Journal of Thermal Biology 123 (2024) 103937

Contents lists available at ScienceDirect

Journal of Thermal Biology

journal homepage: www.elsevier.com/locate/jtherbio

The combined effects of temperature and posture on regional blood flow and haemodynamics

Jason T. Fisher [a,b], Urša Ciuha [a], Igor B. Mekjavić [a,*]

[a] Department of Automatics, Biocybernetics, and Robotics, Jozef Stefan Institute, Ljubljana, Slovenia
[b] International Postgraduate School Jozef Stefan, Jamova 39, SI-1000, Ljubljana, Slovenia

ARTICLE INFO

Keywords:
Microvascular blood flow
Neural control
Haemodynamics
Thermoregulation
Baroreflex
Vasomotor zone

ABSTRACT

Under simultaneous ambient temperature and postural stressors, integrated regional blood flow responses are required to maintain blood pressure and thermoregulatory homeostasis. The aim of the present study was to assess the effect of ambient temperature and body posture on regional regulation of microvascular blood flow, specifically in the arms and legs.

Participants (N = 11) attended two sessions in which they experienced transient ambient conditions, in a climatic chamber. During each 60-min trial, ambient temperature increased from 15.7 (0.6) °C to 38.9 (0.6) °C followed by a linear decrease, and the participants were either standing or in a supine position throughout the trial; relative humidity in the chamber was maintained at 25.9 (6.6) %. Laser doppler flowmetry of the forearm ($SkBF_{arm}$) and calf ($SkBF_{calf}$), and haemodynamic responses (heart rate, HR; stroke volume, SV; cardiac output, CO; blood pressure, BP), were measured continuously. Analyses of heart rate variability and wavelet transform were also conducted.

$SkBF_{arm}$ increased significantly at higher ambient temperatures ($p = 0.003$), but not $SkBF_{calf}$. The standing posture caused lower overall SkBF in both regions throughout the protocol, regardless of temperature ($p < 0.001$). HR and BP were significantly elevated, and SV significantly lowered, in response to separate and combined effects of higher ambient temperatures and a standing position (all $p < 0.05$); CO remained unchanged. Mechanistic analyses identified greater sympathetic nerve activation, and higher calf myogenic activation at peak temperatures, in the standing condition.

Mechanistically and functionally, arm vasculature responds to modulation from both thermoregulation and baroreceptor activity. The legs, meanwhile, are more sensitive to baroreflex regulatory mechanisms.

1. Introduction

In humans, homeothermy is maintained over a wide range of ambient temperatures (T_A) by the autonomic responses of heat production and heat loss. The former being a by-product of metabolism, and the latter achieved via processes of evaporation, conduction, convection, and radiation. In this thermoregulatory zone of ambient temperatures, shivering thermogenesis is initiated below a lower critical temperature (LCT) of T_A and sweating above an upper critical temperature (UCT) of T_A. The variability of subcutaneous insulation is achieved by varying the degree of perfusion of this layer (Mekjavic and Bligh, 1989). The responses of shivering and sweating may also be described as a function of internal body temperature, whereby the inter-threshold zone of core temperatures for shivering and sweating has been defined as the vasomotor zone (Mekjavic et al., 1991). The peripheral vasomotor zone is defined by maximal vasoconstriction at LCT and by maximal vasodilation at UCT, whereby skin blood flow (SkBF) can range from ~0.3 L min^{-1} at LCT to as much as ~6–8 L min^{-1} at UCT (Charkoudian, 2003). The regulation of SkBF is achieved by the interaction of sympathetic neural control mechanisms, sympathetic vasodilator and adrenergic vasoconstrictor nerves. This sympathetic/vasomotor regulation of the microvasculature ensures optimal thermal balance during small variations in ambient temperature. It is now well documented that in the skin vasomotor zone, skin blood flow is regulated by skin temperature (Shepherd, 1966; Savage and Brengelmann, 1996), and modulated by the baroreceptor reflex (Crossley et al., 1966). The interaction between the pressure and temperature regulating systems is most apparent during the transition of posture from supine to upright (Nielsen et al., 1939)

* Corresponding author. Department of Automatics, Biocybernetics, and Robotics, Jozef Stefan Institute, Jamova 39, SI-1000, Ljubljana, Slovenia.
E-mail address: Igor.mekjavic@ijs.si (I.B. Mekjavić).

https://doi.org/10.1016/j.jtherbio.2024.103937
Received 24 April 2024; Received in revised form 23 June 2024; Accepted 31 July 2024
Available online 3 August 2024

and during heating in the upright posture (Rowell et al., 1970).

These systems are exceptionally efficient at regulating homeostasis when in response to an imbalance from one stressor, such as high ambient temperatures or gravity-induced hydrostatic pressure shifts. It is when these systems are required to work simultaneously that responses must become integrated (Heistad et al., 1973). For example, Crossley et al. (1966) suggested that during acute exposure to lower body negative pressure (LBNP), the baroreflex supersedes thermoregulatory control. These results are in contrast, however, to reports indicating a decreased resistance to orthostatic stress under heating (Schlader et al., 2016). For example, the study by Wilson et al, (2002) reported that only four of nine participants were able to withstand orthostatic stress for 10 min after a 0.9 °C increase in core temperature. It is therefore clear that the combination of gravitational and heat stressors establishes a need for interaction of the blood flow mechanisms. What is less clear, is how this interaction of central neural mechanisms affects efferent autonomic vascular control and consequently, microvascular blood flow.

Previous research has alluded to regional disparities in microvascular blood flow, when experiencing external stressors. Early research by Nishiyasu and colleagues (1992) noted that in different scenarios designed to elevate core temperature using ambient temperature and exercise, there were significant differences in upper and lower body blood flow with considerably higher forearm flow observed in all conditions. Hales et al. (1994) also utilized exercise and high ambient temperatures, identifying significant variations in blood flow at rest and during exercise measured at the forearm, forehead, chest, and finger. Regional responses have also been reported in reference to orthostatic/postural stress, with Essandoh and colleagues (1988) testing a number of different postural conditions. They summarized that marked changes in forearm blood flow were not matched by the calf, and that both high- and low-pressure baroreceptors mediate forearm vasoconstriction in response to postural changes. Ciuha et al. (2019) reported that during exposure to transient ambient temperature in a seated position, the perfusion characteristics of the arm and leg differ; with different sympathetic nerve responses provided as a possible reason. Finally, previous work by the same group identified that there was a substantial regional difference in skin perfusion to the fingers and toes, with the higher fingertip perfusion being attributed to greater sensitivity to changes in temperature (Fisher et al., 2022).

The aforementioned research detected regional variations in microvascular blood flow, yet suggested few possible reasons for these variations. Therefore, the aim of the present study was to compare the responses of microvascular blood flow to thermoregulatory and postural stress, in the upper and lower limbs. It is also anticipated that the use of central and peripheral frequency analyses may allude to differing autonomic control of vasomotor tone which may reveal the relative contributions of thermoregulatory and baroreflex drive in different regions. The hypotheses tested were that i) thermal stress alone (i.e., changes in ambient temperature in supine) increases SkBF (predominant thermoregulatory control), with a greater response identified in the forearm microvascular blood flow response, ii) postural stress alone (i.e., supine vs. standing) will cause a decrease in the SkBF (predominant baroreflex control), with a greater response identified in the calf microvascular blood flow response, and iii) a combination of thermal and postural stressors will cause differences in the regional (arm vs. leg) SkBF responses (thermoregulation/baroreflex interaction), altering cardiovascular responses to the transient temperature.

2. Materials and methods

A total of 11 male participants were recruited for the study. Their mean (SD) and range physical characteristics are displayed in Table 1. The protocol was approved by the National Committee for Medical Ethics at the Ministry of Health of the Republic of Slovenia (approval no. 0120–180/2023/7) and conformed to the guidelines of the Declaration of Helsinki. Prior to the start of the study, participants were familiarized with the study protocol and procedures, and gave their written consent for participation. Participants were asked to refrain from caffeine, alcohol, smoking, and intense physical exercise in the 24-h leading up to the study.

Table 1
Mean (SD) and range of participant characteristics.

	Mean (SD)	Range
Age (years)	29.5 (6.7)	23.0–44.0
Body Mass (kg)	81.1 (10.3)	64.4–100.2
Body Stature (cm)	181.5 (6.2)	172.0–193.0
Body Mass Index ($kg \cdot m^{-2}$)	24.6 (3.2)	20.3–31.6
Body Surface Area (m^2)	2.0 (0.1)	1.8–2.2
Blood volume (L)	5.4 (0.5)	4.7–6.1

Body surface area (Mosteller, 1987) and blood volume (Nadler et al., 1962) were calculated using recorded body mass and body stature values.

2.1. Participant information

The minimum required sample size for investigating "repeated measures, within-between factors" was calculated using the results of a previous study (Ciuha et al., 2019). This study identified that during heating there was a difference of 4.9 °C in proximal-distal temperature gradient ($\Delta Tsk_{p\text{-}d}$), an index of skin perfusion, and a difference of 3.0 °C during cooling. Using these data, an effect size (d) between 1.58 and 3.38 for the association between temperature and regional blood flow was computed. Assuming an α of 0.05 and β of 0.99, eight participants would provide sufficient power to detect a statistical difference of a similar magnitude (G*Power Version 3.1.9.2). To account for any potential participant drop-out, a total of 11 participants were screened and recruited for the study. Inclusion/exclusion criteria for participation in the study included: smokers, physically inactive, extreme exposure to hot or cold ambient conditions in one month prior to the onset of the study, a history of freezing or non-freezing cold injuries, a history of microvascular peripheral disease, a history of high or low blood pressure, and diabetes.

2.2. Experimental protocol

Participants attended two separate testing sessions, in which they were positioned in either a supine (SUP) or standing (STA) position for the full duration of a transient ambient temperature protocol described below. Each session was scheduled at the same time of day and conducted on different days with at least 24 h separating the two sessions. Upon arrival at the laboratory participants had their height and naked weight recorded, and were then instrumented in thermoneutral conditions, at a T_A of 23.6 (1.1) °C and relative humidity (RH) of 32.3 (4.3) %. Participants, wearing shorts only, rested in this thermoneutral environment for a further 20-min baseline period, in order to reduce day-to-day variability. Thereafter, the participants were transferred to a climatic chamber (IZR d.o.o., Škofja Loka, Slovenia) in which T_A was maintained at 15.7 (0.6) °C. Once inside the chamber, the participants assumed the designated posture, either SUP or STA. During the SUP trial participants led on a bed at a height of 75 cm. The order of the STA and SUP trials was randomized. The participants were then exposed to a 60-min transient thermal exposure. This exposure comprised an initial 30-min linear increase in T_A to 38.9 (0.6) °C, followed by a 30-min linear decrease in T_A to 15.7 (0.6) °C. The rate of change in T_A was 0.77 $°C \cdot min^{-1}$. RH within the chamber was maintained at 25.9 (6.6) %, and laminar airflow at 0.1 (0.0) $m \cdot s^{-1}$ throughout the trials. A weather station (Kestrel 5400FW, Nielsen-Kellerman, PA, USA) recording T_A and RH was located at a height of 1.5 m. Uniformity of T_A was confirmed within the climatic chamber (3.9 x 2.3 × 2.3 m; 20.6 m^3) at 0.6 m, 1.1 m, and 1.7 m to conform with ISO 7726.

2.3. Measurements

Microvascular blood flow (BF_M). Laser Doppler flowmetry (LDF; MoorVMS-LDF, Moor Instruments, UK) was used to non-invasively determine BF_M of the mid-point of medial aspect of the radius of the right forearm ($SkBF_{arm}$) and muscle-belly of the medial gastrocnemius on the right calf ($SkBF_{calf}$). The device utilizes probes producing a near-infrared laser with a power of 1.0 mW at a wavelength of 780 nm, sampling at 40Hz. The device was calibrated using a fluid undergoing Brownian motion before each testing session. Both measurement sites on the forearm and calf were located on non-glabrous skin, to avoid highly significant and variable effects of arterio-venous anastomoses located within glabrous skin (Walløe, 2016). A permanent marker was used to define locations for replication of the probe placement between sessions. Arbitrary laser doppler flux units were converted into cutaneous vascular conductance (CVC, flux·mmHg^{-1}) as a ratio of LDU flux units to mean arterial pressure (mmHg).

Haemodynamics. Heart rate (HR, min^{-1}) was derived from a five-lead ECG (Finapres NOVA, Finapres Medical Systems B.V., Netherlands). Stroke volume (SV, mL), cardiac output (CO, L·min^{-1}), systemic vascular resistance (SVR, mmHg·min·mL^{-1}), and rate pressure product (RPP, mmHg·min^{-1}) were obtained continuously throughout the protocol period (Finapres NOVA, Finapres Medical Systems B.V., Netherlands). Haemodynamic responses were recorded non-invasively with a finger cuff and calculated using the model flow algorithm (Wesseling et al., 1993) utilizing the finger volume-clamp method and a five-lead electrocardiogram (ECG). Reconstructed systolic and diastolic blood pressures were calculated via direct finger pressure measurements using waveform filtering and level correction (Westerhof et al., 2002), and normalized to the heart level via a height correction unit measuring the hydrostatic pressure difference between the heart and finger. Additionally, participants held their arm in a sling with the measured finger at the heart level.

Skin Temperature (T_{sk}). Measured at minute intervals throughout the protocol using wireless iButton thermistors (type DS1921H, Maxim/Dallas Semiconductor Corp., USA) located at four sites (mid-belly of the bicep brachii, pectoralis major at mid-clavicular level, rectus femoris at femur midpoint, gastrocnemius on medial aspect) on the right side of the body. Weighed T_{sk} was then determined using Ramanathan (1964) equation (T_{sk} = 0.3chest + 0.3arm + 0.2thigh + 0.2calf). A permanent marker was used to define locations for replication of the thermistor placement between sessions. Wireless iButton thermistors have an accuracy of ±1.0 °C, a resolution of 0.125 °C and a range of 15–46 °C.

Tympanic Temperature (T_{ty}). In a previous study (Ciuha et al., 2019) it was established that no significant change in deep body temperature occurred during a similar protocol. As a consequence, the maintenance of deep body temperature during the thermal transient exposure was verified with a non-invasive indicator of deep body temperature; infrared tympanometry. Specifically, tympanic temperature (T_{ty}) of the left ear was measured in triplicate at 5-min intervals throughout the protocol, with the average value used as an indicator of deep body temperature. T_{ty} has been found to have good agreement with esophageal temperature and pulmonary artery temperature in resting humans, with a mean difference between methods of 0.1 °C and 0.85–0. 94 °C, respectively (Brinnel and Cabanac, 1989; Fulbrook, 1997).

Subjective Measures. At 5-min intervals throughout the thermal exposure, participants provided subjective ratings (ASHRAE, 2017) of thermal sensation on a 7-point scale (ranging from cold to hot), and thermal comfort on a 4-point scale (ranging from comfortable to very uncomfortable).

2.4. Mechanistic analyses

Heart Rate Variability (HRV). HRV analysis was used to provides insight into the central autonomic nervous system control. Beat-to-beat heart rate was measured via a 5-lead ECG (described under *haemodynamics*) and the resultant R–R interval (RRi) analyzed using Kubios HRV Software (Version 3.5.0, Kubios Oy, Finland) based on the guidelines produced by Camm et al. (1996). Fast-Fourier transformation (FFT) frequency analysis of the RR-i signal was conducted at 10-min intervals over the full 60-min protocol; with equidistantly sampled data obtained from the RR interval series via a cubic spline interpolation method. A 5-min selection was used at each interval and corrected via threshold-based beat and automatic beat correction algorithms (Lipponen and Tarvainen, 2019). The three main spectral frequencies used were high frequency (HF; 015–0.40 Hz), low frequency (LF; 0.04–0.15 Hz), and very low frequency (VLF; 0.03–0.04 Hz). The parasympathetic nervous system (PNS) index is calculated using mean RR interval, RMSSD, and Poincaré plot index SD1; sympathetic nervous system (SNS) is calculated using mean HR interval, Baevsky's stress index (Baevsky and Berseneva, 2008), and Poincaré plot index SD2. In both indexes, a value of 0 indicates the values resting population averages, whereas positive or negative values indicate the index is above or below population averages; as a result of stress, high intensity exercise, etc. The relative power of each spectral band of frequencies was calculated in proportion to the total power (Sun et al., 1993), and from these the ratio of low frequency (LF) to high frequency (HF) derived in an attempt to derive a quantitative indication of sympathetic/parasympathetic balance.

LDF Wavelet Transform Analysis (WTA). WTA provides information regarding the regulation of skin perfusion occurring via interactions of autonomic stimulation, endothelial control, and myogenic activities (Stefanovska et al., 1999; Bagno and Martini, 2015). Prior spectral investigations of LDF signals using Wavelet Transform Analysis (WTA) have identified six frequency bands which relate to differing vascular control mechanisms: Band I (cardiac; 0.6–2.0 Hz), Band II (respiratory; 0.145–0.6 Hz), Band III (myogenic; 0.052–0.145 Hz), Band IV (Neurogenic; 0.021–0.045 Hz), Band V (endothelial NO-dependent; 0.0095–0.021 Hz), and Band VI (endothelial NO-independent; 0.005–0.0095 Hz). In the present study, WTA analysis was conducted at three time points, using a 2-min stable window at each interval. The three chosen intervals were minute 0 (15.7 (0.6) °C), minute 30 (38.9 (0.6) °C), and minute 60 (15.7 (0.6) °C).

2.5. Statistical analyses

All data was averaged to provide minute values and is reported as mean (SD) throughout. A two-way repeated measures ANOVA compared the effect of two independent variables (the relative change in temperature over time (ΔTemp) and body position) on the dependent variables ($SkBF_{arm}$, $SkBF_{calf}$, HR, SV, CO, SVR, RPP, SBP, DBP, MAP, T_{sk}, T_{ty}). Effect sizes (ES) were calculated using Hedge's G. Three-way ANOVAs at each WTA time-point were conducted, comparing the effect of limb, posture, and frequency interval on WTA results. Finally, segmental linear regressions of T_{sk} (x) and mean CVC (y) were calculated to identify the threshold for increases in BF_M (i.e., upper vasomotor zone); linear regressions post-threshold detected the slope and fit (RMSE) of these data. Data was analyzed using IBM SPSS statistics (Version 26, IL, USA) and Graphpad (Graphpad Prism 9, Version 9.1.2, USA); using an α value of $p < 0.05$.

3. Results

All participants completed the supine protocol condition. However, one participant displayed pre-syncopal symptoms resulting in premature termination of their standing protocol condition. These data were removed from the standing dataset to avoid anomalous results. There was no difference ($p > 0.05$) in haemodynamic and blood flow variables recorded during the final 10 min of the baseline period, ensuring low day-to-day variability within participant.

3.1. Skin and tympanic temperatures

T_{sk} during the SUP condition (32.6 (1.5) °C) was significantly higher than the STA condition (32.2 (1.7) °C) ($p < 0.001$). The difference between the postures was more distinct at lower ambient temperatures (Fig. 1). Thus, the effect of ΔTemp also significantly affected T_{sk} ($p < 0.001$). There was no difference in mean T_{ty} between the two conditions, with an average temperature of 36.9 (0.1) °C in SUP and 36.9 (0.2) °C in the STA condition ($p > 0.05$). Fig. 1 displays the mean (SD) skin temperature in both conditions.

3.2. Subjective ratings

At the onset of the trial where the ambient temperature was lowest, participants rated their thermal sensation as cool/slightly cool (−1.3 (1.0)), and at the highest ambient temperature they rated the exposure as warm/hot (2.4 (0.6)). Upon returning to the low ambient temperatures at the end of the study, participants rated their thermal perception similarly to the start of the protocol (−1.4 (1.0)). Participants reported overall higher thermal comfort during the SUP condition compared to the STA condition ($p = 0.04$). In addition, there was a significant effect of ΔTemp throughout the protocol ($p < 0.001$). At the start of the test (15.7 (0.6) °C), participants thermal comfort was equal between the two postural conditions and described as 'slightly uncomfortable' (0.8 (0.7). Participants' comfort then changed to 'comfortable' at ~25 °C (SUP = 0.1 (0.3), STA = 0.3 (0.3)), before transitioning back to 'slightly uncomfortable' at 38.9 (0.6) °C (SUP = 0.7 (0.6), STA = 1.1 (0.4)).

3.3. Microvascular blood flow

Fig. 2 presents the temporal variation in mean CVC observed in the calf and forearm, in the supine and standing postures. Forearm CVC displayed a significant response to both ΔTemp ($p = 0.003$, $F = 1.599$) and Posture ($p < 0.001$, $F = 275.9$). The lowest forearm CVC during supine was 0.13 flux·mmHg^{-1} whilst in the standing condition it was 0.07 flux·mmHg^{-1}; both conditions observed an increase with temperature up to a maximum mean CVC of 0.24 flux·mmHg^{-1} in SUP and 0.14 flux·mmHg^{-1} in STA. Across the whole protocol, mean forearm CVC in SUP, 0.18 (0.03) flux·mmHg^{-1} was double that of the STA condition, 0.09 (0.02) flux·mmHg^{-1}; indicating the large, significant effect of posture in the arm. Calf CVC was only significantly affected by posture ($p < 0.001$, $F = 144.4$), with a large difference in mean CVC between postures across the whole protocol (SUP = 0.15 (0.02) flux·mmHg^{-1}; STA = 0.09 (0.01) flux·mmHg^{-1}). In neither the arm nor leg, the interaction of both stressors had no effect on CVC, which may be due to little effect of temperature between limbs in the first half of the test. In addition, the timepoints at which the increase in mean CVC occurs varies between the differing conditions. In both the forearm and calf,

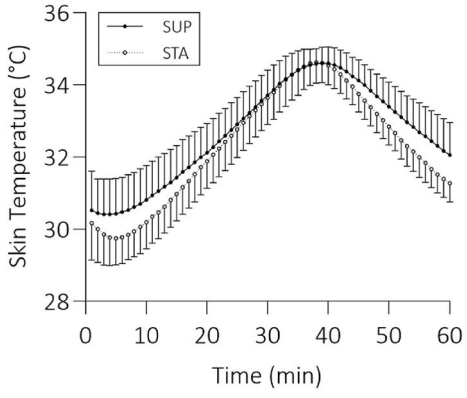
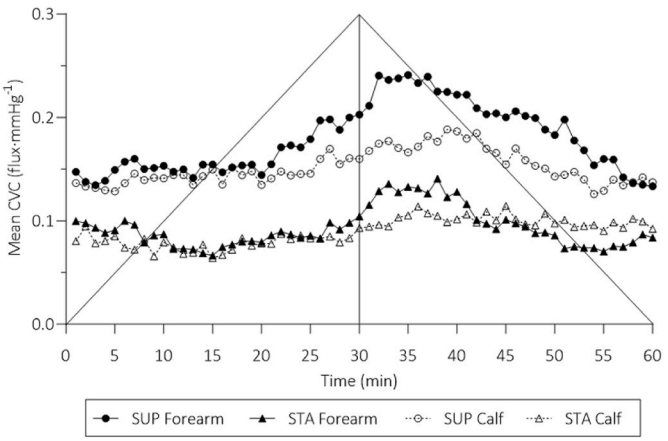


Figure 1. Mean (SD) weighted skin temperature (Tsk) during full protocol, in both supine (SUP) and standing (STA) trials.



Temporal CVC response to transient changes in temperature, and postural conditions.

BF_M begins to substantially increase at 19 min in the SUP condition, and 25 min in the STA condition. However, the time to peak and peak value (i.e., the magnitude) vary considerably between limb region and postural condition. In the forearm, peak BF_M occurs at 31 min in the SUP condition, and 38 min in the STA condition, and in the calf, this happens at 32 min in the SUP condition and 44 min in the STA condition. Therefore, the magnitude of response, during ambient temperature increase, in the forearm was 0.008 flux·mmHg· min^{-1} in SUP and 0.008 flux·mmHg· min^{-1} in STA; while in the calf it was 0.003 flux·mmHg· min^{-1} in SUP and 0.002 flux·mmHg· min^{-1} in STA. For the decrease in temperature, the CVC values reached pre-heating levels, however, the magnitude of response was significantly reduced in the forearm (SUP = 0.004 flux·mmHg· min^{-1}; STA = 0.003 flux·mmHg· min^{-1}), but not in the calf (SUP = 0.004 flux·mmHg· min^{-1}; STA = 0.001 flux·mmHg· min^{-1}).

3.4. Vasomotor threshold

The correlation between T_{sk} and mean CVC (Fig. 3) demonstrates that the threshold for vasodilation occurred at a slightly lower skin temperature in the forearm than in the calf, in both the SUP (forearm = 32.1 °C, calf = 33.0 °C) and STA conditions (forearm = 32.5 °C, calf = 33.3 °C). No observable threshold for vasoconstriction was reached at lower skin temperatures, meaning no data was available for vasoconstriction onset. Regression analyses established that the gain of the

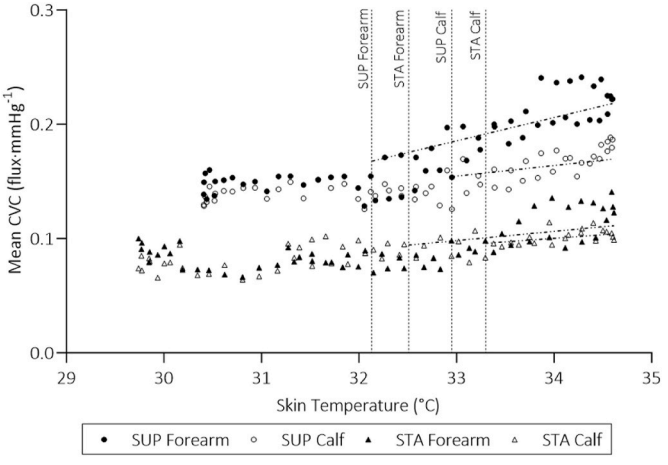


Fig. 3. Mean CVC response as a function of the forearm and calf skin temperature, during both SUP and STA conditions. Dashed lines indicate the thresholds of vasodilation.

response (blood flow (arbitrary units, AU)/CVC (mmHg)) of the forearm in the SUP condition (0.020 flux.mmHg·°C^{-1}) was more than double that of the foot or postural condition (SUP Leg = 0.009 flux·mmHg·°C^{-1}, STA Arm = 0.008 flux·mmHg·°C^{-1}, STA Leg = 0.006 flux·mmHg·°C^{-1}); matching the temporal results observed in Fig. 2. Additionally, RMSE analysis of the variability of individual responses from the best fit identified that the STA condition produced considerably lower values (STA Arm = 0.045 flux·mmHg^{-1}, STA Leg = 0.047 flux·mmHg^{-1}) than the SUP condition (SUP Arm = 0.098 flux·mmHg^{-1}, SUP Leg = 0.096 flux·mmHg^{-1}).

3.5. Haemodynamics

Table 1 provides mean (SD) cardiovascular values at the lowest and highest ambient temperatures observed, in both standing and supine conditions. A lack of hysteresis in haemodynamic variables means no differences were seen between minute-0 and minute-60; hence, only minute-0 is displayed in Table 1. In response to the main effect of ΔTemp, there was a significant increase in HR from 63.2 (10.6) min^{-1} in the cold to 69.5 (13.2) b·min^{-1} in the hot period ($p = 0.008$, F = 1.516, $d = 0.5$). In contrast, there was significant decrease in SV (cold = 93.0 (20.3) mL, hot = 81.3 (20.0) mL, $p < 0.001$, F = 3.309, $d = -0.6$), SBP (cold = 142.0 (14.0) mmHg, hot = 132.6 (14.7) mmHg, $p < 0.001$, F = 4.226, $d = -0.6$), DBP (cold = 109.5 (12.6) mmHg, hot = 105.0 (12.5) mmHg, $p = 0.018$, F = 2.753, $d = -0.4$), and MAP (cold = 89.7 (12.4) mmHg, hot = 88.5 (11.8) mmHg, $p = 0.006$, F = 3.271, $d = -0.1$), as a result of the change in T_A from cold to hot conditions. There were also significant differences as a result of the two postural conditions. HR was significantly higher with 78.6 (9.4)·min^{-1} in the STA condition compared to 59.0 (7.3) min^{-1} the SUP condition ($p < 0.001$, F = 1679, $d = 1.9$); this also occurred in RPP (SUP = 8292.1 (1506.2) mmHg·min^{-1}, STA = 11007.4 (2081.3) mmHg·min^{-1}, $p < 0.001$, F = 15.94, $d = 1.9$), DBP (SUP = 82.8 (10.1) mmHg, STA = 95.6 (10.0) mmHg, $p = 0.002$, F = 13.21, $d = 1.8$), and MAP (SUP = 101.0 (9.9) mmHg, STA = 112.6 (13.2) mmHg, $p = 0.013$, F = 7.655, $d = 1.7$). On the contrary, higher responses were observed in the SUP condition compared to the STA condition in SV only (SUP = 96.1 (18.6) mL, STA = 70.7 (11.1) mL, $p < 0.001$, F = 16.99, $d = -0.6$). Finally, the interaction of both independent variables (ΔTemp and Posture) as stressors caused a significant effect in RPP ($p < 0.001$, F = 4.048), DBP ($p = 0.003$, F = 1.613), and MAP ($p = 0.019$, F = 1.434). In each of these variables the Hot STA condition elicited the highest recorded values, and the Hot SUP produced the lowest values (Table 2). Multiple comparisons analysis of RPP and DBP indicate the crossover between Cold SUP and Hot STA, and Cold STA and Hot SUP, were significantly different from each other.

3.6. Mechanistic analyses

Heart Rate Variability – Fig. 4 displays effects of ΔTemp (indicated by time) and postural condition on a number of key autonomic indices. In response to ΔTemp, significant effects were observed in multiple indices indicating an overall shift towards greater sympathetic activation. PNS at the lowest temperature (i.e., 0-min) was at its peak (SUP = 1.5 (0.2), STA = −0.1 (0.5)), before significantly decreasing to lowest values at minute-40 (SUP = 0.8 (0.2), STA = −1.5 (0.5); $p < 0.001$, F = 13.93). In direct contrast, SNS index at the lowest temperature (0-min) was at its lowest value (SUP = −1.0 (0.2), STA = 0.1 (0.5)), before significantly increasing to a peak at 40-min (SUP = −0.5 (0.2), STA = 1.6 (0.5); $p < 0.001$, F = 12.42). RRi significantly decreased as a result of ΔTemp, with an average decrease of 115.9 (41.5) ms ($p < 0.001$, F = 12.88) from minute 0–30. Finally, the LF/HF ratio significantly increased as a result of ΔTemp ($p < 0.001$, F = 5.821), though this is likely to be solely the influence of the STA condition which increased by from 6.6 (1.8) to 20.12 (4.7) from minute 0–30; compared to an increase from 2.9 (0.2) to 4.0 (0.4) in SUP. This is reflected in the significant interaction of ΔTemp and posture in the LF/HF ratio ($p = 0.003$, F = 4.113). The change in posture condition also caused significant changes in multiple indices. PNS index was significantly lower in the STA condition (−1.0 (0.5)) compared to the SUP condition (1.1 (0.2); $p < 0.001$, F = 24.54, ES = −1.35), whereas the SNS index was significantly higher in the STA condition (SUP = −0.7 (0.2), STA = 1.0 (0.5), $p < 0.001$, F = 24.16, ES = 1.34). The changes in these two indexes between the two conditions signify an increase in sympathetic autonomic activity. Finally, the LF/HF ratio, an indicator of sympho-vagal balance, was significantly higher in the STA condition versus the SUP (SUP = 3.5 (0.4), STA = 14.1 (4.7), $p < 0.001$, F = 52.84, ES = 6.7). In addition, analysis of the spectral frequency distribution identified there was no difference in relative VLF between SUP and STA, however both relative LF (SUP = 60.9 (2.6) %, STA = 85.0 (5.9) %, $p < 0.001$, F = 21.93, ES = 1.8) and relative HF (SUP = 31.9 (2.9) %, STA = 8.0 (3.5) %, $p = 0.002$, F = 17.40, ES = −1.7) were significantly affected. Finally, the interaction of both ΔTemp and posture caused a significant effect in SNS index ($p = 0.003$, F = 4.031),RRi ($p = 0.013$, F = 5.963), and LF/HF ratio as described above.

Wavelet Transform Analysis (WTA) – WTA was conducted on LDF signals recorded at both the forearm and calf, at discreet regions of interest (ROI) at 0, 30, and 60 min (Fig. 5). Three-way ANOVAs conducted at both 0- and 60-min only identified the limb (i.e., forearm or calf) as a significant source of variation in WTA amplitude (0-min – $p < 0.001$, F = 18.36; 60-min – $p = 0.001$, F = 10.53). Multiple comparisons analysis identified that in the 0-min group, STA calf was significantly higher than forearm SUP ($p = 0.039$) or STA ($p = 0.042$) in band 3 (myogenic pathways). In the 30-min ROI, however, limb was again identified as a significant source of variation ($p < 0.001$, F = 30.86) alongside the interaction of limb and posture ($p = 0.015$, F = 5.981); signifying that posture significantly affected vascular control during high ambient temperatures. As in the 0- min analysis, multiple comparisons analysis also noted that STA calf was significantly higher than forearm SUP ($p = 0.039$) or STA ($p = 0.014$) in band 3 (myogenic pathways).

Table 2
Mean (SD) cardiovascular values at absolute lowest (16 °C) and highest (38.6 °C) ambient temperatures, in both supine and standing conditions.

Cardiovascular Parameter	Sig.	Postural condition	Cold Conditions 15.7 °C (Min 0)	Hot Conditions 38.6 °C (Min 30)
Heart Rate *(min^{-1})*	†, *	SUP	57.8 (8.0)	60.0 (7.3)
		STA	70.4 (8.9)	81.5 (8.3)
Stroke Volume *(mL)*	†, *	SUP	96.6 (22.6)	92.1 (20.2)
		STA	85.2 (16.1)	65.0 (6.1)
Cardiac Output *(L·min^{-1})*		SUP	5.6 (1.2)	5.5 (1.0)
		STA	5.8 (0.8)	5.3 (0.6)
Rate Pressure Product *(mmHg·min^{-1})*	*, #	SUP	8957.2 (1651.5)	8018.4 (1539.8)
		STA	10612.9 (2065.8)	11654.9 (2127.8)
Systemic Vascular Resistance *(mmHg·min·mL^{-1})*		SUP	1.1 (0.5)	1.0 (0.3)
		STA	1.1 (0.2)	1.2 (0.2)
Systolic Arterial Pressure *(mmHg)*	†	SUP	138.9 (11.5)	128.8 (12.1)
		STA	143.4 (16.8)	137.3 (16.7)
Diastolic Arterial Pressure *(mmHg)*	†, *, #	SUP	105.9 (11.5)	99.3 (9.2)
		STA	112.2 (13.1)	112.3 (12.7)
Mean Arterial Pressure *(mmHg)*	†, *, #	SUP	86.3 (11.7)	82.4 (9.0)
		STA	92.7 (12.0)	96.5 (10.7)

† = significant effect of ΔTemp, * = significant effect of posture, # = significant interaction of both independent variables, $p < 0.05$.

4. Discussion

In the present study, the role of central (HRV) and peripheral (WTA) mechanisms of microvascular blood flow were assessed in relation to

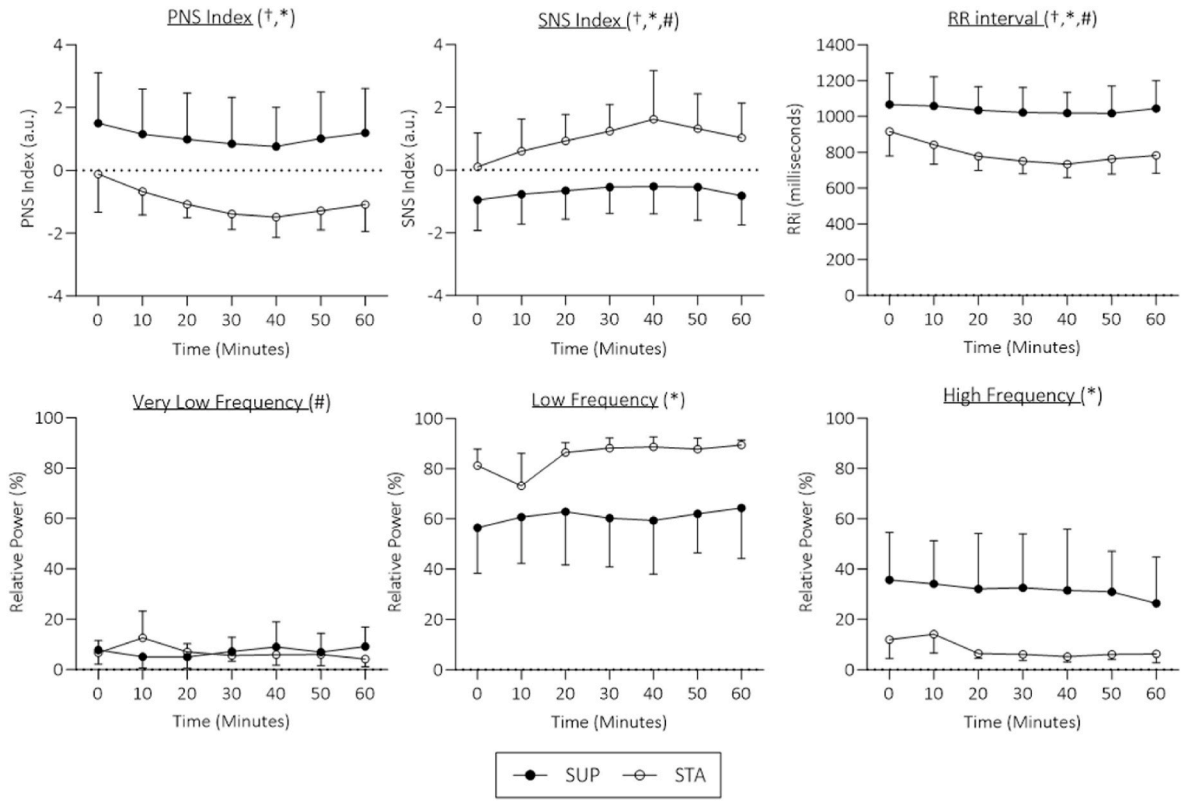


Fig. 4. Impacts of ΔTemp (indicated by time) and postural condition on heart rate variability indices. PNS = parasympathetic nervous system, SNS = sympathetic nervous system, † = significant effect of ΔTemp, * = significant effect of posture, # = significant interaction of both independent variables, $p < 0.05$.

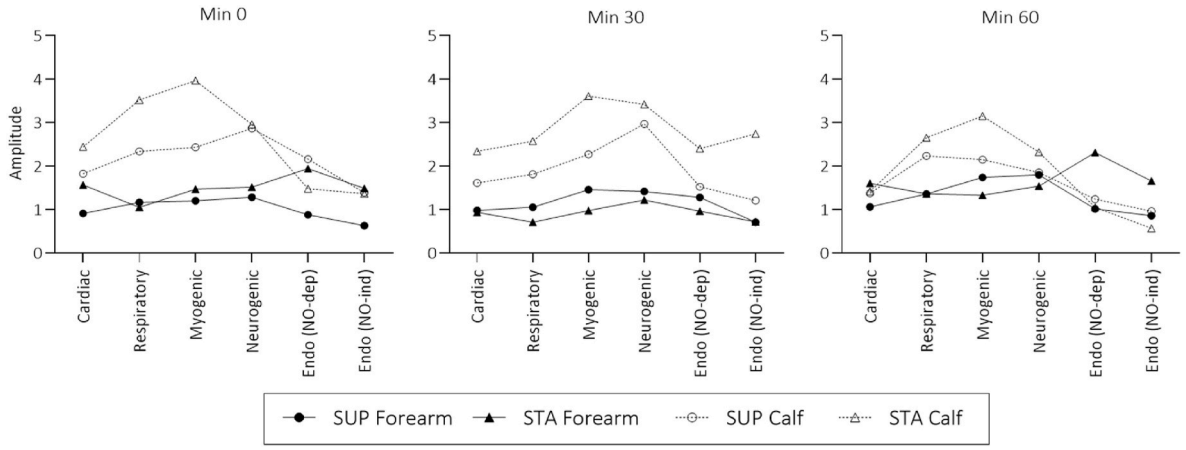


Fig. 5. Relative contributions of vascular activities (denoted by frequency bands on x-axis) calculated by WTA of LDF signals. Analyses conducted at 0-, 30-, and 60-min. Lines between data points do not represent continuous data, only to provide visual aid.

regional vascular responses of the forearm and calf, and its impact on the vasomotor zone. The main findings of this study are that, as previously suggested by Ciuha et al. (2019) and Fisher et al. (2022), there are regional differences in the microvascular response to one or more stressors. The results of the present study suggest, both mechanistically and functionally, that while the microvasculature of the legs remains predominantly baroreflex-controlled, the microvasculature of the arms receives input (and thus interaction) from both (skin temperature and arterial pressure) vascular regulatory mechanisms. Calf CVC minimally responded to the significant increase in ambient temperature during the heating phase of the protocol, and thus was solely affected by the change in posture from supine to standing; thus, confirming that postural stress alone causes a decrease in the SkBF (predominant baroreflex control), with a greater response identified in the calf microvascular blood flow response. Forearm CVC, however, responded to both thermal and postural stressors. There was a 95.1 % increase in CVC during hot conditions when compared to cold conditions, which subsequently decreased by the same magnitude albeit at a slower rate during cooling; a 46.4 % decrease in forearm CVC during the standing condition was also observed. This confirms that thermal stress alone will increase SkBF (predominant thermoregulatory control), with a greater response identified in the forearm microvascular blood flow response, and that a combination of thermal and postural stressors will cause differences in the regional (arm vs. leg) SkBF responses (thermoregulation/baroreflex interaction); altering cardiovascular responses to the transient temperature.

4.1. Functional LDF and haemodynamic response

The effect of posture (or gravity) is observed in the differences between the SUP and STA conditions in a cool ambient. In response to a change in posture, there is a reduction in overall blood flow to the microvascular circulatory system due to a redistribution of blood to different regions of the body. In the STA condition, the influence of gravity redistributes 70% of circulating blood volume below the heart level, creating a cascade of haemodynamic responses to maintain the flow of oxygenated blood to the brain and other vital organs. These responses, including increases in HR, SBP, and DBP, whilst SV decreases, have been commonly observed; thus, were not unexpected in the present study. In the absence of physical and physiological countermeasures to increase orthostatic tolerance such as muscle tensing/pumping (Wieling et al., 2015), symptomatic or episodic orthostatic hypotension and syncope may be likely. Concurrently, responses to heat stress as a lone stressor are commonly understood and are observed in the present study when comparing the difference in responses at 15.7 (0.6) °C and 38.9 (0.6) °C. In situations of greater heat gain via higher temperatures or longer exposure, it is possible that thermoregulatory control of leg vasculature may override the observed baroreflex control. It is also possible that the lessened thermoregulatory input, observed in the present study, in the leg may be a precursor to accelerated damage in certain situations including cold exposure. It has been observed in regional cold-induced vasodilation (CIVD) that a reduced response occurs in the leg regions, which may leave these regions open to greater risk of freezing and non-freezing cold injuries during prolonged cold exposure (Cheung and Mekjavic, 2007; Tsoutsoubi et al., 2022). The combination of changes in ambient temperature and the STA condition produced the requirement for interaction of both thermoregulatory and baroreflex mechanisms. Indeed, this condition produced a lower microvascular flow as circulating blood volume was required for other vital roles. Nonetheless, forearm microvascular flow increased, albeit to a lower magnitude, during the standing trial in response to higher ambient temperatures; indicative of a thermoregulatory drive. This indicates that the interaction of thermal and baroreceptor pathways, while initiated at a central level (Heistad et al., 1973), create differing functional regional responses. This finely balanced interaction is essential in the maintenance of suitable internal body temperatures and appropriate oxygenation of the brain to avoid syncope. One participant in the present study displayed an inability of sustaining this balance, thus experiencing pre-syncopal symptoms. The failure of this balance under heat and orthostatic stress is also observed in literature; Schlader et al. (2016) show a significant leftward shift in a Kaplan-Meier survival probability curve. Similarly, Lind et al. (1968) stated that no participants experienced syncope during 70 °C head-up tilt for 5-min in normothermia, however 25% experienced syncope in a hot ambient climate.

4.2. Vasomotor zone

Upper and lower thresholds for sweating (UCT) and shivering (LCT) define the vasomotor zone (Mekjavic et al., 1991), which may be defined on the basis of either core (Mekjavic et al., 1991) or peripheral (skin temperature; Kakitsuba et al., 2007) temperature thresholds. The present study clearly displays the relationship between T_{sk} and BF_M, in differing postural conditions and regions of the body, which reveal the upper threshold of the vasomotor zone (UCT); denoting vasodilation of BF_M. In agreement with our observations of the forearm exhibiting predominant thermoregulatory control, though still interactive with the baroreflex, the 'vasomotor threshold' occurred earlier in this limb regardless of posture. In fact, the onset of vasomotor activity occurred at a skin temperature 0.9 °C lower in the forearm than in the calf, and the slope of the response (indicating magnitude of BF_M response) was more than double that of the leg. While the UCT was detected in the present study, it appears that skin cooling at the lower ambient temperatures was not sufficient to elicit vasoconstrictive action; thus, the LCT remained undetected. Taniguchi et al. (2011) proposed that the onset of vasoconstriction is reached after 53 min from a starting temperature of 35.5 °C, with a skin cooling rate of 2 °C•h^{-1}. Assuming a similar cooling rate and a peak starting T_{sk} of 34.6 °C, the LCT should have been reached in the present after ~35 min. However, differences in the cooling methods (i.e., ambient air vs. water cooling) may have lengthened the time to threshold in the present study. In addition, whilst the postural condition appeared to have a smaller influence on vasodilation threshold, causing only an average difference regardless of region of 0.3 °C, it did appear to influence the individual variability of the response; RMSE analysis revealed that the variability in STA responses was half that of the SUP condition. It may therefore be considered that the thermoregulatory response alone (i.e., heating in SUP) produces a variety of responses which may be influenced by such inter- and intra-individual characteristics including anthropometry, acclimation, physical fitness, etc., (Ioannou et al., 2022). However, interaction of thermoregulatory and baroreflex responses (i.e., heating in STA) appears to produce a more specific response, which may be due to the preservation of carotid-cardiac modulation of heart rate rather than carotid-vascular responses (Crandall, 2008).

4.3. Central autonomic control

As discussed earlier, several studies have identified the existence of a regional response (Essandoh et al., 1988; Nishiyasu et al., 1992; Hales et al., 1994; Ciuha et al., 2019; Fisher et al., 2022), and alluded to possible reasons for the variation. None, however, have recorded the central and peripheral autonomic responses to differing environmental stressors. In the present study, HRV provided an understanding of the varying sympathetic and parasympathetic neural control at any given temperature, whilst also indicating the source of variation via spectral frequency analysis. Transient change in ambient temperature caused a response in the central sympathetic response, which also resulted in reduced RRi and an increase in HR. The HRV response to acute exposure to heat stress was anticipated, whereby SNS control is activated to regulate thermal balance. These responses have been observed in acute and continuous cooling protocols (Sawasaki et al., 2001), acute hot and cool air temperature exposure (Liu et al., 2008), and long duration hot air exposure (Carrillo et al., 2016); yet only the temporal aspect of heating is often considered, rather than the relationship between T_{sk} or deep body temperature and HRV. It is also clear that the change in posture from SUP to STA represents an orthostatic stressor which activates the SNS regulation of blood flow. Fig. 4 illustrates that in the SUP condition, parasympathetic withdrawal occurs, whilst an increase in SNS activity shifts the sympathovagal balance (LF/HF ratio) towards 'sympathetic dominance'. These results match those of previous research relating to differences between different postures (Acharya et al., 2005), and to graded levels of orthostatic tilt (Montano et al., 1994). As with these previous studies, the observed HRV response of increasing LF (sympathetic) and decreasing HF (vagal) to changes in posture are a baroreceptor response to maintain blood flow to vital organs under diminished venous return caused by lower-limb pooling (>500 mL). Redistribution of blood reduces stretch and unloads arterial baroreflexes, therefore inducing sympathetic adrenergic vasoconstriction of peripheral vasculature (Stewart, 2012) and splanchnic circulation (Fink and Osborn, 2023) to return central blood volume; among other passive blood pooling recoil responses. It is also well understood that slight tachycardia that occurs during standing is a result of SNS vagal activity withdrawal in sinoatrial node activity (Montano et al., 1994). The combination of these responses to increases in SNS activity during standing are major benefits for orthostatic tolerance. However, it is possible that when conflicting neural responses are required, such as during heating and orthostasis, peripheral efferent pathways may alleviate some of the stress on the autonomic system.

4.4. Efferent autonomic control

Peripheral efferent control refers to the interaction of endothelial and myogenic actions, and sympathetic nerves; which regulate flow of blood to the skin via changes in vessel diameters (Bagno and Martini, 2015). Peripheral vascular control is initiated via rostral ventrolateral medullary neurons, passing through intermediolateral cell columns in the spinal cord and activating synapses on sympathetic ganglia which result in vasoactive outputs in blood vessels via norepinephrine (Freeman et al., 2018). Spectral analyses of LDF signals via WTA is suggested to elucidate the activation of different areas due to this peripheral efferent response, by associating the response with a specific frequency interval. In the present study, WTA identified significant differences in the frequency intervals' amplitudes between limbs at all three measured temperatures, which are clearly related to higher myogenic and neurogenic activation in the legs, whilst the arms have clearly definable central control mechanism at either low or high temperatures. This is concurrent with our theory that the arms receive input from two (or more) regulatory mechanisms, whereas in the legs the dominant role is regulation of blood pressure. It was also noted that under peak heat stress there was a significant effect of posture on efferent control, and further analysis identified that the calf exhibited greater activation of myogenic pathways in both cool and hot conditions. This suggests that baroreflex control of blood flow occurs independently of thermoregulatory drive, even under heat stress up to ~40 °C ambient temperature. The ability of the baroreceptor system to override thermoregulation has also been observed during local- and whole-body heating, and LBNP (Crossley et al., 1966; Lind et al., 1968). Research by Pawelczyk and Levine (2002) provides a potential reason as to the greater sympathetic activity in the calf in the present study, postulating that vascular responsiveness of the arms and legs to α-receptor agonists is heterogeneous, with legs displaying larger sensitivity. Further, greater sympathetic tone is required in the lower limbs to maintain circulatory function at rest. After 60-min in the STA condition, the observed reduction in myogenic activities in the leg may be due to reductions in synaptic control responsible for baroreflex efferent activation. This response is similar to those seen in muscle fatigue (Sesboüé and Guincestre, 2006), overtraining syndrome (Carrard et al., 2022), and afferent synaptic pathways (Hay and Hasser, 1998). It is also possible that these changes in efferent baroreflex control are the product of transient outward K^+ current, caused by overuse of the Na^+-K^+ pump, during sustained carotid sinus baroreceptor activation which result in a decline in depolarization frequency, thus reducing vasoconstrictor action in vascular smooth muscle (Chapleau et al., 1995; Ko et al., 2008). It may also be speculated that chronic high-frequency stimulation of afferent baroreceptor pathways (i.e., sympathetic ganglion) may decrease discharge frequency of excitatory potentials (Hay and Hasser, 1998), reducing the requirement for an efferent response (Freeman et al., 2018). It is viable that these factors may contribute to the causes of orthostatic intolerance in the absence of mechanical movement.

4.5. Limitations and future perspectives

Deep body temperature was not directly recorded in the present study, as previous research indicates that the change in temperature and exposure time would not be sufficient to produce any significant change, as reported by Ciuha et al. (2019). Future studies may wish to lengthen the exposure times to compare the regional responses to shifts in deep body temperature. T_{sk} was monitored using thermistors with a high resolution of 0.125 °C but a relatively low accuracy of ±1.0 °C. However, research conducted on iButton thermistors by Smith et al. (2009) report an accuracy closer to ± 0.5 °C with a mean bias from a verified mercury thermometer of +0.121 °C. In the present study, T_{sk} was recorded to indicate the level of heat stress experienced by participants, however, further studies seeking to specifically determine vasomotor zone thresholds should utilize devices with higher accuracy. The two conditions used in the present study produce different levels of stress on the body's thermoregulatory and baroreflex control. The SUP condition focuses purely on thermoregulatory stress, whereas the STA condition creates a conflict between thermoregulatory and baroreflex mechanisms. An issue that remains unresolved is the interaction of constant ambient temperature and transient levels of gravitational stress in the head-to-foot direction in the regional regulation of blood flow.

5. Conclusion

We conclude that, mechanistically and functionally, the arm vasculature responds swiftly to modulation from multiple regulatory mechanisms including thermoregulation and baroreceptor activity. The legs, meanwhile, are more sensitive and strongly innervated by baroreflex regulatory mechanisms. These observed regional responses aid the haemodynamic response to multiple stressors, however if the interaction is unbalanced syncope or heat illness may occur.

Data availability statement

Data available on request.

Funding

Jason T. Fisher is recipient of a Slovene Research and Innovation Agency Young Investigator Scholarship (PR-10488). This work was supported by the Slovene Research and Innovation Agency (ARIS Program grant no. P2-0076).

CRediT authorship contribution statement

Jason T. Fisher: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Urša Ciuha:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Igor B. Mekjavić:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

References

Acharya, U.R., Kannathal, N., Hua, L.M., Yi, L.M., 2005. Study of heart rate variability signals at sitting and lying postures. J. Bodyw. Mov. Ther. 9, 134–141.

ASHRAE, A., 2017. ASHRAE Standard 55: Thermal Environmental Conditions for Human Occupancy. American Society of Heating, Refrigerating and Air-Conditioning Engineers, Atlanta, GA, USA.

Baevsky, R., Berseneva, A., 2008. Methodical Recommendations Use Kardivar System for Determination of the Stress Level and Estimation of the Body Adaptability Standards of Measurements and Physiological Interpretation. Moscow.

Bagno, A., Martini, R., 2015. Wavelet analysis of the Laser Doppler signal to assess skin perfusion. In: 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). IEEE, pp. 7374–7377.

Brinnel, H., Cabanac, M., 1989. Tympanic temperature is a core temperature in humans. J. Therm. Biol. 14, 47–53.

Camm, A.J., Malik, M., Bigger, J.T., Breithardt, G., Cerutti, S., Cohen, R.J., Coumel, P., Fallen, E.L., Kennedy, H.L., Kleiger, R.E., 1996. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 93, 1043–1065.

Carrard, J., Rigort, A.-C., Appenzeller-Herzog, C., Colledge, F., Königstein, K., Hinrichs, T., Schmidt-Trucksäss, A., 2022. Diagnosing overtraining syndrome: a scoping review. Sports Health 14, 665–673.

Carrillo, A.E., Flouris, A.D., Herry, C.L., Poirier, M.P., Boulay, P., Dervis, S., Friesen, B.J., Malcolm, J., Sigal, R.J., Seely, A.J., 2016. Heart rate variability during high heat stress: a comparison between young and older adults with and without Type 2 diabetes. Am. J. Physiol. Regul. Integr. Comp. Physiol. 311, R669–R675.

Chapleau, M.W., Cunningham, J.T., Sullivan, M.J., Wachtel, R.E., Abboud, FoM., 1995. Structural versus functional modulation of the arterial baroreflex. Hypertension 26, 341–347.
Charkoudian, N., 2003. Skin blood flow in adult human thermoregulation: how it works, when it does not, and why. In: Mayo Clinic Proceedings. Elsevier, pp. 603–612.
Cheung, S.S., Mekjavic, I.B., 2007. Cold-induced vasodilatation is not homogenous or generalizable across the hand and feet. Eur. J. Appl. Physiol. 99, 701–705.
Ciuha, U., Tobita, K., McDonnell, A.C., Mekjavic, I.B., 2019. The effect of thermal transience on the perception of thermal comfort. Physiol. Behav. 210, 112623.
Crandall, C.G., 2008. Heat stress and baroreflex regulation of blood pressure. Med. Sci. Sports Exerc. 40, 2063.
Crossley, R., Greenfield, A., Plassaras, G., Stephens, D., 1966. The interrelation of thermoregulatory and baroreceptor reflexes in the control of the blood vessels in the human forearm. J. Physiol. 183, 628–636.
Essandoh, L.K., Duprez, D.A., Shepherd, J.T., 1988. Reflex constriction of human limb resistance vessels to head-down neck flexion. J. Appl. Physiol. 64, 767–770.
Fink, G.D., Osborn, J.W., 2023. The splanchnic circulation. In: Primer on the Autonomic Nervous System. Elsevier, pp. 223–226.
Fisher, J.T., Ciuha, U., Ioannou, L.G., Simpson, L.L., Possnig, C., Lawley, J., Mekjavic, I. B., 2022. Cardiovascular responses to orthostasis during a simulated 3-day heatwave. Sci. Rep. 12, 19998.
Freeman, R., Abuzinadah, A.R., Gibbons, C., Jones, P., Miglis, M.G., Sinn, D.I., 2018. Orthostatic hypotension: JACC state-of-the-art review. J. Am. Coll. Cardiol. 72, 1294–1309.
Fulbrook, P., 1997. Core body temperature measurement: a comparison of axilla, tympanic membrane and pulmonary artery blood temperature. Intensive Crit. Care Nurs. 13, 266–272.
Hales, J., Nielsen, B., Yanase, M., 1994. Skin blood flow during severe heat stress: regional variations and failure to maintain maximal levels. In: Temperature Regulation. Springer, pp. 195–200.
Hay, M., Hasser, E.M., 1998. Measurement of synaptic vesicle exocytosis in aortic baroreceptor neurons. Am. J. Physiol. Heart Circ. Physiol. 275, H710–H716.
Heistad, D.D., Abboud, F.M., Mark, A.L., Schmid, P.G., 1973. Interaction of thermal and baroreceptor reflexes in man. J. Appl. Physiol. 35, 581–586.
Ioannou, L.G., Foster, J., Morris, N.B., Piil, J.F., Havenith, G., Mekjavic, I.B., Kenny, G.P., Nybo, L., Flouris, A.D., 2022. Occupational heat strain in outdoor workers: a comprehensive review and meta-analysis. Temperature 9, 67–102.
Kakitsuba, N., Mekjavic, I.B., Katsuura, T., 2007. Individual variability in the peripheral and core interthreshold zones. J. Physiol. Anthropol. 26, 403–408.
Ko, E.A., Han, J., Jung, I.D., Park, W.S., 2008. Physiological roles of K+ channels in vascular smooth muscle cells. J. Smooth Muscle Res. 44, 65–81.
Lind, A., Leithead, C., McNicol, G., 1968. Cardiovascular changes during syncope induced by tilting men in the heat. J. Appl. Physiol. 25, 268–276.
Lipponen, J.A., Tarvainen, M.P., 2019. A robust algorithm for heart rate variability time series artefact correction using novel beat classification. J. Med. Eng. Technol. 43, 173–181.
Liu, W., Lian, Z., Liu, Y., 2008. Heart rate variability at different thermal comfort levels. Eur. J. Appl. Physiol. 103, 361–366.
Mekjavic, I.B., Bligh, J., 1989. The increased oxygen uptake upon immersion: the raised external pressure could be a causative factor. Eur. J. Appl. Physiol. Occup. Physiol. 58, 556–562.
Mekjavic, I.B., Sundberg, C.J., Linnarsson, D., 1991. Core temperature" null zone". J. Appl. Physiol. 71, 1289–1295.
Montano, N., Ruscone, T.G., Porta, A., Lombardi, F., Pagani, M., Malliani, A., 1994. Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. Circulation 90, 1826–1831.
Mosteller, R., 1987. Simplified calculation of body surface area. N. Engl. J. Med. 317, 1098.
Nadler, S.B., Hidalgo, J.U., Bloch, T., 1962. Prediction of blood volume in normal human adults. Surgery 51, 224–232.
Nielsen, M., Herrington, L.P., Winslow, C.-E., 1939. The effect of posture upon peripheral circulation. American Journal of Physiology-Legacy Content 127, 573–580.
Nishiyasu, T., Shi, X., Gillen, C.M., Mack, G.W., Nadel, E.R., 1992. Comparison of the forearm and calf blood flow response to thermal stress during dynamic exercise. Med. Sci. Sports Exerc. 24, 213–217.
Pawelczyk, J.A., Levine, B.D., 2002. Heterogeneous responses of human limbs to infused adrenergic agonists: a gravitational effect? J. Appl. Physiol. 92, 2105–2113.
Ramanathan, N., 1964. A new weighting system for mean surface temperature of the human body. J. Appl. Physiol. 19, 531–533.
Rowell, L.B., Brengelmann, G.L., Blackmon, J.R., Murray, J.A., 1970. Redistribution of blood flow during sustained high skin temperature in resting man. J. Appl. Physiol. 28, 415–420.
Savage, M.V., Brengelmann, G.L., 1996. Control of skin blood flow in the neutral zone of human body temperature regulation. J. Appl. Physiol. 80, 1249–1257.
Sawasaki, N., Iwase, S., Mano, T., 2001. Effect of skin sympathetic response to local or systemic cold exposure on thermoregulatory functions in humans. Auton. Neurosci. 87, 274–281.
Schlader, Z.J., Wilson, T.E., Crandall, C.G., 2016. Mechanisms of orthostatic intolerance during heat stress. Auton. Neurosci. 196, 37–46.
Sesboüé, B., Guincestre, J.-Y., 2006. Muscular fatigue. Ann. Readapt. Med. Phys 49, 348–354.
Shepherd, J.T., 1966. Role of the veins in the circulation. Circulation 33, 484–491.
Smith, A.H., Crabtree, D., Bilzon, J., Walsh, N., 2009. The validity of wireless iButtons® and thermistors for human skin temperature measurement. Physiol. Meas. 31, 95.
Stefanovska, A., Bracic, M., Kvernmo, H.D., 1999. Wavelet analysis of oscillations in the peripheral blood circulation measured by laser Doppler technique. IEEE (Inst. Electr. Electron. Eng.) Trans. Biomed. Eng. 46, 1230–1239.
Stewart, J.M., 2012. Mechanisms of sympathetic regulation in orthostatic intolerance. J. Appl. Physiol. 113, 1659–1668.
Sun, J., Eiken, O., Mekjavic, I., 1993. Autonomic nervous control of heart rate during blood-flow restricted exercise in man. Eur. J. Appl. Physiol. Occup. Physiol. 66, 202–206.
Taniguchi, Y., Lenhardt, R., Sessler, D.I., Kurz, A., 2011. The effect of altering skin-surface cooling speeds on vasoconstriction and shivering thresholds. Anesth. Analg. 113, 540–544.
Tsoutsoubi, L., Ioannou, L.G., Mantzios, K., Ziaka, S., Nybo, L., Flouris, A.D., 2022. Cardiovascular stress and characteristics of cold-induced vasodilation in women and men during cold-water immersion: a randomized control study. Biology 11, 1054.
Walløe, L., 2016. Arterio-venous anastomoses in the human skin and their role in temperature control. Temperature 3, 92–103.
Wesseling, K., Jansen, J., Settels, J., Schreuder, J., 1993. Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J. Appl. Physiol. 74, 2566–2573.
Westerhof, B.E., Guelen, I., Parati, G., Groppelli, A., van Montfrans, G.A., Wieling, W., Wesseling, K.H., Bos, W.J.W., 2002. Variable day/night bias in 24-h non-invasive finger pressure against intrabrachial artery pressure is removed by waveform filtering and level correction. J. Hypertens. 20, 1981–1986.
Wieling, W., Van Dijk, N., Thijs, R., de Lange, F., Krediet, C.P., Halliwill, J., 2015. Physical countermeasures to increase orthostatic tolerance. J. Intern. Med. 277, 69–82.
Wilson, T.E., Cui, J., Zhang, R., Witkowski, S., Crandall, C.G., 2002. Skin cooling maintains cerebral blood flow velocity and orthostatic tolerance during tilting in heated humans. J. Appl. Physiol. 93, 85–91.