Finger constrictor and thermoperceptual responsiveness to localised cooling following 5 weeks of intermittent regional exposures to moderately augmented transmural vascular pressure

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ABSTRACT

Purpose: To examine the effects of prolonged intermittent exposures to moderately increased transmural pressure on finger vasoreactivity and thermoperception to localised cooling.

Methods: Eleven men completed a 5-week regimen (3 sessions-week⁻¹; 55 min-session⁻¹), during which the vasculature in one arm (EXP) was exposed intermittently (10-min exposure: 5-min pause) to increased transmural pressure (from +65 mmHg week-1 to +105 mmHg week-5). Before and after the regimen, finger cutaneous vascular conductance (CVC), temperature (T avg), and thermoperception (thermal sensation, discomfort and pain) were monitored during a 30-min hand cold (8 °C water) provocation trial. The responses of the non-trained hand were examined during an additional cold trial.

Results: After the regimen, baseline finger CVC and T avg were higher in both hands (p ≤ 0.01). During cooling, neither finger CVC nor T avg were modified (p > 0.05). Yet the magnitude of the cold-induced drop of CVC was augmented in both hands, and to a similar extent (p ≤ 0.02). The regimen alleviated thermal pain in both hands (p ≤ 0.02); the sensation of coldness and thermal discomfort were attenuated mainly in the EXP hand (p = 0.02).

Conclusions: Present findings indicate that iterative local exposures to augmented intravascular pressure do not alter finger vasoreactivity to localised cooling. The pressure training, however, might impair finger basal vasomotor tone, and aggravate the magnitude of constrictor responsiveness to cooling. The pressure training also elicits thermoperceptual desensitisation to noxious thermal stimulus. To large extent, these vascular and perceptual adjustments seem to be transferred to the cutaneous vasculature of the non-trained limb.

1. Introduction

Direct localised cooling evokes, promptly and in a stimulus-dependent manner, an adrenergically-mediated increase in cutaneous vasomotor tone, minimising heat loss to the surroundings. In glabrous skin regions (e.g., finger) however, the initial vasoconstriction is typically interrupted by episodes of vasodilatation (cold-induced vasodilation, CIVD; Lewis, 1930), which transiently elevate skin temperature, and alleviate thermal pain and discomfort (Keramidas et al., 2010; Kreh et al., 1984). The mechanisms underlying CIVD remain unsettled (for review, see Cheung and Daanen, 2012); yet the arteriovenous anastomoses, wherein a major locus of the response resides, seem to play a major role (Bergersen et al., 1999).

Recurrent evidence has suggested that, in healthy humans, sustained or repeated manipulations of local intravascular pressure alter in vivo mechanical properties of precapillary resistance vessels (for review, see Eiken et al., 2014). Thus, a 5-week pressure-training regimen, during which intermittent moderate elevations in the transmural pressure of the vasculature of one arm were provoked, enhanced the wall stiffness of arteries and arterioles (Eiken and Kolegard, 2011). This adaptive response, limited solely to the limb subjected to the pressure-training stimulus, may be associated with functional (i.e., enhanced myogenic tone) and/or structural (i.e., changes in elastic recoil) vascular alterations. Conceivably, the venoarteriolar response, describing a rapid locally-mediated reduction in blood flow when the limb venous pressure is raised >25 mmHg (Crandall et al., 2002; Henriksen et al., 1973;
Okazaki et al., 2005), might also be modulated by such a regimen. It is therefore reasonable to assume that the vascular dysfunction and/or remodeling ensued from iterative local intravascular pressure increments may also modify the cutaneous vascular responsiveness to thermal stress. Interestingly, cross-sectional studies have demonstrated that the constrictor reactivity of non-glabrous skin (forearm) to either thermal stress. Interestingly, cross-sectional studies have demonstrated that the constrictor reactivity of non-glabrous skin (forearm) to either heat or cold is augmented in patients with essential hypertension, in whom functional and structural modifications in the microvasculature are commonly engendered by systemic arterial pressure elevations (cf. Rizzoni and Agabiti Rosei, 2006).

Accordingly, the present study aimed to investigate, in healthy normotensive men, if, or to what extent, finger cutaneous vasoreactivity to localised cooling would be modulated by long-term, iterative intravascular pressure elevations. A within-subject design was employed, wherein finger blood flow and temperature, as well as regional thermoperception, were monitored during a hand cold (8 °C water) provocation trial, before and after a 5-week pressure-training regimen, during which the vasculature in one arm (henceforth, EXP arm) was exposed intermittently to high transmural pressure. To eliminate any inter-individual variation, the vasomotor function of the contralateral (i.e., not pressure-trained; CON) hand was also examined during an additional cold provocation trial. We hypothesised that the pressure-training regimen would increase finger cold-induced vasoconstriction; a response that would be confined to the EXP hand. On the basis of previous work indicating that cross-desensitisation may occur between pain/discomfort evoked by pressure distension of local blood vessels and by local cold provocation (Keramidas et al., 2014), we further hypothesised that the cold-induced pain and discomfort would be ameliorated after the pressure training. Yet, inasmuch as the habituation to pain is transferable, at least partly, to the non-trained limb (Eiken and Kolegard, 2011; Eiken et al., 2012; Keramidas et al., 2014), we anticipated that any thermoperceptual adjustment would be evident in both hands.

2. Methods

2.1. Ethics approval

The experimental protocol was approved by the Human Ethics Committee of Stockholm (2014/1801–32), and conformed to the standards set by the Declaration of Helsinki. Subjects were informed in detail about the experimental procedures before giving their written consent to participate, and were aware that they could terminate their participation at any time. The study was part of a larger project investigating the functional and structural adaptations of precapillary vessels in response to 5 weeks of intermittent local vascular pressure increment (see Eiken et al., 2021).

2.2. Subjects

Eleven healthy male students participated in the study [mean (range): age 25 (21–31) years, body mass 77.4 (60.3–97.7) kg, height 183 (170–193) cm, total skinfold thickness 93.0 (58.5–150.0) mm, body fat 12.8 (7.3–20.7) %]. Subjects were normotensive, non-smokers, were not taking any medication, and had no history of any cold injury. All were physically active on a recreational basis; and they were asked to maintain their exercise and dietary routines, as well as to avoid cold exposure throughout the intervention period. Ten of the subjects were right-handed, and one was left-handed.

2.3. Study design

The study was performed between October and April in a laboratory of the Division of Environmental Physiology, Royal Institute of Technology (Stockholm, Sweden). All subjects completed a 5-week local vascular pressure-training regimen, during which the blood vessels in the non-dominant (EXP) arm were exposed intermittently to high transmural pressure (see below for details). The contralateral (i.e., dominant) arm served as the CON arm. Two days before and three days after the pressure-training regimen, subjects underwent two 30-min hand cold-water immersions, one with the EXP hand, and the other with the CON hand; the trials were separated by a 30-min interval. The order of the trials, which for each individual was kept constant between the two testing sessions (before and after the pressure-training regimen), was alternated among subjects: the first provocation was with the EXP hand for six subjects, and with the CON hand for five subjects. The pre- and post-trials were performed at the same time of the day. Testing was conducted by the same investigators. Subjects were instructed to abstain from alcohol and strenuous exercise for 24 h prior to each trial, and to refrain from caffeine during the testing day.

2.3.1. Local cold provocation

Before each trial, subjects were accustomed to the laboratory ambient conditions for ~40 min, while they were instrumented. The mean (standard deviation) temperature, relative humidity and barometric pressure were 24.5 (0.8) °C, 23 (4)% and 752 (9) mmHg, respectively. Subjects were always clad in T-shirt, short trousers and socks; and they remained in an upright sitting position throughout. Each trial commenced with a 5-min baseline phase, during which subjects rested with both hands on a customized hand-support at the level of their hips. Thereafter, the tested hand was covered with a thin plastic bag, and was immersed up to the ulnar and radial styloid processes for 5 min in 35.0 (0.1) °C water (warm-water immersion; WWI phase). Next, subjects immersed their hand, which was still in the plastic bag, in a different tank filled with 8.0 (0.1) °C water for a 30-min period (cold-water immersion; C WI phase) (Mekjavic et al., 2013). The water was continuously stirred, and its temperature was monitored by a thermometer (Physitemp Instruments Inc., Clifton, NJ, USA). After the completion of the CWI phase, the hand was removed from the water, and a 15-min spontaneous rewarming (RW) phase ensued, during which the hand was resting on the hand-support as in the baseline phase. Cardiovascular, thermal and perceptual responses were monitored throughout the local cold provocation trial (see the Instrumentation Section).

2.3.2. Pressure-training regimen

The training was performed 3 days-week−1; the duration of each session was 55 min. Throughout each session, the EXP arm was positioned inside an airtight Plexiglas cylinder (length: 66 cm, diameter: 25 cm), and was hermetically sealed to the opening of the cylinder slightly distally of the axilla, by use of a short self-sealing rubber sleeve. The cylinder was placed at the level of the heart. Pressure in the cylinder was reduced to the desired level by use of a vacuum pump; the cylinder was equipped with a pressure-release safety valve set to open at a pressure differential of 130 mmHg. Each session consisted of four 10-min sub-atmospheric pressure exposures, intervened by 5-min pauses with normal atmospheric pressure. During the 10-min exposure, the local transmural pressures in the enclosed vasculature were gradually increased over a 1-min period, and then maintained at the targeted plateau: the local transmural pressures in the enclosed blood vessels were increased by 65 mmHg during the 1st week, by 75 mmHg the 2nd week, by 85 mmHg the 3rd week, by 95 mmHg the 4th week and by 105 mmHg the 5th week. The plateau pressure was also slightly gauged so that the perceived arm pain never exceeded 3 (i.e., moderate) on a 10-point scale (from 0—no pain to 10—maximal pain) (Fig. 1).

2.4. Instrumentation

2.4.1. Systemic cardiovascular responses

Beat-to-beat systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures were measured using a volume-clamp technique (Finometer, Finapres Medical Systems BV, Amsterdam, the Netherlands), with the pressure cuff placed around the middle phalanx of the non-immersed
middle finger, and with the reference pressure transducer positioned at the level of the heart. The Finometer-derived values were verified intermittently by electro-sphygmomanometry (Omron, M6, Kyoto, Japan). Heart rate (HR) was derived from the arterial pressure curves as the inverse of the inter-beat interval. Cardiac stroke volume (SV) was estimated by a three-element model of arterial input impedance from the arterial pressure waveform (Modelflow, Finometer; Wesseling et al., 1993). Cardiac output (Q) was calculated by multiplying SV with HR.

2.4.2. Finger skin blood flow

Local skin blood flow was monitored at a rate of 40 Hz on the palmar side of the distal phalanx of the immersed index finger by laser-Doppler flowmetry (VMS-LDF2; Moor Instruments, Axminster, UK) using an optic probe (VP1/7; Moor Instruments, UK), which was firmly connected to the skin with double-sided adhesive tape. The probe was calibrated before each session against Brownian motion with a standardized colloidal suspension of polystyrene microspheres. Skin blood flow was reported as cutaneous vascular conductance (CVC), calculated as skin blood flow divided by MAP. Finger CVC data were presented as absolute values, as well as relative changes (ΔCVC) from the WWI phase.

2.4.3. Thermometry

Skin temperatures of the immersed fingers were measured with copper-constantan (T-type) thermocouple (each conductor was 0.2 mm in diameter) probes (Physitemp Instruments Inc., Clifton, NJ, USA), which were attached to the skin on the middle of the palmar side of the distal phalanx of each finger. The primary insulation of the thermocouples was attached directly to the skin with thin air-permeable tape. Temperatures were sampled at 1 Hz with a NI USB-6215 data acquisition system, and processed with LabVIEW software (National Instruments, Austin, Texas, USA). The average (Tavg), minimum (Tmin), and maximum (Tmax) temperature of each finger obtained during each phase was calculated using a custom-made computer program based on TestPoint (v7, Norton, MA). Considering the well-described heterogeneity of the CIVD response among fingers (Cheung and Mekjavic, 2007; Norbrand et al., 2017), the incidence of CIVD events, and magnitude of finger CIVD was assessed only by the skin temperature data. Thus, the TestPoint program was also used to detect any finger CIVD event, defined as a local skin-temperature wave in terms of ≥1 °C increase lasting for a minimum duration of 3 min. In case of a CIVD event, the temperature amplitude (∆T), defined as the difference between the lowest temperature recorded just before the CIVD and the highest temperature reached during the CIVD, was also determined.

During the baseline, and at the end of the CWI phase, the tympanic temperature was measured using an infrared thermometer (ThermoScan IRT3020, Braun, Kronberg, Germany). Two consecutive measurements were obtained each time, and the higher of the two values was used for subsequent analysis.

2.4.4. Perceptual measurements

During the baseline, CWI (at minutes 1, 2, 3, 4, 5 and every 5 min thereafter) and RW (at minutes 1, 5, 10 and 15) phases, subjects were asked to provide ratings of their immersed-hand thermal sensation (from 1-cold to 7-hot), thermal comfort (from 1-comfortable to 4-very uncomfortable) and pain (from 0-no pain to 10-maximal pain). At the same time intervals, the general affective valence was also assessed by means of the feeling scale (from −5-very bad to +5-very good).

2.5. Statistical analyses

An a priori power calculation was based on a previous study (Eikiken and Kolegard, 2011) examining the effects of the pressure-training regimen on the mechanical properties of precapillary resistance vessels, using α = 0.05 and β = 0.85 (G*Power 3.1 software, Heinrich-Heine-Universität, Düsseldorf, Germany; Faul et al., 2007). Data from the baseline and WWI phases were calculated as averages of each 5-min period. All physiological data obtained during the CWI and RW phases were reduced to 60-sec averages. Normality of distribution for all datasets was assessed using the Shapiro-Wilk test. A 2-way (hand (EXP vs. CON) × testing period (pre vs. post)) repeated measures analysis of variance (ANOVA) was employed for all physiological variables. When ANOVA revealed significant effects, multiple pairwise comparisons were performed with Tukey honestly significant difference post hoc test. To evaluate pre vs. post training differences within each hand, comparisons were performed with paired, two-tailed t-tests. Differences in perceptual responses were evaluated with Friedman’s test, followed by a Wilcoxon test. Effect size was calculated using Cohen’s d (values of <0.2, <0.5 and ≥0.5 are considered as small, moderate and large, respectively) and r (values of <0.1, <0.3 and ≥0.8 are considered as small, moderate and large, respectively) for the parametric and nonparametric pairwise-comparisons, respectively. Statistical analyses were conducted using Statistica 8.0 (StatSoft, Tulsa, OK) and Prism 8.0 (GraphPad Software Inc., San Diego, CA, USA). Unless otherwise stated, data are presented as mean values with 95% confidence intervals (CIs), which were calculated using a non-central t-distribution. The α-level of significance was set a priori at 0.05.

3. Results

3.1. Finger CVC and Tavg during the baseline and WWI phases

Baseline CVC and Tavg in both hands were higher after the pressure-training regimen (p ≤ 0.01; Fig. 2A). CVC remained elevated (p ≤ 0.001; Fig. 2B), and Tavg tended to be increased (p = 0.07; Fig. 2B) during the post-training WWI phase. No differences were noted between hands at any time point (p > 0.05).

3.2. Finger CVC and skin temperature during the CWI and RW phases

Regardless of which hand, CVC was not modified by the pressure-training, during either the CWI (p = 0.23) or the RW (p = 0.92) phases (Fig. 3A). Yet, in the post-training CWI phase, the magnitude of cold-induced drop in finger CVC (i.e., ΔCVC) was augmented in both hands, and to a similar extent (EXP hand: p = 0.02, d = 0.62, and CON hand: p = 0.01, d = 0.84; Fig. 3B). Finger ΔCVC in the CON hand (p = 0.01, d = 0.90), but not in the EXP hand (p = 0.19, d = 0.52), was greater in the post- than in the pre-training RW phase (Fig. 3C).
0.22) did not vary between trials (Table 1). RW T avg was also similar in the two trials (EXP hand: pre = 24.2 [2.5] °C, post = 24.7 [2.6] °C, and CON hand: pre = 23.4 [2.9] °C, post = 24.3 [2.6] °C; p = 0.60).

3.3 Arterial pressures, HR, SV, $\dot{Q}$ and tympanic temperature

The mean values of SAP, DAP, MAP, HR, SV and $\dot{Q}$ are summarized in Table 2. SAP, DAP and MAP (Fig. 4) were enhanced during the CWI phase ($p < 0.001$). None of the systemic haemodynamic responses differed between trials, or were altered by the pressure-training regimen ($p > 0.05$). Tympanic temperature differed neither between nor across the trials (EXP hand: pre: Baseline = 36.2 [0.3] °C, CWI = 36.2 [0.3] °C, post: Baseline = 36.1 [0.3] °C, CWI = 36.2 [0.3] °C, and CON hand: pre: Baseline = 36.3 [0.4] °C, CWI = 36.3 [0.4] °C, post: Baseline = 36.1 [0.3] °C, CWI = 36.1 [0.3] °C, p = 0.90).

3.4 Perceptual responses

During the baseline and WWI phases, thermal sensation, thermal comfort, and affective valence were similar in all trials ($p > 0.05$; Table 3). Mean and individual values for thermal sensation, thermal comfort and pain obtained during the CWI and RW phases are depicted in Fig. 5. Subjects perceived their EXP hand less cold in the post-training than in the pre-training CWI phase ($p = 0.02, r = 0.47$). In the EXP hand, the cold-induced discomfort was also ameliorated ($p = 0.02, r = 0.49$); and tended to be lower than in the CON hand after the training ($p = 0.06, r = 0.39$). Neither the sensation of coldness ($p = 0.26, r = 0.26$) nor the thermal discomfort ($p = 0.10, r = 0.34$) were modified in the CON hand. During the post-training CWI phase, the cold-evoked pain was attenuated in both hands, and to a similar extent (EXP hand: pre = 1 (−4−3), post = 2 (−2−4), and the CON hand: pre = 1 (−4−3), post = 2 (−2−4); $p < 0.01$). Subjects felt more pleasant during the post-training RW of the EXP [mean (range) pre = 2 (−2−5), post = 2 (0−5)] hand ($p = 0.01$).

4. Discussion

Using a within-subject design, the study evaluated, in healthy men, finger vasomotor function and thermoreception to direct localised cooling following a 5-week period of intermittent transmural pressure increments in the vasculature of an arm. The pressure-training regimen did not increase the cutaneous vasomotor tone during the local cold provocation. Yet, considering the post-training elevation in cutaneous
basal blood flow and temperature, the magnitude of cold-induced vasoconstriction was slightly augmented after the training regimen. Contrary to our hypothesis, the response was prevalent in the EXP hand, as well as in the CON hand. Consistent with our secondary hypothesis, the pressure-training regimen diminished the cold-evoked pain in both hands; still, the sensation of coldness and thermal discomfort were attenuated mainly in the EXP hand.

4.1. Effects of pressure training on finger vasomotor function

After the pressure-training regimen, finger blood flow and temperature were consistently elevated throughout the pre-cooling phases. The

Table 1

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Values are mean (95% confidence interval). Values for CIVDs are mean (total incidence). Fingers: I, thumb; II, index; III, middle; IV, ring; V, small.
increase, which was manifested in both hands in nine out of eleven subjects, was independent of any confounding influence from variations in ambient temperature: in all trials, subjects were accustomed to the room temperature, which was carefully controlled and maintained at \( \sim 24.5 \, ^\circ\text{C} \) (pre: \( 24.4 (0.7) \, ^\circ\text{C} \), post: \( 24.5 (0.9) \, ^\circ\text{C} \); \( p = 0.27 \)), for at least a 30-min period prior to the initiation of the baseline recording (Wright et al., 2006). In addition, the trials were performed at the same time of the day to control for any circadian fluctuations in skin blood flow (Krauchi and Wirz-Justice, 1994). Subjects’ general thermal status, and baseline autonomic tone were also similar in the two trials, as indicated by the pre-immersion values of tympanic temperature, HR and arterial pressures, respectively. Although psychogenic stress may modulate, in a transient manner, acral cutaneous circulation (Delli et al., 1972), it is highly unlikely that any post-training alteration in subjects’ emotional state (e.g., reduced anticipatory stress) could explain the persistent increase in finger CVC.

The modest elevation in finger basal skin blood flow noted after the pressure training is indeed surprising, and its mechanistic origin cannot be elucidated by the current design. Of interest in this regard is the original observation by Duff (1956) that, compared to in normotensive individuals, hand blood flow was slightly enhanced in essential hypertensive patients with discrete increases in arterial pressure; whereas conversely it was reduced in patients with severe hypertension. In our study, since the rise in finger CVC was prevalent in both hands, we assume that the response was attributable to a training-dependent modification of systemic, rather than of local, mediator(s) of cutaneous vascular tone. During thermoneutrality, finger blood flow is highly variable, and is governed by neural, and endothelial mechanisms (for reviews, see Johnson et al., 2014; Taylor et al., 2014). Notably, based on the data from our recent work (Eiken et al., 2021) that is part of the same cohort as the present, the basal circulating values of plasma endothelin-1 (ET-1) were enhanced by \( \sim 30\% \) after the pressure-training regimen. ET-1 is a potent vasoconstrictor; and increased concentrations have been detected in individuals with essential hypertension (Schneider et al., 2000), as well as with primary Raynaud phenomenon (Sulli et al., 2009). ET-1’s mode of action however depends on the receptor subtype activated, and in particular the location of these receptors. That is, although ET-1 induces cutaneous vasoconstriction primarily via ET-A receptors, ET-B receptors may mediate either vasoconstriction or vasodilatation, depending on their localisation (Kellogg et al., 2001; Verhaar et al., 2006). In addition, the trials were performed at the same time of the day to control for any circadian fluctuations in skin blood flow (Krauchi and Wirz-Justice, 1994). Subjects’ general thermal status, and baseline autonomic tone were also similar in the two trials, as indicated by the pre-immersion values of tympanic temperature, HR and arterial pressures, respectively. Although psychogenic stress may modulate, in a transient manner, acral cutaneous circulation (Delli et al., 1972), it is highly unlikely that any post-training alteration in subjects’ emotional state (e.g., reduced anticipatory stress) could explain the persistent increase in finger CVC.

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Table 2
Mean [95% of confidence interval] values of systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures, heart rate (HR), stroke volume (SV), and cardiac output (Q) obtained during the cold provocation trials, pre and post a 5-week pressure-training regimen.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pre-training</th>
<th>Post-training</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>WWI</td>
</tr>
<tr>
<td>EXP hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q (l·min(^{-1}))</td>
<td>6.6 [0.6] 6.7 [0.7] 6.5 [0.5] 6.4 [0.7]</td>
<td>6.5 [0.7] 6.6 [0.7] 6.5 [0.6] 6.5 [0.6]</td>
</tr>
<tr>
<td>CON hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q (l·min(^{-1}))</td>
<td>6.4 [0.6] 6.5 [0.7] 6.4 [0.7] 6.2 [0.7]</td>
<td>6.1 [0.6] 6.1 [0.6] 6.1 [0.6] 6.2 [0.6]</td>
</tr>
</tbody>
</table>

Fig. 4. Mean [95% confidence interval] and individual changes in mean arterial pressure (ΔMAP; relative to the warm-water immersion phase) during the cold-water immersion (CWI) of the pressure-trained (EXP) and non-trained (CON) hand, pre and post a 5-week pressure-training regimen.

Table 3
Mean (range) values of thermal sensation, thermal comfort, pain and affective valence during the baseline and warm-water immersion (WWI) phases of the pressure-trained (EXP) and non-trained (CON) hand, pre and post a 5-week pressure-training regimen.

<table>
<thead>
<tr>
<th>Trial</th>
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<th>Post-training</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>WWI</td>
</tr>
<tr>
<td>EXP hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thermal comfort</td>
<td>1 1 1 1</td>
<td>1 1 1 1</td>
</tr>
<tr>
<td>Pain</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
</tr>
<tr>
<td>Affective valence</td>
<td>3 (0–4) 3 (0–4) 3 (0–4) 3 (0–5)</td>
<td>3 (0–4) 3 (0–4) 3 (0–4) 3 (0–5)</td>
</tr>
<tr>
<td>CON hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thermal comfort</td>
<td>1 1 1 1</td>
<td>1 1 1 1</td>
</tr>
<tr>
<td>Pain</td>
<td>0 0 0 0</td>
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</tr>
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<td>Affective valence</td>
<td>3 (0–4) 3 (0–4) 3 (0–5) 3 (0–5)</td>
<td>3 (0–4) 3 (0–4) 3 (0–5) 3 (0–5)</td>
</tr>
</tbody>
</table>
vessels, whereas its impact on the arteriovenous anastomoses, which are located predominantly on the palmar side of the fingers, may be minute. Hence, the mechanisms underlying the post-training elevation in finger perfusion remain unclear and need to be investigated further.

The 5-week pressure-training did alter the in vivo mechanical properties of precapillary resistance vessels (see Eiken et al., 2021), conforming with the findings of previous similar work (Eiken and Kolegard, 2011), but ostensibly failed to modify the finger cutaneous vasomotion to localised cooling. Based on the premise that the intensity of a vasomotor response to a given stimulus is depended largely on its basal level of activity (Hodges et al., 2007; O’Leary, 1991), it might however be expected that the cold-evoked reduction in finger CVC and

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Fig. 5. Mean [95% confidence interval] and individual values of thermal sensation (upper graphs), thermal comfort (middle graphs), and pain (lower graphs) during the cold-water immersion (CWI; A), and spontaneous rewarming (RW; B) of the pressure-trained (EXP) and non-trained (CON) hand, pre and post a 5-week pressure-training regimen. Significant difference * between pre and post trials.
$T_{noy}$ had been attenuated post training. Instead, despite the elevated basal perfusion of the acral cutaneous microcirculation, the absolute values in finger CVC and $T_{noy}$ attained during the CWI phases, as well as the incidence of CIVD events, did not differ between the pre- and post-training trials. It appears therefore that the magnitude of finger constriction instigated by the localised cooling (i.e., the relative change from the pre-immersion values) might be augmented after the pressure-training regimen. The response, which prevailed in both hands alike, was probably independent of any inter-trial variation in the degree of sympathetic discharge produced by the cold stress (Fig. 4). Presumably, the acral constrictror response observed in the present study, might have been dictated by the severity of the cold stimulus employed; thus, the 8 °C water may have overridden any potential influence from the pre-immersion finger vasomotor state. Alternatively, and considering the post-training shift in the basal levels of ET-1 (see Eiken et al., 2021), the magnitude of finger vasoreactivity might conceivably be linked to greater cold-induced elevation of ET-1. An increase in ET-1 is typically prompted by localised cold stress, and is associated with the reductions in skin blood flow (Fryerquist et al., 1990; Nakamura et al., 2003). Still, the cold-induced release of ET-1 does not determine the CIVD occurrence (Nakamura et al., 2003), which appears to be governed primarily by central sympathetic components (Flouri and Cheung, 2005; Hodges et al., 2018; Keramidas et al., 2019). Possibly, the pressure-training regimen might also have enhanced the venoarteriolar response, even though the impact of prolonged intravascular pressure loading on this reflex is unknown. During limb dependency, the cutaneous venoarteriolar reflex appears however to be unaffected following sustained periods of pressure unloading encountered in bedrest (Gabrielsen et al., 1999) and spaceflight (Gabrielsen and Norsk, 2007), whereas it may be attenuated in patients with essential hypertension (Cesarone et al., 1999).

4.2. Effects of pressure training on hand thermo-reception and -nociception

In line with previous work (Eiken and Kolegard, 2011), a gradual desensitisation to pain provoked by the transvascular pressure increments occurred during the course of the training intervention (Fig. 1). This hypoalgesic effect has mainly been ascribed to training-induced reductions in local venous distensibility, resulting in reduced stimulation of perivascular unmyelinated and thinly myelinated nerve endings. Along with such peripheral adaptations, training-related adjustments at a central nervous level might also be involved (Heinricher et al., 2009; Rennefeld et al., 2010); in view of the evidence that the habituation to pain evoked by venous overdistension is not limited to the site of the repetitive vascular pressure treatments, but is to some extent also transferred to untreated regions (i.e., the contralateral limb; Eiken and Kolegard, 2011).

Interestingly, and in accord with our previous work (Keramidas et al., 2014), the training-induced nociceptive habituation was generalised across two different sensory modalities: that is, the blunted pain responsiveness to mechanical stimulus was transferred to the noxious alised across two different sensory modalities: that is, the blunted pain and Kolegard, 2011). site of the repetitive vascular pressure treatments, but is to some extent justments at a central nervous level might also be involved ( Heinricher endings. Along with such peripheral adaptations, training-related ad ditions occurred during the course of the training intervention -nociception

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Interestingly, and in accord with our previous work (Keramidas et al., 2014), the training-induced nociceptive habituation was generalised across two different sensory modalities: that is, the blunted pain responsiveness to mechanical stimulus was transferred to the noxious stimulus (8 °C) thermal stimulus. Likewise, the sensations of coldness and thermal discomfort were alleviated after the pressure-training, especially in the EXP hand. The post-training sensory and hedonic evaluation of the fixed cold stimulus was dissociated from the actual thermal and vaso motor state of the hand. These thermoperceptual changes were noted throughout the CWI phase, and did not describe any temporal variation; presumably indicating that both the cutaneous receptors, activated during the initial phase of cooling, and the perivascular receptors, stimulated during protracted deep cooling (Fruhstorfer and Lindblom, 1983; Klemeni and Arndt, 1992), might have been desensitised to cold. Yet the observed heterotopic habituation effects (i.e., in the non-trained limb), as well as the stimulus generalisation, support the notion that the training-induced thermoperceptual adaptation was mediated mainly by central circuit modifications (Rennefeld et al., 2010; Rhudy et al., 2010; Sanchez et al., 2020).

4.3. Conclusions

Present findings indicate that long-term, iterative local exposures to moderately augmented transvascular pressure gradients do not alter acral skin vasoreactivity to direct localised cooling. Yet the repeated manipulations of the transmural pressure might reduce finger basal vasomotor tone, and potentiate the magnitude of constrictor responsiveness to cooling. The vascular-pressure-training regimen appears to also elicit regional thermoperceptual desensitisation, alleviating the cold-induced pain and discomfort. These vascular and perceptual adjustments are not restricted to the limb exposed to the repeated intra vascular pressure loading, but to large extent seem to prevail also in the cutaneous vasculature of the contralateral, non-trained limb. Future studies are warranted, to clarify mechanisms underlying the cutaneous vascular adaptations to local moderate elevations of transvascular pressures.

CRediT authorship contribution statement

M.E.K., R.K., and O.E. conception and design of research; M.E.K., R. K., P.S. performed experiments; M.E.K. analyzed data; M.E.K., R.K. and O.E. interpreted results of experiments; M.E.K. prepared figures; M.E.K. drafted manuscript; M.E.K., R.K., P.S. and O.E. edited and revised manuscript. All authors approved the final version of manuscript.

Declaration of competing interest

No conflicts of interest, financial or otherwise, are declared by the authors.

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