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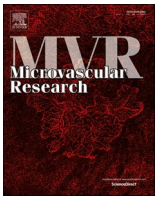

Acute impact of aerobic exercise on local cutaneous thermal hyperaemia

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ABSTRACT

Little is known about the acute changes in cutaneous microvascular function that occur in response to exercise, the accumulation of which may provide the basis for beneficial chronic cutaneous vascular adaptations. Therefore, we examined the effects of acute exercise on cutaneous thermal hyperaemia. Twelve healthy, recreationally active participants (11 male, 1 female) performed 30-minute cycling at 50 % (low-intensity exercise, LOW) or 75 % (high-intensity exercise, HIGH) maximum heart rate. Laser Doppler flowmetry (LDF) and rapid local skin heating were used to quantify cutaneous thermal hyperaemia before (PRE), immediately following (IMM) and 1-h (1HR) after exercise. Baseline, axon reflex peak, axon reflex nadir, plateau, maximum skin blood flow responses to rapid local heating (42 °C for 30-min followed by 44 °C for 15-min) at each stage were assessed and indexed as cutaneous vascular conductance [CVC = flux / mean arterial blood pressure (MAP), PU·mm Hg^{-1}], and expressed as a percentage of maximum (%CVC_{max}). Exercise increased heart rate (HR), MAP and skin blood flow (all $P < 0.001$), and to a greater extent during HIGH (all $P < 0.001$). The axon reflex peak and nadir were increased immediately and 1-h after exercise (all comparisons $P < 0.01$ vs. PRE), which did not differ between intensities (peak: $P = 0.34$, axon reflex nadir: $P = 0.91$). The endothelium-dependent plateau response was slightly elevated after exercise ($P = 0.06$), with no effect of intensity ($P = 0.58$) nor any interaction effect ($P = 0.55$). CONCLUSION: Exercise increases cutaneous microvascular axonal responses to local heating for up to 1-h, suggesting an augmented sensory afferent function post-exercise. Acute exercise may only modestly affect endothelial function in cutaneous microcirculation.

1. Introduction

The positive cardiovascular effects of chronic exercise on the prevention/amelioration of cardiovascular disease (CVD) and CVD risk factors are well documented (Green et al., 2008; Blair and Morris, 2009). Exercise has direct benefits on the entire vascular tree, inducing functional and structural vascular adaptations in both macrovessels (Tinken et al., 2008) and microvessels, including the cutaneous microvasculature (Padilla et al., 2011). The skin and its microvasculature play a critical role in blood flow regulation, sensory function and thermoregulation (Johnson et al., 2014). The regulation of body temperature, or homeothermy, is achieved primarily by autonomic manipulation of the cutaneous microvasculature and sweat glands (Smith and Johnson, 2016) through sympathetic noradrenergic and sympathetic cholinergic efferent neurons. Non-neuronal mechanisms, including the local activation of chemically-mediated mechanisms, further support alterations in cutaneous blood flow (Johnson et al., 2014).

Rapid local skin heating elicits a biphasic vasodilatory response (Minson, 2010). The initial peak of vasodilation is mediated via an axon reflex through local sensory and adrenergic nerves (Minson et al., 2001; Houghton et al., 2006; Hodges et al., 2008). Following this, a more prolonged vasodilation, or plateau, is established, which is predominantly mediated by nitric oxide (NO) (Choi et al., 2014) but is also dependent on other vasoactive products, such as endothelium-derived hyperpolarizing factors (EDHFs), and sympathetic axon-derived neuropeptides (Hodges et al., 2008). This largely endothelium-dependent plateau response can provide an index of microvessel function, the impairment of which may be a critical initial contributory step in the development of CVD and associated risk factors (Holowatz et al., 2008). Indeed, local skin heating protocols have been used to index cutaneous microvascular (dys)function when comparing healthy and diseased individuals, including those associated with ageing (Black et al., 2008),

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diabetes mellitus (Fuchs et al., 2017) and physical (in)activity (Tew et al., 2011b; Atkinson et al., 2018), as well as before and after interventions (Brunt et al., 2016; Woodward et al., 2018).

The benefits of chronic exercise on the cutaneous microvasculature are well known. Exercise training increases cutaneous axon reflex responses to local heating (Tew et al., 2011a), as well as vasodilatory capacity and vascular reactivity in response to both neural, e.g., exercise or whole-body heat stress, and non-neural stimuli, e.g., local heating or pharmacological administration (Boegli et al., 2003; Black et al., 2008; Simmons et al., 2011; Lanting et al., 2017). These long-term functional cutaneous vascular adaptations may be mediated, at least in part, through regular alterations to the mechanical loading of vessels (Lu and Kassab, 2011), locally released biochemical products (Tinken et al., 2010) and/or episodic increases in blood flow and/or skin temperature (Carter et al., 2014; Green et al., 2017). Assessment of changes in skin microvasculature in response to acute exercise may provide insight into the basis for beneficial chronic vascular adaptations (Green et al., 2011). Furthermore, determination of potential skin microvascular function changes in response to acute exercise are also important to understand in order to develop optimal assessment protocols of microvascular function that may take place after bouts of exercise/physical activity, or other conditions that induce alterations in skin blood flow, such as heat exposure.

During exercise, as heat production from active musculature increases, various neurally-mediated skin blood flow reflexes occur (Smith and Johnson, 2016). After some initial sympathetic vasoconstriction to aid redistribution of blood flow to the active musculature, and once a core/body temperature threshold is surpassed, sympathetic cholinergic mediated active skin vasodilation occurs until a plateau of blood flow is established. To date, little work has explored the impact of acute exercise on the skin microcirculation. Previous studies considering the acute effects of exercise have mainly focused on macrovascular function and have observed mixed results (Dawson et al., 2013), likely owing to differences in methodology adopted in these studies. The studies do suggest that exercise intensity represents a key factor influencing the magnitude and direction of post-exercise changes in vascular health, for example, higher intensity exercise results in impaired macrovascular function (Dawson et al., 2013). There is a lack of data available concerning the effects of acute exercise on cutaneous microvessel function with divergent responses to acetylcholine iontophoresis and post-occlusion reactive hyperaemia (PORH) after incremental exhaustive rowing in sedentary and trained athletes (Stupin et al., 2018). The aim of this study was, therefore, to investigate the effect of acute exercise on local cutaneous thermal hyperaemia. A secondary aim of this study was to investigate the impact of exercise intensity on any potential changes to cutaneous thermal hyperaemia. The hypotheses of the study were that the cutaneous plateau response to local heating would be impaired after high, but not low, intensity exercise (Birk et al., 2013; Stupin et al., 2018).

2. Materials and methods

2.1. Participants

Participants (n = 12, 1 female) who were recreationally active (as assessed by short IPAQ physical activity questionnaire, <4 sessions per week), healthy (as assessed by PARQ health screening form), young (age range 20–40 years, mean = 25.7 ± 5 years), and non-smokers were recruited. Individuals with cardiovascular disease history, local forearm infection, limitations of physical activity, smokers or persons taking medication (including oral contraception) were excluded. The sample size (effect size of 0.75, beta = 0.80, alpha = 0.05) was calculated using previously reported data (Birk et al., 2013; Stupin et al., 2018). Participants were informed of the procedures prior to participation and provided written and verbal informed consent. This study was approved by the Liverpool John Moores University Research Ethics Committee in accordance with the Declaration of Helsinki (ref: 17SPS010). Height and weight measurements were collected at the first laboratory visit (mean height [m] 1.8 ± 0.1, weight [kg] 78 ± 13, BMI 24 ± 3).

2.2. Experimental design

Participants attended the laboratories on two occasions for 30-min of exercise on a cycle ergometer (Lode Corival CPET, Lode B. V., Groningen, NL) at 50 % (low-intensity exercise, LOW) or 75 % (high-intensity exercise, HIGH) age-predicted maximum heart rate (HR_{pred} = 208 − [0.7 × age]) (Tanaka et al., 2001; Birk et al., 2013) (Fig. 1). Prior to (PRE), immediately following (IMM), and 1-h following the cessation of exercise (1HR), forearm cutaneous thermal hyperaemia was assessed. The order of the exercise visits was randomised and counterbalanced, separated by 4–7 days, and visits were performed at the same time of day to minimise circadian variation (Jones et al., 2010). The female participant was tested in the early follicular stage (days 1–7) of the menstrual cycle to minimise hormonal involvement (Charkoudian et al., 2000). Participants reported to the laboratories having fasted from food for 4 h, abstained from alcohol and caffeine for 16 h, and refrained from exercise for 24 h prior to testing. Participants were advised to ingest 500 ml of water prior to testing to avoid dehydration. All testing visits took place in the same humidity and temperature controlled laboratory (23.3 ± 0.28 °C).

2.3. Cutaneous thermal hyperaemia assessment

Laser Doppler flowmetry (LDF; Moor Instruments VP2/PH2 laser probe, Moor Instruments, Axminster, UK) and local skin heating protocols were used to quantify cutaneous thermal hyperaemia (Roustit and Cracowski, 2013). Participants were positioned supine for instrumentation and baseline stabilisation. LDF probes were attached using adhesive tape to the volar aspect of the non-dominant forearm of participants, avoiding hair and visible veins. Resting baseline measurements were collected for 5 min at local skin temperature. Local skin heating, using heating units with LDF probe housing ports (Moor Instruments VHP-1 heating probe, Moor Instruments, Axminster, UK), commenced thereafter at a rate of 0.1 °C/s to 42 °C and was held for 30-min, eliciting an initial peak vasodilation within 10-min, and a rebound nadir. Following this, skin blood flow continued to increase for 20-min until a stable plateau was established. Local skin temperature was then increased to 44 °C (0.1 °C/s) for a further 15-min, after which a maximal value of cutaneous local vasodilation was produced (Minson et al., 2001; Minson, 2010).

Local heating of skin may be susceptible to a 'desensitisation' phenomenon, whereby a single skin site which is previously exposed to a heating protocol has a reduced functional response upon subsequent heating (Ciplak et al., 2009; Frantz et al., 2012). In order to avoid this issue for the sequential heating protocols employed in the current study, three separate LDF probes were positioned on the forearm, separated by at least 2 cm. The three separate sites allowed for the comparison of skin function at sites not previously heated (PRE, site A; IMM, site B; 1HR, site C). Digital photographs were taken of probe placements, and anatomical landmarks were annotated and measured for reproducibility in future visits.

Intermittent systolic and diastolic blood pressure and heart rate were measured during the local heating protocols and exercise using an automated sphygmomanometer (Dinamap Procare 100, GE Medical Systems Ltd., Buckinghamshire, UK). Mean arterial pressure (MAP) was calculated using MAP = 2/3 diastolic BP + 1/3 systolic BP. Intra-exercise heart rate was continuously monitored using short-range telemetry (Polar FT1 and T31, Polar UK). Local skin temperature was recorded directly from the LDF probes/heating units.

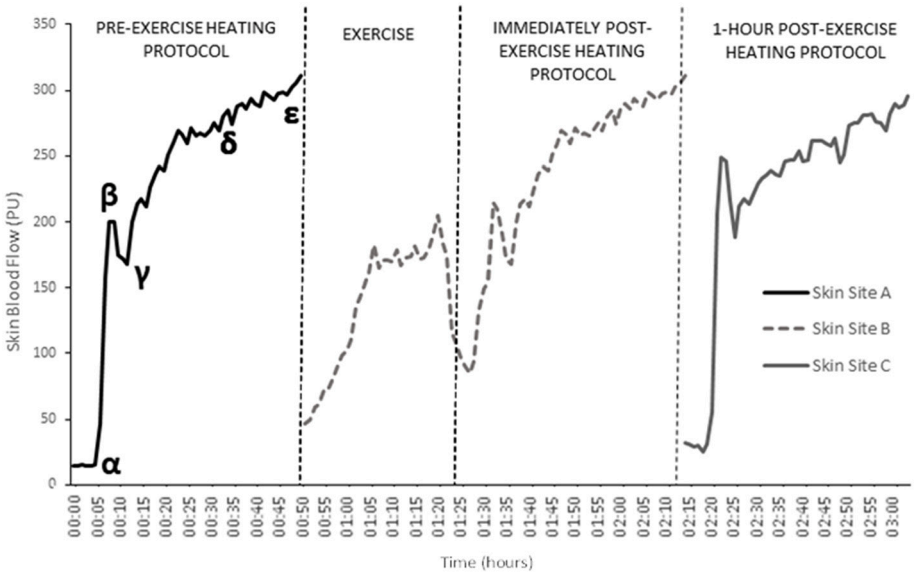

Fig. 1. Representative example tracing of skin blood flow responses to local heating before and after exercise at 3 distinct sites. Baseline measurements were recorded at local skin temperature (α). Local heating produces an initial axon-mediated reflex vasodilation that peaks within 10-min of heating (β), followed by a subsequent nadir (γ). Heating is maintained for 30-min at 42 °C, by the end of which a stable "plateau" response is achieved (δ). Heating then increases further to 44 °C; the skin microvascular response reaches a stable maximal plateau after around 20-min of heating (ε), at which point local heating ceases. Abbreviations used: PU, arbitrary perfusion units.

2.4. Data analysis

Microvascular flux (movement of red blood cells within the skin microvessels) was collected and quantified in arbitrary perfusion units (PU) by the LDF probes. Flux measurements were collected online (PowerLab 4/25, ADInstruments Ltd., Oxford, UK) and stored for analysis at a later date (LabChart v8.1.8, ADInstruments Ltd.). Minute averages from the recorded data were extracted and stored for offline analysis. Resting values were averaged over 5-min; the axon reflex peak was defined as the largest minute average value to occur after commencement of heating within 10-min, and the axon reflex nadir as the lowest minute average following the axon reflex peak within the same 10-min. The 42 °C plateau value was defined as the minute average prior to increasing heat to 44 °C. Maximal values of flux were defined as the average of the final 5-minutes flux at 44 °C. Protocols for heating were programmed and saved offline (moorVMS-PC v4.0.6, Moor Instruments Ltd.). LDF flux values were divided by MAP to provide an index of cutaneous vascular conductance (CVC = flux / MAP, PU·mm Hg^{-1}), to account for potential effects of changes in blood pressure on skin blood flow, and expressed as a percentage of maximum (%CVCmax = [CVC / CVC_{max}] × 100).

2.5. Statistical analysis

A linear mixed model was employed with stage (3 levels: PRE vs. IMM vs. 1HR) and intensity (2 levels: LOW vs. HIGH) as factors for each timepoint of the local heating response, e.g., baseline, axon reflex peak, axon reflex nadir, plateau and maximum. Haemodynamics and local skin temperatures pre/intra exercise were compared using linear mixed models, with main effects of time (pre- vs intra-exercise) and intensity of exercise (LOW vs. HIGH). Analyses were performed using SPSS (IBM SPSS Statistical Package 24). Statistical significance was set at $P < 0.05$ and data expressed as mean ± 1 standard deviation.

3. Results

3.1. Exercise responses

Exercise induced significant changes to all haemodynamic variables (Table 1). By design, exercise work rate was significantly higher during HIGH and there were significant differences between intra-exercise LOW and HIGH data in all variables except diastolic blood pressure and MAP, clearly indicating that the two testing conditions were physiologically distinct from one another.

3.2. Blood pressure responses

The MAP responses during the PRE, IMM and 1HR local heating protocols are presented in Table 2. There was no main effect of intensity ($P = 0.19$) and there was no main effect of stage ($P = 0.25$). There was a significant interaction between stage and time point ($P = 0.02$), whereby MAP was well maintained during local heating pre-exercise; it decreased by approximately 5 mm Hg approximately 45–60 min after exercise and returned back to pre-exercise baseline 1.5–2 h post-exercise.

3.3. Cutaneous thermal hyperaemia

Example tracings of raw skin microvascular blood flux responses to local heating around an acute bout of exercise are illustrated in Fig. 1.

Table 1
Exercise responses immediately following 30-min of low and high intensity exercise compared to baseline. Data reported as mean ± 1 SD.

	Low-intensity exercise		High-intensity exercise		Comparison		
	Pre-exercise	Intra-exercise	Pre-exercise	Intra-exercise	Pre vs. Intra-exercise	Low vs. high intensity	Time × intensity interaction
Systolic BP (mm Hg)	119 ± 9	138 ± 10	118 ± 8	156 ± 19	<0.001	0.025	0.016
Diastolic BP (mm Hg)	64 ± 8	71 ± 11	62 ± 5	79 ± 20	0.002	0.435	0.135
MAP (mm Hg)	82 ± 8	93 ± 9	81 ± 5	105 ± 17	<0.001	0.118	0.033
Heart Rate (beats·min^{-1})	54 ± 8	104 ± 6	55 ± 9	147 ± 6	<0.001	<0.001	<0.001
Forearm skin temperature (°C)	31.5 ± 1.2	32.0 ± 1.3	31.7 ± 1.4	33.0 ± 1.0	<0.001	0.012	0.036
Work (W)	–	84 ± 15	–	152 ± 25	–	<0.001	–

Table 2
Mean arterial blood pressure (mean ± 1 SD) responses before, immediately following, and 1-h after 30-min of exercise at LOW and HIGH intensities. $P < 0.05$ for interaction of timepoint * stage.

Stage	Pre-exercise					Immediately post-exercise					1 h post-exercise				
Time-point	Baseline	Axon Peak	Axon Nadir	Plateau	Max	Baseline	Axon Peak	Axon Nadir	Plateau	Max	Baseline	Axon Peak	Axon Nadir	Plateau	Max
LOW (mm Hg)	81 ± 6	80 ± 6	80 ± 7	80 ± 5	79 ± 7	83 ± 7	82 ± 9	80 ± 6	82 ± 8	82 ± 6	81 ± 6	81 ± 7	81 ± 7	81 ± 7	82 ± 7
HIGH (mm Hg)	80 ± 5	79 ± 6	79 ± 6	77 ± 5	78 ± 4	83 ± 5	81 ± 6	80 ± 4	79 ± 6	76 ± 6	76 ± 5	77 ± 5	76 ± 6	78 ± 7	78 ± 6

There was no main effect of stage ($P = 0.63$) or intensity ($P = 0.39$), nor an interaction effect ($P = 0.16$) for the maximal CVC response to 44 °C heating (LOW: PRE, 3.8 ± 1.1 PU·mm Hg^{-1}; IMM 3.9 ± 0.9 PU·mm Hg^{-1}; 1HR, 3.6 ± 1.2 PU·mm Hg^{-1}. HIGH: PRE 3.3 ± 0.8 PU·mm Hg^{-1}; IMM, 3.5 ± 0.9 PU·mm Hg^{-1}; 1HR, 3.8 ± 0.3 PU·mm Hg^{-1}). Data are therefore presented as $\%CVC_{max}$.

3.4. Comparison of cutaneous thermal hyperaemia

3.4.1. Baseline

There was a main effect of intensity ($P < 0.001$) and stage ($P < 0.001$), as well as an interaction between intensity and stage ($P < 0.001$). LOW resulted in an increase in baseline $\%CVC_{max}$ at IMM (PRE 6.2 ± 1.7 vs IMM 16.2 ± 11.3 $\%CVC_{max}$, $P = 0.03$) and was still increased at 1HR (PRE vs 1HR 10.5 ± 6.1 $\%CVC_{max}$, $P = 0.05$), with no difference between IMM and 1HR ($P = 0.29$). HIGH increased baseline at IMM (PRE 7.0 ± 3.6 vs IMM 46.6 ± 14.2 $\%CVC_{max}$, $P < 0.001$), with baseline blood flow returning to pre-exercise levels after 1HR (PRE vs 1HR 11.2 ± 6.7 $\%CVC_{max}$, $P = 0.22$). Baseline $\%CVC_{max}$ at IMM was significantly greater than at 1HR ($P < 0.001$). Baseline $\%CVC_{max}$ IMM was greater following HIGH than LOW ($P < 0.001$), but there was no difference in baseline $\%CVC_{max}$ at 1HR ($P = 0.79$) (Fig. 2).

3.4.2. Axon reflex peak

There was a main effect of stage ($P < 0.001$), but no main effect of intensity ($P = 0.34$) and no interaction effect of stage and intensity ($P = 0.37$). The axon reflex peak was increased IMM compared to PRE (PRE 60.0 ± 16.7 vs IMM 72.7 ± 16.4 $\%CVC_{max}$, $P = 0.001$). The axon reflex peak was still increased 1HR compared to PRE (PRE vs 1HR 75.3 ± 17.1 $\%CVC_{max}$, $P = 0.001$). There was no difference between IMM and 1HR responses ($P = 0.99$).

3.4.3. Axon reflex nadir

There was a main effect of stage ($P < 0.001$), but no main effect of intensity ($P = 0.91$) and no interaction effect of stage and intensity ($P = 0.29$). The axon reflex nadir, compared to PRE, increased at both IMM (PRE 46.8 ± 17.7 vs IMM 64.0 ± 17.3 $\%CVC_{max}$, $P < 0.001$) and at 1HR (PRE vs 1HR 59.3 ± 17.5 $\%CVC_{max}$, $P = 0.01$), with no significant difference between IMM and 1HR responses ($P = 0.60$).

3.4.4. Plateau response

There was no main effect of stage ($P = 0.06$), intensity ($P = 0.58$), nor any interaction effect of stage and intensity ($P = 0.55$) for plateau responses. There was a modest, but non-significant, increase to plateau responses IMM compared to PRE (PRE 85.5 ± 7.1 vs IMM 90.3 ± 3.4 $\%CVC_{max}$, $P = 0.06$). There was no difference in plateau responses at 1HR compared to PRE (PRE vs 1HR 88.8 ± 11.7 $\%CVC_{max}$, $P = 0.55$).

4. Discussion

The aim of this study was to investigate the effects of acute exercise on local cutaneous thermal hyperaemia in healthy young individuals.

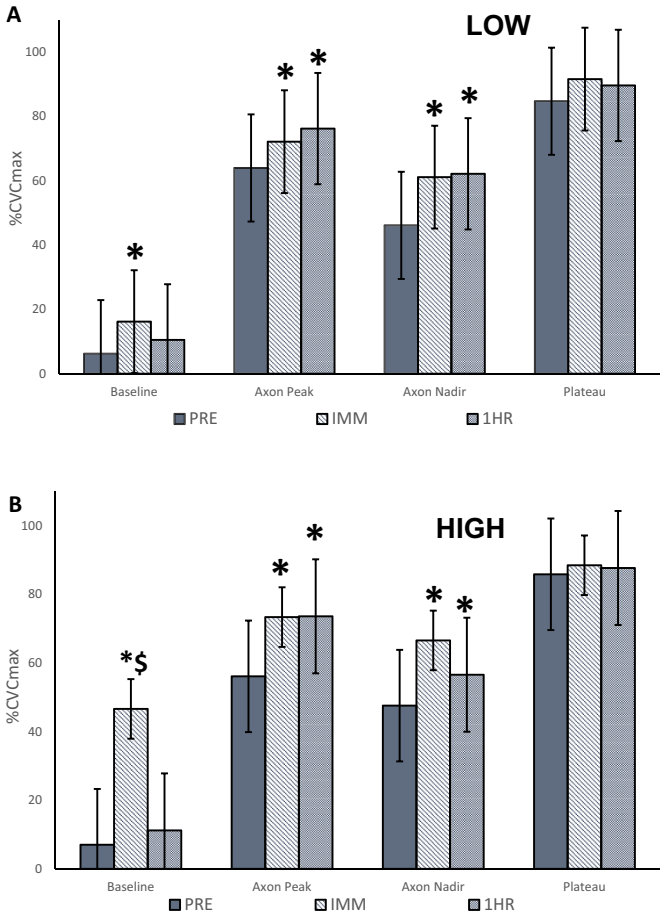

Fig. 2. Cutaneous thermal hyperaemia responses to rapid local heating, expressed as $\%CVC_{max}$, before, immediately and 1-h after A) low-intensity exercise, and; B) high-intensity exercise. *$P < 0.05$ vs. pre-exercise within each intensity, $^{\$}P < 0.05$ vs. Baseline IMM during LOW.
$\%CVC_{max}$, percentage of maximal cutaneous vascular conductance; PRE, pre-exercise responses; IMM, immediately post-exercise responses; 1HR, 1-hour post-exercise responses.

Cutaneous blood flow responses to rapid local heating were assessed before, immediately and 1-h after 30-min of low or high-intensity continuous cycling exercise. The main findings are twofold; 1) an acute bout of exercise causes an increased cutaneous axonal response following exercise, which sustains for at least 1-h post-exercise and was not dependent on exercise intensity, and 2) cutaneous endothelium-dependent vasodilation was largely unaffected by an acute bout of exercise. These findings have implications for the understanding of chronic skin microvascular adaptations to repeated exercise bouts, as well as the design of protocols involving the assessment of local cutaneous microvascular function.

Rapid local skin heating protocols elicit an initial axon-mediated vasodilation (or peak), followed by a more prolonged vasodilation, or plateau, response. In both phases, vasodilation occurs through complex pathways that lead to the production of NO and smooth muscle relaxation via hyperpolarization from EDHFs (Johnson et al., 2014). In the present study, acute exercise increased the axon reflex-mediated vasodilation peak (as well as the subsequent rebound nadir). The mechanisms of the axon reflex and nadir are not entirely clear, but are purportedly mediated via a number of mechanisms, including activation of transient receptor potential vanilloid-1 receptors in C-fibre afferent nociceptive neurons (Wong and Fieger, 2010), and to a lesser extent, neurokinin-1 receptor activation by substance P and calcitonin gene-related peptide released by nociceptive neurons (Schmelz et al., 1997), β2 receptor activation via norepinephrine and neuropeptide Y released by sympathetic adrenergic nerves (Houghton et al., 2006; Hodges et al., 2008; Hodges and Sparks, 2013), as well as EDHF-mediated activation of calcium activated potassium (KCa) channels (Brunt and Minson, 2012). It is unknown whether exercise augmented any of these mechanisms, e.g., local nociceptive nerve activation, neurotransmitter release and/or responsiveness of the vasculature to these neurotransmitters, which would have contributed to the elevated post-exercise cutaneous axon reflex and nadir. Such alterations could have been mediated via exercise and/or thermoregulatory-induced adjustments, such as increases in sympathetic nerve activity (Ray and Wilson, 2004; Smith and Johnson, 2016), skin blood flow and/or skin/core temperatures. It is likely that core temperature did increase during exercise and to a greater extent during HIGH, given the greater skin blood flow response compared to LOW.

The implications of an elevated cutaneous axon reflex after exercise are not entirely clear. An increased axon reflex may minimise the heat transferred to local tissues to protect the skin from damage (Minson et al., 2002) and reduce the risk of pressure-induced ischaemic damage (Fromy et al., 2010). That said, the vasodilation associated with the axon reflex is transient so any alterations to the amount of heat transferred to the local tissues may be minimal. Given the role of sensory nerves in the cutaneous axon reflex and nadir, it is unclear if cutaneous thermal sensory function is modified after an exercise bout; findings of limited research are equivocal (Kemppainen et al., 1985; Ruble et al., 2005). A recent study (Stupin et al., 2018) reported that cutaneous vascular responses to post-occlusion reactive hyperaemia (PORH) were unchanged after incremental rowing exercise to exhaustion in sedentary individuals. These findings are somewhat inconsistent with the present study's findings of an elevated axon reflex response post-exercise and are likely due to differences in the method of vascular function assessment and the mechanisms of the cutaneous responses between local thermal and physical stimulation (Berghoff et al., 2002; Roustit and Cracowski, 2013).

In the present study, cutaneous endothelium-dependent vasodilation was largely unaffected by an acute bout of exercise. The largely endothelium-dependent plateau response to local heating was modestly increased ($P = 0.06$, Cohen's D effect size 0.96) immediately after exercise with no effect of intensity, suggesting cutaneous vascular endothelial function was possibly improved by acute exercise. These findings are somewhat in contrast to previous studies investigating acute exercise effects on conduit vessels, which reported reductions or increases in FMD post-exercise (Gonzales et al., 2011; Johnson et al., 2012; Dawson et al., 2013). It has been suggested that 1) an immediate decrease in macrovascular function occurs after exercise cessation, which is followed by a (supra)normalisation response, and, 2) the magnitude of the nadir and (supra)normalisation and duration of this biphasic pattern of response is influenced by numerous factors (e.g., the exercise stimulus, the aerobic capacity of the subject population, methodological factors, changes in arterial diameter, and antioxidant status) (Dawson et al., 2013). Differences in micro- vs. macrovascular function responses to acute exercise are likely due to inherent differences in structure and function between conduit and skin vessels, as well as the different intra-exercise haemodynamic changes that occur in the more proximal 'conduit' macrovessels relative to the distal skin microvasculature (Rizzoni et al., 2015). Furthermore, although both the FMD response and the plateau response to local skin heating rely on NO, the latter is more heavily influenced by NO (Minson, 2010). These differences in macro vs. microvascular function could underlie these disparate findings of conduit and cutaneous blood vessel responses to acute exercise. Stupin et al. (2018) observed elevated cutaneous vascular responses to acetylcholine iontophoresis after incremental rowing exercise, which is consistent with the modest elevation in the endothelium-dependent plateau response to local heating in the present study and might be attributable to exercise-induced increased anti-oxidative capacity (Stupin et al., 2018) and/or elevations in NO bioavailability, and/or endothelium sensitivity to NO.

A secondary aim of the present study was to investigate the impact of exercise intensity on any potential changes to cutaneous thermal hyperaemia. Despite clear differences in the cardiovascular, as well as many other, responses between the LOW and HIGH trials in the present study, there was no effect of intensity on the post-exercise elevated axon reflex and nadir. These findings suggest that changes in cutaneous vascular axon reflexes are not dependent on the intensity of the preceding exercise bout. In contrast to the aforementioned responses in a sedentary cohort in the previous study by Stupin et al. (2018), blunted cutaneous vascular responses to PORH and acetylcholine iontophoresis were evident after incremental exercise to exhaustion in a trained cohort. Given that decreases in macrovascular function post-exercise are more likely with increased intensity and duration of the preceding exercise bout (Birk et al., 2013), the higher absolute exercise workloads and duration in the trained rowers possibly caused the impaired cutaneous vascular function post-exercise observed by Stupin et al. (2018). However, given the methodological differences between the latter study and the present study, e.g., PORH and acetylcholine iontophoresis and local cutaneous thermal hyperaemia, respectively, mechanistic differences associated with these techniques may explain the contrasting findings between the studies. In the present study, there was no main effect of intensity on the endothelium-dependent plateau response to local heating. Whether a higher intensity and/or longer exercise bout than that used in the HIGH trial would have resulted in a reduced cutaneous endothelial, as well as axon reflex, function is not clear. Furthermore, cutaneous vascular function was assessed on the previously active forearm in the former study by Stupin et al. (2018), rather than an inactive limb in the present study. Whether differences exist between active vs. inactive limbs in potential changes in post-exercise cutaneous microvascular function is not known.

4.1. Practical implications

The findings of the present study have important practical implications when assessing cutaneous vascular function, particularly the design of protocols involving the assessment of cutaneous axon reflexes. Present findings have shown that an acute bout of exercise increases the cutaneous axonal response for at least 1-h post activity, which should be borne in mind when conducting an axon reflex test and interpreting responses after exercise/physical activity. Furthermore, caution should also likely be taken when performing assessments following heat exposure, which also results in elevations in skin blood flow. The findings of the present study also contribute towards the understanding of chronic skin microvascular adaptations to exercise, whereby repeated elevations in cutaneous axon reflex (and possibly endothelial function) responses after recurrent exercise bouts may accumulate and result in beneficial neural and microvascular adaptations to exercise interventions (Black et al., 2008; Simmons et al., 2011; Lanting et al., 2017; Green et al., 2017; Atkinson et al., 2018).

4.2. Limitations

There are some limitations worthy of consideration. Differences in heating rate do alter the contribution of the mechanisms involved in the cutaneous vascular responses to local heating (Hodges and Johnson, 2009; Roberts et al., 2017). It is therefore possible that a different local heating protocol may have yielded different findings; however the logistics of alternative heating protocols, such as slow local heating (Black et al., 2008; Choi et al., 2014), might have prevented immediate and delayed post-exercise assessments. A further protocol related limitation is that as skin blood flow reached near maximal levels (~90–95 % of CVC_{max}) during the plateau phase of local heating, a ceiling effect may have occurred and that any elevations in the plateau phase may have been very small and/or masked by the near maximal levels. An alternative rapid local heating protocol to a lower temperature, e.g., local heating to 39 °C, would have induced a plateau response at a lower skin blood flow which could have allowed clearer changes in cutaneous endothelial function to be revealed (Choi et al., 2014). Following HIGH exercise, minor post-exercise hypotension (PEH) was present, consistent with previous research (Halliwill et al., 2013). PEH is thought to be mediated by both central and local mechanisms, such as prolonged vasodilatory activity in previously active tissues mediated via histamine (Barrett-O'Keefe et al., 2013; Luttrell and Halliwill, 2017), that possibly could have contributed to the elevated axon reflex vasodilation following acute exercise. Histamine has been shown to be only a modest mediator of the axon reflex response to local heating in skin microvessels, however, albeit in the rested, e.g., pre-exercise, state (Wong and Minson, 2011), and elevated axon reflex vasodilation was present after both LOW and HIGH exercise (e.g., not just after HIGH).

In conclusion, the findings of the present study indicate acutely increased cutaneous axonal responses to local heating following exercise, suggesting augmented sensory afferent function post-exercise. In addition, acute exercise appeared to only slightly elevate endothelial-dependent plateau phase responses to local heating, indicating that cutaneous endothelial function may be modestly augmented post-exercise.

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CRediT authorship contribution statement

DL, HJ and HC contributed to the conception or design of the work. DL, ST, HJ, KR, HC and DT contributed to the acquisition, analysis, or interpretation of data for the work and drafting of the work or revising it critically for important intellectual content. All authors approved the final version of the manuscript, agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and that all persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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