency.[20,24,25] The thermal impulse for the 'core' and gastrocnemius during early recovery was ~3 times larger following the passive warming, but as for the shear stress response, it is unresolved as to whether this would confer a similarly-larger stimulus for adaptation; e.g., what is the threshold perturbation, and for which adaptation in which tissues? Nevertheless, it seems reasonable to conclude that lower-limb heating may be a suitable stimulus to induce such temperature elevations independent of exercise.

Flow-mediated dilation

FMD has been used as a "vascular health" outcome in thousands of studies. Despite its widespread usage, a systemic understanding of FMD (and its components) to different stimuli (exercise[36] and discrete stressors) is still lacking. The lower-limb arteries are seldom studied; FMD is assessed predominantly in the brachial artery, yet we are often most interested in the lower limbs for reasons described in the Introduction. Where it has been looked at, the arterial function in the upper limb appears to be a poor predictor of that in the lower limb.[64] Furthermore, much remains unknown about the acute vascular effects of exercise (or other stressors); in particular the relationship of the shear stimulus, the resultant acute FMD response, and the associated long-term adaptation. This study provided a unique opportunity to assess the acute responses of 2 different interventions targeting the same outcome response (i.e., increased antegrade shear in the SFA). Moreover, no comparative data exist for the effect of *heating* on lower-limb FMD. Only one study to our knowledge has looked at the effect of acute exercise on lower-limb FMD; this was within one hour of finishing a marathon, and femoral FMD was reduced.[60]

With this background in mind, a hypothesis regarding the likely SFA FMD change was difficult, as the acute effects of exercise (and even more so, other interventions) on FMD (in the SFA as well as other arteries) are both equivocal and insufficiently characterized at present. These effects depend on timing of measurement, intensity, duration and mode of exercise, the cohort studied and factors such as diameter changes intrinsic to the study.[36] Indeed, conflicting data exist, with several acute exercise studies reporting no change in FMD with an increase in D_{base},[60,61] as in this study, although others have described a reduction in FMD with increased D_{base} following exercise.[62,63] Due to the paucity of comparative data for our study, we did not expect to be able to formulate a hypothesis on the lower-limb responses based on previous findings of upper-limb FMD responses during similar stress.

Several factors may explain the lack of change in FMD. Oxidative stress generated during exercise, particularly higher-intensity exercise, has been suggested to explain the reported reduction in FMD following exercise. However, exercise training improves antioxidant status;[64] therefore, given that our participants typically exercised at least 3 d per week, they may have been better able to tolerate the acute oxidative stimulus generated by the intervention, resulting in little or no perturbation of FMD. Similarly, the exercise was of moderate intensity (65-75% age-predicted HR maximum), which may not have induced much oxidative response in this cohort. Substantial variability in both D_{base} and FMD responses would also conceal any small effect of either intervention. The variation shown here seemed large (Table 2 and Fig. 4); however most studies of this nature do not adequately present individual variation, making comparison difficult. There were no significant correlations evident between FMD and shear rate or diameter to help explain this variability (data not presented). Acute changes in diameter, although controlled for here with the allometric scaling, may present a limitation for the use and interpretation of FMD in an experimental crossover setting.

Application

Some individuals may stand to benefit from such a stressor more than others; for example, patients with peripheral arterial disease, who have a severely limited exercise capacity as a consequence of their condition. Repeated dry sauna therapy in a peripheral arterial disease cohort demonstrated a significant reduction in symptoms and an improvement in several measures of leg perfusion;[65,66] however, mechanisms for this and measures of cardiovascular response were not included. Patients with heart failure have also been treated with sauna resulting in improved cardiac function and reduction of arrhythmias.[15,30,31] The extent to which heat can provide health benefits in clinical groups appears promising but has not yet been fully explored.

Conclusion

Heat, administered by sitting with the lower limbs immersed in hot water may have potential to be used as a stand-alone stressor, at least as a way to induce transient increased peripheral artery shear rate, increased core and muscle temperature, and transitory hypotension. The lower-limb heating protocol was well-tolerated in this young, healthy group. Future studies should focus on the tolerance and physiological responses to a passive heat stimulus such as this in other population groups, and importantly, the adaptations to repetitive exposure. Patient populations, who have much to gain from exercise but often have a compromised ability to perform exercise, would benefit from a potent and time-efficient means of inducing the health-related adaptations of exercise by such alternative methods.

Abbreviations

BP	blood pressure
D_{base}	baseline diameter
DBP	diastolic blood pressure
D_{peak}	peak diameter
FMD	flow-mediated dilation
HR	heart rate
MAP	mean arterial pressure
$\dot{Q}$	cardiac output
SBP	systolic blood pressure
SFA	superficial femoral artery
SR	shear rate
SV	stroke volume
T_c	core temperature
T_m	muscle temperature
ΔT	change in temperature

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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