Control of blood pressure in the cold: differentiation of skin and skeletal muscle vascular resistance

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Funding information
Wilderness Medical Society; Tyrolean Science Fund – TWF

Handling Editor: Damian Bailey

Abstract
The primary aim of this investigation was to determine the individual contribution of the cutaneous and skeletal muscle circulations to the cold-induced pressor response. To address this, we examined local vascular resistances in the cutaneous and skeletal muscle of the arm and leg. Thirty-four healthy individuals underwent three different protocols, whereby cold air to clamp skin temperature (27°C) was passed over (1) the whole-body, (2) the whole-body, but with the forearm pre-cooled to clamp cutaneous vascular resistance, and (3) the face. Cold exposure applied to the whole body or isolated to the face increased mean arterial pressure (all, \( P < 0.001 \)) and total peripheral resistance (all, \( P < 0.047 \)) compared to thermoneutral baseline. Whole-body cooling increased femoral \( (P < 0.005) \) and brachial artery resistance \( (P < 0.003) \) compared to thermoneutral baseline. Moreover, when the forearm was pre-cooled to remove the contribution of cutaneous resistance \( (P = 0.991) \), there was a further increase in lower arm vasoconstriction \( (P = 0.036) \) when whole-body cooling was superimposed. Face cooling also caused a reflex increase in lower arm cutaneous \( (P = 0.009) \) and brachial resistance \( (P = 0.050) \), yet there was no change in femoral resistance \( (P = 0.815) \) despite a reflex increase in leg cutaneous resistance \( (P = 0.010) \). Cold stress causes an increase in blood pressure through a change in total peripheral resistance that is largely due to cutaneous vasoconstriction with face cooling, but there is additional vasoconstriction in the skeletal muscle vasculature with whole-body cooling.

KEYWORDS
cutaneous resistance, face cooling, forearm vascular resistance, leg vascular resistance, whole-body cooling
Cold ambient temperatures increase the risk of cardiovascular events and mortality, which interestingly does not occur only during extremely cold ambient temperatures, but largely during moderate cold exposure (Gasparrini et al., 2015). The link between the cold and cardiovascular events is not fully elucidated but is likely linked to the rise in arterial blood pressure, especially in those with pre-existing medical conditions.

One of the major cardiovascular responses to cold is a robust rise in arterial blood pressure. As heart rate and stroke volume (i.e., cardiac output) are unaffected by moderate cold exposure (Durand et al., 2004; Schlader et al., 2016; Wilson et al., 2007), the rise in blood pressure is entirely mediated by an increase in total peripheral resistance. However, the site and mechanisms of vasoconstriction remain to be fully elucidated. This is because, although brachial blood flow is typically used as an index of skeletal muscle vasoconstriction (Limberg et al., 2020), it is influenced by changes in downstream cutaneous vascular resistance. Based on human experimental studies, it is known that local cooling increases the activity of non-nociceptive cutaneous thermoreceptors (Hensel & Boman, 1960), and both local and whole-body cooling cause reflex increases in skin sympathetic nerve activity (Greaney et al., 2015) and cutaneous vascular resistance (Hodges et al., 2006; Stephens et al., 2004). However, while previous studies have observed a reduction in brachial blood flow that is suggestive of skeletal muscle vasoconstriction in the cold (Wilson et al., 2007), it cannot be separated from the known cutaneous vasoconstriction. Moreover, an increase in skeletal muscle vasoconstriction is not in line with other experiments documenting that muscle sympathetic nerve activity remains unchanged during cold exposure, at least in young healthy individuals (Cui et al., 2007; Greaney et al., 2014). Ultimately the question remains if cold exposure causes vasoconstriction in skeletal muscle or only the cutaneous circulation.

Another factor influencing the overall interpretation of which circulations contribute to the total peripheral resistance response to cold stress is whether areas of greater thermosensitivity are activated (e.g., the face and/or hands that are typically excluded from the water-perfused suit model). For example, applying ice to the forehead clearly increases muscle sympathetic nerve activity (Heindl et al., 2004), and cutaneous and forearm vascular resistance (Schlader et al., 2016). Moreover, whole-body cold exposure including the head (10°C air) evokes muscle sympathetic hyperactivity, which was directly related to the cold-induced hypertensive response (Fagius & Kay, 1991). However, while applying ice to the face evokes the classic diving reflex (Heath & Downey, 1990; Heindl et al., 2004), this stimulus does not reflect normal environmental cold exposure (i.e., cold air). Thus, at present, it is unknown if moderate cold exposure applied to the face causes an increase in cutaneous and/or skeletal muscle vasoconstriction and contributes to the expected rise in blood pressure.

Based on the background provided above, the overall aims of this investigation were twofold: to (1) isolate the contribution of cutaneous and skeletal muscle vascular resistance during whole-body cold exposure (not including the face), and (2) examine how real-world cooling of the face effects cutaneous and skeletal muscle vascular resistance and arterial blood pressure. In both protocols, an additional level of regional heterogeneity was obtained by assessing both arm and leg vascular resistances. To achieve these aims, cold exposure was applied via a fan to the whole body (not including the face) and/or the face alone, while measuring local vascular resistances in the skin, as well as brachial and femoral arteries. Moreover, in one trial, forearm skin was pre-cooled prior to whole-body cooling to remove the influence of cutaneous vasoconstriction on changes in forearm vascular resistance. The primary hypothesis was that cold exposure would cause a profound increase in cutaneous vascular resistance, but minimal change in skeletal muscle vasoconstriction. Consequently, the cutaneous circulation may be responsible for the majority of the change in total peripheral resistance during both whole-body and face cooling.

## METHODS

### 2.1 Participants

All participants (female, n = 12; male, n = 22; age, 28 ± 4 years; height, 1.76 ± 0.08 m; weight, 70.8 ± 10.5 kg; body surface area, 1.86 ± 0.17 m²) were university students recruited via personal communication, all of whom were non-smokers, physically active and free of any vascular, cardiac, cerebral, respiratory, metabolic and gastrointestinal diseases. Participant characteristics for the three individual studies are presented in Table 1. Females were studied in their self-reported early-follicular phase of their menstrual cycle (day 1–7) (Sims & Heather, 2018). Participants were asked to abstain from any strenuous exercise (24 h), caffeine and alcohol (12 h) as well as to avoid foods rich in nitric oxide (48 h) before measurements. Written informed consent was obtained after a verbal and written explanation of the study protocol and potential risks associated with study participation. The University of Innsbruck ethics committee approved the studies (Ref.


| Characteristic | WC(n = 12) | iWC(n = 12) | FC(n = 10) |
|---------------|-----------|-------------|------------|
| Age (years)   | 28 ± 4    | 29 ± 4      | 27 ± 5     |
| Height (m)    | 1.80 ± 0.09 | 1.75 ± 0.08 | 1.74 ± 0.06 |
| Weight (kg)   | 72.8 ± 11.0 | 70.2 ± 10.8 | 69.0 ± 10.1 |
| BMI (kg m⁻²)  | 22.5 ± 2.3 | 22.9 ± 2.5  | 22.7 ± 2.5 |
| BSA (m²)      | 1.91 ± 0.18 | 1.85 ± 0.17 | 1.83 ± 0.15 |

Abbreviations: BMI, body mass index; BSA, body surface area; FC, facial cooling; iWC, whole-body cooling with isolation of muscle blood flow; WC, acute whole-body cooling (Du Bois & Du Bois, 1989).

No.: 34/2018, which followed the principles of the Declaration of Helsinki, except for trial registration.

2.2 Experimental protocol

All studies were independent investigations (i.e., no crossover design) and were conducted in the cardiovascular and exercise physiology laboratory at the University of Innsbruck (elevation, 574 m; ambient temperature, 23.7 ± 1.1°C). Participants were instructed to void their bladder before anthropometric measures, and thereafter three experimental protocols were performed.

2.2.1 Study 1: whole-body cooling (WC)

Upon arrival, participants (female, n = 3; male, n = 9) were equipped with a rectal thermomister for assessment of core temperature and changed into shorts (males) or shorts and sports bra (females). Once in the experimental position (semi-recumbent mesh bed, angle, 30°) and fully instrumented, the whole body, excluding the head, was covered with a commercially available emergency blanket to clamp thermoneutral mean weighted skin temperature (~32°C). This set-up was repeated in all three experiments. After resting for 20 min and ensuring stable haemodynamics and mean skin temperature, thermoneutral baseline measurements were obtained starting with a 5-min data collection of haemodynamic (heart rate), metabolic (oxygen consumption) and thermoregulatory parameters (mean skin temperature, rectal temperature, local skin blood flow and temperature). Thereafter, blood pressure, cardiac output (to calculate total peripheral resistance) and thermal comfort were determined and then followed by measurements of right brachial and superficial femoral artery blood flow. Blood pressure was also obtained in triplicate during the measurements of both brachial and femoral flow to calculate local vascular resistance and conductance. Subsequently, the emergency thermal blanket was removed and cold stress (target mean skin temperature, ~27°C), without facial cooling, was applied via a commercially available fan (wind speed, 14 km/h) (FGD-18, Proklima, Mannheim, Germany). While we did not have access to the additional thermocouples during this study, pilot studies (n = 4) suggested that cheek temperature does not decrease more than ~1°C (baseline, 24.6 ± 1.3 vs. cold, 24.1 ± 1.3°C) during our model of whole-body cooling. As soon as the mean skin temperature was stable (~24 min), the protocol was repeated.

2.2.2 Study 2: whole-body cooling with isolation of muscle vascular resistance (iWC)

The protocol was identical to WC (see description above; female, n = 5; male, n = 7). However, before applying the whole-body cold stimulus via the fan, the left forearm was pre-cooled with a custom-made water-perfused sleeve (Cole-Parmer Polystat 10124-03, Cole-Parmer GmbH, Cambridgeshire, UK) to clamp forearm skin temperature at ~27°C (mean skin temperature during WC). In the left forearm, skin temperature, skin blood flow, brachial artery blood flow and brachial arterial blood pressure were obtained at baseline (thermal neutral), at the end of locally isolated pre-cooling (iPC), and at the end of whole-body pre-cooling (iWC).

2.2.3 Study 3: facial cooling (FC)

Upon arrival, participants (female, n = 4; male, n = 6) positioned themselves in the experimental position and were fully instrumented, while dressed in shorts and a T-shirt to keep the body thermoneutral. After a 20-min rest, thermoneutral baseline haemodynamic (heart rate) and thermoregulatory parameters (mean skin temperature, skin blood flow and temperature) were obtained. Subsequently, blood pressure and cardiac output were determined (to calculate total peripheral resistance) followed by the assessment of thermal comfort as well as right brachial and superficial femoral artery blood flow. Blood pressure was also obtained in triplicate during the measurement of both brachial and femoral artery blood flow to calculate local vascular resistance and conductance. Thereafter, the participant’s face was cooled using a custom-made device that cooled ambient air convectively through a snowcapped aluminium pipe and directed to the participant’s face. From pilot experiments, air temperature exiting the device (~14°C) was used to cool the face such that the mean face temperature matched whole-body cooling in experiments 1 and 2 (target, ~27°C). After the mean face temperature reached the target value (~24 min) all measurements were repeated.

2.3 Measurements: thermoregulatory parameters

Rectal temperature was measured via a thermomister, self-inserted 15 cm past the anal sphincter (Tram-rac, Solar 8000M, GE Marquette, Boston, MA, USA). Whole-body skin temperature was estimated from the area-weighted (ISO9886, 2004) mean skin temperature from eight sites (forehead, scapula, upper chest, upper arm, lower arm, hand, anterior thigh and calf) (ISO9886, 2004) using individual polyvinyl insulated t-type copper/constantan thermocouples (OMEGA
Engineering Inc., Norwalk, CT, USA and TC-2000, Sable Systems, North Las Vegas, NV, USA). In the FC trial, mean skin temperature was corrected to exclude forehead temperature. This was done by multiplying the weighting factor for the forehead (0.07) with the respective forehead temperatures and adding the difference to the baseline mean skin temperature. Local skin temperatures (e.g., thigh, forearm, cheek and forehead) were obtained with an integrated thermistor and laser-Doppler flowmeter (VMS-LDF, Moor Instruments, Devon, UK). For the estimation of local skin blood flow, the large-area optic probe (2 mm ring of collecting fibres) emitted laser light (wavelength, 785 nm; intensity, ~1 mW) onto the skin to measure cutaneous red cell flux and is presented as perfusion units. Cutaneous red cell flux was not reported for the face. The McGinnis 13-point scale was utilized to quantify thermal comfort (1 = ‘so cold I am helpless’, 7 = ‘comfortable’, 13 = ‘so hot I am sick and nauseate’) (Hollies et al., 1979).

2.4 | Cardiorespiratory parameters

Systolic and diastolic blood pressure were measured at each time point in triplicate (and reported as the mean) by electrophygmanometry with a microphone placed over the brachial artery to detect Korotkoff sounds (Tango, M2, SunTech Medical Inc., Morrisville, NC, USA). Heart rate was continuously determined via three-lead electrocardiography (Tram-rac, Solar 8000M, GE Marquette). Cardiac output was initially (WC, n = 7) assessed by inert gas rebreathing (Innocor, COSMED, Rome, Italy) using nitrous oxide (blood soluble, 5%), and sulfur hexafluoride (blood insoluble, 1%). However, due to technical malfunction during WC, cardiac output was subsequently estimated with echocardiography using a 5-MHz volume sector-array probe (IE33, Philips, Amsterdam, Netherlands) by an experienced sonographer (K.M.). For the estimation of stroke volume via echocardiography, the diameter of the left ventricular outflow tract (LVOT) and the LVOT velocity time integral (VTI) were obtained during systole. Stroke volume was then calculated according to current guidelines ([π × (LVOT diameter/2)^2] × LVOT VTI) (Quinones et al., 2002). Consequently, cardiac output was calculated directly from the inert gas rebreathing technique or as the product of stroke volume and heart rate for echocardiography. Respiratory parameters and oxygen consumption were obtained via online integration of expired oxygen and carbon dioxide through a mixing chamber (Moxus metabolic system, AEI Technologies Inc., Lewisburg, WV, USA) and ventilation from a pneumotachometer (Hans Rudolph Inc., Shawnee, KS, USA).

2.5 | Peripheral blood flow parameters

Brachial and superficial femoral artery diameters (custom-made wall tracking software) (Coolbaugh et al., 2016) and mean blood velocities (Doppler audio converter, Penn State, Hershey, PA, USA) were measured over 30 s at each stage with an 11-MHz linear-array Doppler probe (IE33, Philips) to determine forearm and leg blood flow, respectively. One important caveat here is that while reference is made to ‘forearm blood flow’ throughout the majority of the manuscript, as performed this technique cannot discount the hand circulation.

2.6 | Data acquisition and analyses

All variables (except vascular diameter, systolic and diastolic blood pressure, cardiac output, rectal temperature, and thermal comfort) were sampled at 0.4 kHz using the PowerLab data acquisition system (ADInstruments, Oxford, UK) and analysed with LabChart (Version 8, ADInstruments).

2.6.1 | Calculations

Mean arterial blood pressure was calculated by the sum of one-third systolic and two-thirds diastolic blood pressure. Oxygen consumption (STPD) was obtained according to the Haldane equation ([VE × (FIo2 – (FEO2/100))], where FIo2 and FEO2 are inspired and expired fractions of oxygen and VE is volume corrected minute ventilation (SPTD). Blood flow in the brachial and superficial femoral arteries was calculated as the timed averaged mean velocity multiplied by the cross-sectional lumen areas estimated from the arterial diameter. Local vascular resistances were calculated as blood flow or perfusion units divided by mean arterial blood pressure. Local vascular conductance was calculated and mean arterial blood pressure was divided by blood flow. Since the cold yielded an increase in systemic resistance and consequently arterial blood pressure, resistance was our primary outcome. Yet, both indices were calculated and reported for transparency.

2.7 | Statistical analyses

All data were tested for normal distribution using the Shapiro–Wilk test. Thereafter, the response to each condition, in terms of absolute change score (Δ) (i.e., thermoneutral baseline versus cold stress), was compared using Student’s paired t-test, except the pre-cooling trial, which was analysed by a repeated measures (baseline, IPC and IWC) ANOVA with Tukey’s multiple post hoc tests. If data did not meet the assumption of normal distribution, a non-parametric Wilcoxon, Mann-Whitney, or Kruskal–Wallis test was performed. Cohen’s d effect sizes were calculated to determine the magnitude of effects and interpreted as d = 0.2 (small), 0.5 (medium) and 0.8 (large) (Cohen, 1992). Forearm and leg vascular resistance data from study 1 were used to calculate the sample sizes for studies 2 and 3. Effect sizes ranged from 1.2 to 1.4, which indicates 10 participants would be required to observe a similar vasoconstrictor response with local, whole body or face cooling with an 80% statistical power. Primary data entry and descriptive calculations were performed using Microsoft Excel for Windows 2016. Further statistical and graphical procedures were completed on Prism (Version 9.3.1, GraphPad Software Inc., San Diego, CA, USA) and open-source vector graphic software (Inkscape Version 1.1.1, http://www.inkscape.com).
3 | RESULTS

Ultrasound data for the leg ($n = 1$) and left pre-cooled forearm ($n = 1$) were removed from the analysis in study 2 due to bursts of shivering and poor signal quality, respectively. Data for cardiac output and consequently total peripheral resistance were unavailable due to technical malfunction ($n = 1$).

3.1 | Study 1: whole-body cooling

As expected, acute whole-body cooling decreased mean skin temperature to the target of $27.3 \pm 0.6 \degree C$ ($P < 0.001$, Figure 1a) with only a minimal change in core temperature of $-0.19 \degree C$ ($P = 0.019$, Figure 1a), and a modest increase in thermal discomfort ($P < 0.001$, Figure 1a) and whole-body oxygen consumption ($P < 0.001$). Moreover, cold caused an increase in systolic ($P = 0.002$), diastolic ($P < 0.001$) and mean arterial pressure ($P < 0.001$, Figure 1a) but did not affect heart rate ($P = 0.149$), stroke volume ($P = 0.187$) and thus cardiac output ($P = 0.742$, Figure 1a). Total peripheral resistance ($P = 0.041$, Figure 1a) increased in response to acute whole-body cooling, which coincided with an increase in brachial ($P = 0.003$, Figure 1b) and femoral ($P = 0.005$, Figure 1b) artery resistance. Vascular conductance in the brachial ($P = 0.002$) and femoral ($P = 0.004$) arteries decreased similarly (Table 2).

3.2 | Study 2: whole-body cooling with isolation of muscle vascular resistance

Pre-cooling the left forearm clamped local skin temperature to $26.8 \pm 0.4 \degree C$ ($P < 0.001$, Figure 2a), and elevated skin vascular resistance ($P = 0.021$, Figure 2b), increased brachial artery conductance ($P = 0.016$, Figure 2b) and decreased brachial artery conductance ($P = 0.014$, Table 3). Thereafter, imposing whole-body cooling caused similar cardiovascular and thermoregulatory responses to the first experimental protocol (see Table 3 for an overview). Importantly, left pre-cooled forearm skin temperature remained clamped within $1 \degree C$ during whole-body cooling (pre-cooled $26.8 \pm 0.4 \degree C$ vs. whole-body cooling $25.5 \pm 0.3 \degree C$, $P < 0.001$, Figure 2a) and skin temperature of the right arm was reduced to the same magnitude as local cooling (thermal neutral, $29.7 \pm 0.9 \degree C$ vs whole-body cooling, $25.7 \pm 0.9 \degree C$, $P < 0.001$, Table 3). As such, whole-body cooling did not affect skin vascular resistance in the left pre-cooled arm ($P = 0.991$, Figure 2b), but increased skin vascular resistance in the right arm ($P = 0.003$, Table 3).

Moreover, there was a reflex-mediated increase in forearm vascular resistance in the left pre-cooled arm ($P = 0.036$, Figure 2b).

3.3 | Study 3: isolated facial cooling

Isolated face cooling caused a decrease in forehead, cheek and thus mean face temperature (all $P < 0.001$), ultimately reaching
Summary of thermoregulatory, metabolic and cardiovascular responses in study 1: whole-body cooling (WC)

| Variable                        | Condition | BL       | WC       | P       | Effect size, d |
|---------------------------------|-----------|----------|----------|---------|----------------|
| Thermoregulatory and metabolic  |           |          |          |         |                |
| $T_{re}$ (°C)                   |           | 36.9 ± 0.2 | 36.7 ± 0.3 | 0.019   | −0.84          |
| $T_c$ (AU)                      |           | 7 (1)    | 4 (1)    | <0.001  | −2.97          |
| Mean $T_{sk}$ (°C)              |           | 31.9 ± 0.4 | 27.3 ± 0.6 | <0.001  | −8.84          |
| $V_{O_2}$ (l min$^{-1}$)        |           | 0.35 ± 0.13 | 0.47 ± 0.18 | <0.001  | 0.75           |
| Cardiovascular                  |           |          |          |         |                |
| SBP (mmHg)                      |           | 112 ± 10 | 120 ± 11 | 0.002   | 0.83           |
| DBP (mmHg)                      |           | 67 ± 8  | 76 ± 7  | <0.001  | 1.27           |
| MAP (mmHg)                      |           | 82 ± 8  | 91 ± 8  | <0.001  | 1.21           |
| $Q_c$ (l min$^{-1}$)            |           | 4.9 (2.3) | 4.9 (3.1) | 0.803   | −0.05          |
| HR (beats min$^{-1}$)           |           | 60 ± 12 | 56 ± 11 | 0.149   | −0.32          |
| SV (ml)                         |           | 95 ± 35 | 100 ± 34 | 0.187   | 0.14           |
| TPR (mmHg l$^{-1}$ min$^{-1}$)   |           | 16.6 ± 6.7 | 18.8 ± 7.2 | 0.041   | 0.31           |
| Right leg                       |           |          |          |         |                |
| BF (ml min$^{-1}$)              |           | 96.2 ± 21.7 | 77.7 ± 29.1 | 0.041   | −0.72          |
| VR (mmHg ml$^{-1}$ min$^{-1}$)   |           | 0.92 (0.22) | 1.10 (0.83) | 0.004   | 1.19           |
| VC (ml min$^{-1}$ mmHg$^{-1}$)   |           | 1.15 ± 0.22 | 0.83 ± 0.27 | 0.004   | −1.31          |
| Right forearm                    |           |          |          |         |                |
| BF (ml min$^{-1}$)              |           | 36.1 ± 19.5 | 22.1 ± 6.5 | 0.007   | −0.96          |
| VR (mmHg ml$^{-1}$ min$^{-1}$)   |           | 2.30 (1.79) | 4.60 (0.75) | 0.003   | 1.13           |
| VC (ml min$^{-1}$ mmHg$^{-1}$)   |           | 0.44 (0.25) | 0.22 (0.04) | 0.002   | −1.19          |

For non-normally distributed data ($T_c$, $Q_c$, VR leg, VC and VR forearm), the median (interquartile range) is reported. $n = 12$. Abbreviations: BF, blood flow; BL, baseline; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial blood pressure; mean $T_{sk}$, mean weighted skin temperature; $Q_c$, cardiac output; SBP, systolic blood pressure; SV, stroke volume; $T_{re}$, thermal comfort; TPR, total peripheral resistance; $T_{sk}$, rectal temperature; VC, vascular conductance; $V_{O_2}$, oxygen consumption; VR, vascular resistance; WC, whole-body cooling.

Figure 3b) or in femoral vascular resistance ($P = 0.815$, Figure 3b) and femoral vascular conductance ($P = 0.977$, Table 4).

4 DISCUSSION

This investigation aimed to assess the regional control of vascular resistance in response to cold stress. The main novel findings were that whole-body skin surface cooling (target ~27°C, excluding the face) causes an increase in vascular resistance within both the skeletal muscle and cutaneous circulations. However, during isolated mild face cooling, total peripheral resistance was increased mainly due to a reflex increase in cutaneous vascular resistance. Therefore, the mechanism responsible for the rise in blood pressure during cold exposure is dependent on the site of cooling.

Whole-body skin surface cooling causes a well-known increase in arterial blood pressure (Cui et al., 2007; Durand et al., 2004; Greaney et al., 2014; Wilson et al., 2007), despite minimal changes in core temperature and no overt signs of shivering. In agreement with previous studies (Wilson et al., 2007), we observed a robust rise in total...
Whole-body cooling causes an increase in total vascular resistance due to cutaneous and skeletal muscle vascular resistance. (a) Representative time series data of local forearm skin temperature ($T_{sk}$) of the right (purple) and left (pink) forearm at baseline, during pre-cooling of the left forearm and subsequently during whole-body cooling. The average rectal temperature ($T_{re}$, white and black circles) is shown at the end of baseline and whole-body cooling. Whole body cooling increased mean arterial pressure (MAP) with no change in cardiac output ($\dot{Q}_C$), and thus total peripheral resistance increased (TPR). Moreover, there was vasoconstriction in the right forearm and leg. (b) Skin (SR) and forearm (VR) vascular resistance increased in the pre-cooled arm (iPC) with a further increase in forearm vascular resistance during whole-body cooling (iWC), despite no further change in skin vascular resistance. Normally distributed data were analyses using paired t-tests and non-normally distributed data (thermal comfort, VR leg, VR right forearm) were analysed using Wilcoxon signed rank tests. Data in (b) were analysed with a repeated measures analysis of variance, with Tukey post hoc tests. n = 12, except for ultrasound-derived variables for the leg and left (pre-cooled) forearm (n = 11).

and local peripheral vascular (forearm and leg) resistance. In previous studies, the mechanism(s) contributing to the rise in resistance was not clear, because traditional measurements of limb blood flow are the product of both downstream skeletal muscle and cutaneous circulations. In the current study, isolated forearm skin surface cooling caused an increase in forearm resistance that was similar in magnitude to whole-body surface cooling. Moreover, superimposing whole-body skin surface cooling caused further vasoconstriction at the level of the brachial artery, but not the cutaneous circulation, indicative of an increase in skeletal muscle vascular resistance. Collectively, these data highlight that whole-body skin surface cooling causes local and/or reflex cutaneous vasoconstriction and additional vasoconstriction in the skeletal muscle vasculature. Interestingly, while the contribution of the cutaneous circulation to total vascular resistance or conductance is assumed to be low during thermoneutral or cool conditions (Wilson et al., 2007), our data highlight that the cutaneous circulation alone (i.e. local forearm cooling) can increase forearm vascular resistance (4.05 mmHg ml$^{-1}$ min$^{-1}$) to a similar magnitude as orthostatic stress via upright tilt and/or –20 to –40 mmHg lower body negative pressure ($\sim$2.6–3.7 mmHg ml$^{-1}$ min$^{-1}$, calculated from Claydon et al. (2019). Therefore, it is likely that the cutaneous circulation contributes significantly to the regulation of blood pressure during cold exposure.

The observed increase in skeletal muscle vasoconstriction during whole-body skin surface cooling is interesting in light of prior observations that sympathetic nerve activity does not change during periods of cold stress (Cui et al., 2007; Greaney et al., 2014). Collectively, these data suggest that cold stress may cause a post-junctional alteration in vasoconstrictor responsiveness or circulating hormones become the major factor influencing systemic vasoconstriction (Durand et al., 2004). However, while an interesting hypothesis, it does not easily explain the rapid and consistent increase in vasoconstriction across visceral circulations when skin temperature is cooled to $\sim$27°C (Wilson et al., 2007). On close inspection, these apparently disparate findings may be due to differences in the degree of cold stress between investigations, whereby both Cui et al. (2007) and Greaney et al. (2014) slightly preheated individuals ($\sim$34°C) to obtain baseline values, and their cold stimulus ($\sim$30°C) was similar to the thermoneutral skin temperatures observed in the current
investigation (31.9°C). When cold stress is more severe (~10°C air temperature), muscle sympathetic nerve activity clearly increases and is related to the elevation in blood pressure (Fagius & Kay, 1991). Thus, while speculative, it seems that more severe skin cooling is required to increase sympathetically mediated vasoconstriction of the visceral and skeletal muscle circulations, which can be observed when the skin is pre-cooled. These data are in line with the progressive increase in afferent activity of non-noxious cutaneous thermoreceptors in response to cold stimuli (Hensel & Boman, 1960). However, why sympathetic activity is not increased with mild cooling (Cui et al.,

| TABLE 3 | Summary of thermoregulatory, metabolic and cardiovascular responses in study 2: whole-body cooling with isolation of muscle vascular resistance (iWC) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable        | BL      | iPC      | iWC      | P      | Effect size, d            |
| Thermoregulatory and metabolic |
| \( T_{sk} (^\circ C) \) | 37.0±0.3 | 37.0±0.3 | 0.732 | 0.03 |
| \( T_{c} (AU) \) | 7 (0)   | 6 (1)    | 0.002 | −2.10 |
| Mean \( T_{sk} (^\circ C) \) | 31.8±0.6 | 27.3±0.7 | <0.001 | −6.59 |
| \( \dot{V_{O_2}} (l \text{ min}^{-1}) \) | 0.30±0.05 | 0.39±0.07 | <0.001 | 1.51 |
| Cardiovascular  |
| \( SBP (mmHg) \) | 114±14   | 122±14   | 0.001 | 0.56 |
| \( DBP (mmHg) \) | 66±12    | 72±10    | 0.002 | 0.56 |
| \( MAP (mmHg) \) | 82±12    | 89±11    | <0.001 | 0.58 |
| \( Q_c (l \text{ min}^{-1}) \) | 4.1±0.9 | 4.2±0.8  | 0.485 | 0.08 |
| \( HR (\text{beats min}^{-1}) \) | 60±10    | 57±9     | 0.055 | −0.30 |
| \( SV (ml) \) | 70±16    | 74±14    | 0.012 | 0.31 |
| \( TPR (mmHg l^{-1} \text{ min}^{-1}) \) | 20.7±3.0 | 21.8±3.2 | 0.047 | 0.38 |
| Right leg       |
| \( BF (ml \text{ min}^{-1}) \) | 110.7±35.3 | 81.6±31.2 | 0.001 | −0.87 |
| \( VR (mmHg ml^{-1} \text{ min}^{-1}) \) | 0.82(0.27) | 1.24(0.55) | 0.002 | 1.00 |
| \( VC (ml \text{ min}^{-1} mmHg^{-1}) \) | 1.38±0.49 | 0.91±0.31 | 0.001 | −1.14 |
| Right forearm   |
| \( BF (ml \text{ min}^{-1}) \) | 38.3(32.9) | 23.2(7.1) | 0.001 | −1.24 |
| \( VR (mmHg ml^{-1} \text{ min}^{-1}) \) | 1.9(1.6) | 3.7(1.0) | <0.001 | 2.03 |
| \( VC (ml \text{ min}^{-1} mmHg^{-1}) \) | 0.54(0.40) | 0.27(0.08) | <0.001 | −1.21 |
| \( T_{sk} (^\circ C) \) | 29.7±0.9 | 25.7±0.9 | <0.001 | −4.46 |
| \( BF_{sk} (AU) \) | 20.0(9.8) | 13.8(7.7) | 0.021 | −0.84 |
| \( SR (mmHg AU^{-1}) \) | 4.14±1.43 | 6.59±2.22 | 0.003 | 1.31 |
| Isolated pre-cooling, left forearm |
| \( BF (ml \text{ min}^{-1}) \) | 43.5(23.4) | 23.0(22.0) | 14.7(13.2) | 0.032 | <0.001 | 0.602 | −1.09 | −1.68 | −0.86 |
| \( VR (mmHg ml^{-1} \text{ min}^{-1}) \) | 2.12±0.95 | 4.05±2.10 | 5.49±1.47 | 0.016 | <0.001 | 0.036 | 1.18 | 2.73 | 0.80 |
| \( VC (ml \text{ min}^{-1} mmHg^{-1}) \) | 0.47(0.23) | 0.29(0.21) | 0.18(0.08) | 0.023 | 0.015 | 0.035 | −1.03 | −1.50 | −1.00 |
| \( T_{sk} (^\circ C) \) | 30.7±1.3 | 26.8±0.4 | 25.5±0.3 | <0.001 | <0.001 | <0.001 | −4.05 | −5.56 | −3.67 |
| \( BF_{sk} (AU) \) | 34.1±16.7 | 20.4±11.1 | 20.0±8.7 | 0.032 | 0.052 | 0.978 | −0.97 | −1.06 | −0.04 |
| \( SR (mmHg AU^{-1}) \) | 2.92±1.33 | 5.29±2.53 | 5.35±2.76 | 0.021 | 0.054 | 0.991 | 1.17 | 1.12 | 0.02 |

For non-normally distributed data (\( T_{c} \), VR leg, BF, VR, VC and \( BF_{sk} \), right forearm, BF and VC left forearm), the median (interquartile range) is reported. n= 12, except for ultrasound-derived variables for the leg and left (pre-cooled) forearm (n = 11). Abbreviations: BF: blood flow; BF\(_{sk}\), local skin blood flow; BL: baseline; DBP: diastolic blood pressure; HR: heart rate; iPC: isolated pre-cooling; iWC: isolated whole-body cooling; MAP: mean arterial blood pressure; Mean \( T_{sk}\), mean weighted skin temperature; \( Q_c\), cardiac output; SBP: systolic blood pressure; \( T_{c}\), thermal comfort; \( T_{sk}\), rectal temperature; VC: vascular conductance; \( \dot{V_{O_2}}\), oxygen consumption; VR: vascular resistance; SR, local skin vascular resistance; SV, stroke volume; TPR, total peripheral resistance; \( T_{sk}\), local skin temperature.
TABLE 4  Summary of thermoregulatory, metabolic and cardiovascular responses in study 3: facial cooling (FC)

| Variable | Condition | BL | FC | P | Effect size, d |
|----------|-----------|----|----|---|---------------|
| **Thermoregulatory and metabolic** | | | | | |
| $T_{sk}$ (AU) | | 7 ± 0 | 6 ± 1 | 0.008 | −2.18 |
| Mean $T_{sk}$ (°C) | | 31.6 ± 0.5 | 30.6 ± 0.6 | <0.001 | −1.76 |
| Mean $T_{sk}$ corrected (°C) | | 31.1 ± 0.5 | 30.6 ± 0.6 | <0.001 | −1.03 |
| $T_{sk}$ face (°C) | | 31.9 ± 0.9 | 25.3 ± 0.3 | <0.001 | −9.25 |
| **Cardiovascular** | | | | | |
| SBP (mmHg) | | 112 ± 8 | 119 ± 11 | 0.005 | 0.74 |
| DBP (mmHg) | | 68 ± 5 | 72 ± 6 | 0.002 | 0.78 |
| MAP (mmHg) | | 82 ± 5 | 88 ± 7 | >0.001 | 0.88 |
| $Q_{c}$ (l min$^{-1}$) | | 3.7 ± 1.2 | 3.5 ± 0.7 | 0.343 | −0.25 |
| HR (beats min$^{-1}$) | | 55 (17) | 49 (8) | 0.055 | −0.51 |
| SV (ml) | | 67 ± 17 | 70 ± 15 | 0.392 | 0.20 |
| TPR (mmHg l$^{-1}$ min$^{-1}$) | | 23.2 ± 7.4 | 26.8 ± 7.5 | 0.034 | 0.48 |
| **Right leg** | | | | | |
| BF (ml min$^{-1}$) | | 100.1 ± 33.9 | 105.7 ± 31.5 | 0.315 | 0.17 |
| VR (mmHg ml$^{-1}$ min$^{-1}$) | | 0.93 ± 0.32 | 0.91 ± 0.29 | 0.815 | −0.06 |
| VC (ml min$^{-1}$ mmHg$^{-1}$) | | 1.19 ± 0.39 | 1.19 ± 0.32 | 0.977 | −0.01 |
| $T_{sk}$ (°C) | | 29.4 ± 1.0 | 29.4 ± 1.0 | 0.911 | −0.03 |
| BF$_{sk}$ (AU) | | 28.8 ± 10.6 | 26.9 ± 13.0 | 0.096 | −0.17 |
| SR (mmHg AU$^{-1}$) | | 3.06 (2.02) | 3.27 (4.48) | 0.010 | 0.47 |
| **Right forearm** | | | | | |
| BF (ml min$^{-1}$) | | 37.9 (65.4) | 27.7 (35.6) | 0.064 | −0.48 |
| VR (mmHg ml$^{-1}$ min$^{-1}$) | | 2.50 ± 1.29 | 3.17 ± 1.61 | 0.050 | 0.46 |
| VC (ml min$^{-1}$ mmHg$^{-1}$) | | 0.38 (0.72) | 0.34 (0.33) | 0.049 | −0.56 |
| $T_{sk}$ (°C) | | 29.9 ± 1.3 | 26.5 ± 1.6 | 0.055 | −0.28 |
| BF$_{sk}$ (AU) | | 21.2 (22.1) | 16.2 (15.5) | 0.002 | −0.36 |
| SR (mmHg AU$^{-1}$) | | 4.17 ± 1.95 | 5.89 ± 3.00 | 0.009 | 0.68 |

For non-normally distributed data (HR, SR leg, BF, VC and BF$_{sk}$ forearm), the median (interquartile range) is reported. $n = 10$ except for cardiac output ($n = 9$) and total peripheral resistance ($n = 8$). Abbreviations: BF, blood flow; BF$_{sk}$, local skin blood flow; BL, baseline; DBP, diastolic blood pressure; FC, Isolated face cooling; HR, heart rate; MAP, mean arterial blood pressure; Mean $T_{sk}$, mean weighted skin temperature; $Q_{c}$, cardiac output; SBP, systolic blood pressure; SR, local skin vascular resistance; SV, stroke volume; $T_{c}$, thermal comfort; TPR, total peripheral resistance; $T_{sk}$, local skin temperature; VC, vascular conductance; VR, vascular resistance.

Despite the likelihood that afferent activity is modestly elevated remains to be discovered, but it may require a certain threshold of cutaneous afferent activity to be reached and/or the interaction of central modulation of the autonomic nervous system. A similar mechanism may explain the rightward shift in the baroreflex with mild cooling (Cui et al., 2007), and based on our data a presumed left and upward shift during more moderate cold stress similar to exercise (Moralez et al., 2018).

Classically, face cooling to evoke the diving reflex (typically using ice water or ice packs) causes an increase in muscle sympathetic nerve activity and an increase in blood pressure (∼18 mmHg) concomitant with a rise in brachial and femoral vascular resistance (Fisher et al., 2015; Heindl et al., 2004; Schlader et al., 2016) and a reflex increase in cutaneous vascular resistance (Brown et al., 2003; Schlader et al., 2016). This is in contrast to the current investigation wherein progressive face cooling (25.3°C) only increased blood pressure by ∼6 mmHg. Under this experimental model, forearm vascular resistance and forearm cutaneous resistance both increased. Yet, while leg cutaneous vascular resistance also increased during face cooling, it had little effect on total leg vascular resistance assessed at the superficial femoral artery. Because femoral vascular resistance did not change, we interpret these data to suggest that face cooling causes a principally reflex cutaneous vasoconstriction (which is observed at the level of the brachial artery) and minimal to no vasoconstriction at the level of the skeletal muscle. These data also highlight the need to tightly control skin blood flow in the forearm when attempting to assess resistance...
Face cooling causes an increase in total vascular resistance primarily due to cutaneous vasoconstriction. (a) Representative time series data of local mean face skin temperature ($T_{sk}$, pink) averaged from the forehead and cheek (pink) and the corrected mean weighted skin temperature (purple) during isolated face cooling (FC). Isolated face cooling caused an increase in mean arterial pressure (MAP) with no change in cardiac output ($\dot{Q}_C$), and thus total peripheral resistance (TPR) increased after removal of an ‘outlier’ highlighted in red. Both data sets for TPR are presented for transparency. (b) Isolated face cooling increased forearm vasoconstriction via a reflex increase in forearm cutaneous vasoconstriction, which also slightly decreased forearm skin temperature. Face cooling also caused a reflex increase in leg cutaneous resistance, but this did not impact leg vascular resistance or leg skin temperature. All analyses were paired $t$-tests; if data failed normal distribution (SR leg), the Wilcoxon signed rank test was performed. $n = 10$, except for cardiac output ($n = 9$) and total peripheral resistance ($n = 8$).

vessel function in human skeletal muscle. Yet, changes in cutaneous blood flow at the leg have less impact on resting femoral artery blood flow, likely due to differences in the ratio of total muscle mass (i.e., total vascular resistance/conductance) to skin surface area of the forearm versus the leg.

4.1 Applied implications of these findings

One of the major observations in the current study is that whole-body and face cooling cause similar absolute increases in mean arterial blood pressure (face cooling, 6 mmHg vs. whole-body cooling 7–9 mmHg), which has a large component due to cutaneous vasoconstriction. While the contribution of the cutaneous circulation to total peripheral resistance is low, at least at rest and/or relative to heat stress, cutaneous vasoconstriction likely contributes significantly to hypertension in the cold. These data indicate that appropriate planning of insulation to minimize the fall in face and/or body skin temperature may be a simple countermeasure to reduce the adverse cardiovascular health consequences associated with exposure to cold environments (Gasparini et al., 2015). Another observation is that cold stress can cause non-coherent changes in local skin temperature and skin blood flow. For example, during isolated and whole-body cooling, forearm skin temperature continued to fall (Figure 2a) but forearm skin vascular resistance remained unchanged (Figure 2b). Additionally, face cooling caused a reflex increase in leg skin vascular resistance (Figure 3b), yet no measurable decrease in skin temperature (Figure 3b). These data cast doubt on the ubiquitous use of skin temperature as a surrogate of skin blood flow, especially under modest provocations.

4.2 Limitations

The major limitation of the current investigation was the lack of direct muscle sympathetic nerve recordings. As such, our interpretation of the data is based on a previous report where muscle sympathetic nerve activity was elevated, but unfortunately, skin temperatures were not measured (Fagius & Kay, 1991). Nevertheless, under the current experimental protocol, measuring sympathetic nerve activity would have been challenging, with the potential for needle movement during intermittent bursts of shivering when the cold stress was initially applied. Therefore, we decided to examine end-organ responses in a large number of participants (total $n = 34$) over three separate protocols to confirm the primary haemodynamics before further mechanistic investigations. Another limitation was that we did not precisely quantify shivering or muscle tonus. If shivering or muscle activation is present, brachial blood flow cannot be used as a surrogate for local vascular resistance independent of ‘exercise’ hyperaemia. Nonetheless, we are confident that the participants were not overtly shivering during measurements used for analysis via visual inspection, examination of the ECG signal quality, and careful monitoring of brachial and femoral blood flow. Pilot experiments, where shivering was apparent, clearly demonstrated a rhythmic increase in blood flow post bursts of shivering in order to maintain oxygen delivery.
to ‘exercising’ skeletal muscle. These oscillations in blood flow were not apparent in our measurements. Nonetheless, a higher degree of muscle tone may have been present, and future research could aim to utilize surface or intramuscular electromyography to measure tonic motor unit activity. Another limitation was that we did not perform a fourth study with a pre-cooled forearm during face cooling to isolate the skeletal muscle. However, after we did not observe a concurrent increase in femoral vascular resistance despite a modest increase in cutaneous leg resistance, we inferred the major contribution was from the cutaneous circulation and this additional protocol was not necessary. Finally, we acknowledge that the measurement of blood flow through the brachial artery and thus the calculation of forearm vascular resistance also includes the adipose and bone circulations, which may limit our interpretation of isolating muscle vascular resistance. Yet, to the best of our knowledge, vascular resistance in these circulations is extremely low and it is not clear that ultrasonography has the resolution to detect small changes in these circulations if they even exist in response to cold. Thus, in our opinion, they do not limit the overall interpretation of the data. Albeit with less temporal resolution, alternative approaches such as microdialysis (Richey et al., 2022) or positron-emission tomography aiming (Heinonen et al., 2011) to measure muscle blood flow independent of the cutaneous circulation could be implemented.

4.3 Conclusion

In conclusion, cold stress imposed on the whole body or face causes an increase in blood pressure through a change in total peripheral resistance that has a major contribution from the cutaneous circulation. Moreover, whole-body surface cooling caused additional reflex-mediated vasoconstriction in the skeletal muscle vasculature, likely to conserve heat due to larger cold stress. These data suggest that protection of cutaneous afferents from cold environmental temperatures or warming procedures in the periphery when face cooling is unavoidable may reduce the risk for an increase in blood pressure and adverse health consequences of cold environments.

AUTHOR CONTRIBUTIONS

Justin S. Lawley, Samuel J. Oliver, Daniel Gagnon and Hendrik Mugele were involved with the conception and design of the experimental protocols, results interpretation, and drafting or critically revising important intellectual content. Kyohei Marume, Justin S. Lawley and Hendrik Mugele were responsible for data acquisition. Hendrik Mugele performed data analysis. Sachin B. Amin, Carmen Possnig, Lucie C. Kühn, Lydia Riehl, Robin Pieper and Eva-Lotte Schabbehard aided in data acquisition and revising the manuscript. All authors have read and approved the final version of this manuscript and 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. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

ACKNOWLEDGEMENTS

We would like to thank the participants for dedicating their time and effort in these experiments. We would also like to thank Joost van Putten and Christoph Hasler for their technical support in performing the experiments.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Mugele, H., Marume, K., Amin, S. B., Possnig, C., Kühn, L. C., Riehl, L., Pieper, R., Schabbehard, E.-L., Oliver, S. J., Gagnon, D., & Lawley, J. S. (2023). Control of blood pressure in the cold: differentiation of skin and skeletal muscle vascular resistance. *Experimental Physiology*, 108, 38–49. [https://doi.org/10.1113/EP090563](https://doi.org/10.1113/EP090563)