Exposure to acute noxious heat evokes a cardiorespiratory shock response in humans

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ABSTRACT

Background: Noxious acute cold stimuli cause cold shock via the sympathetic nervous system. However, no studies have investigated respiratory “heat shock” in response to noxious acute heat stimuli (> 42 °C).

Methods: In the present study, we examined whether short-duration whole-body immersion (for 5 min) in noxious hot water (45 °C) is a sufficient stimulus to induce a respiratory acute shock response.

Results and conclusion: Our results indicate that short-duration whole-body immersion in noxious 45 °C water produces a significantly greater body temperature, heart rate, and perceptual and respiratory strain than immersion in innocuous warm 37 °C water (p < .05). The initial first minute of hot water immersion (HWI) at 45 °C (vs. immersion at 37 °C) caused a cardiorespiratory shock response, which manifested as acute hyperventilation, and increased ventilatory tidal volume, respiratory exchange ratio, and heart rate (p < .05). Adjustment to this initial respiratory heat shock response within the first minute of immersion was observed as compared with remaining HWI time (1–5 min).

Introduction

The evolution of a body’s ability to detect (sense), avoid, or deal with noxious (cold or hot) temperatures is crucial for the survival of a living organism [1,2]. Over the past decades, several family members of temperature-activated, so-called thermo-transient receptor potentials (TRPs) have been put forward as potential molecular temperature sensors. They are highly expressed in skin and can be functionally activated by changes in the whole range of physiologically relevant temperatures, from painful heat through intermediate warmth to painful cold [1,3,4]. The activity of these thermo-TRP channels is regulated through their temperature-evoked currents, which increase in a steep but graded manner across their temperature-activation range [1]. The higher the thermo-TRP channel current, the higher the centrally driven thermo-regulatory response. The involvement of several thermo-TRP channels with overlapping expression in nociceptor neurons has been suggested as a powerful mechanism that ensures avoidance of noxious (cold or hot) temperatures [3,5].

Noxious stressors (e.g., pain, cold, hypoxia) cause an increase in the minute ventilation rate in humans [6]. Evidence indicates that respiratory cold shock is maximal during the first minute of whole-body naked immersion in water at a temperature below 15 °C [7]. It evokes particularly hazardous inspiratory gasps, hyperventilation, tachycardia, peripheral vasoconstriction, and increased blood pressure [6,8,9], leading to increased risk in near-drowning incidents and drowning deaths after accidental immersion in open waters [10]. Intriguingly, no such respiratory “heat shock” response has been found in innocuous warm (≤ 41 °C) [1], whole-body water immersion [11,12]. However, more recently, triple (TKO) and double (DKO) knockout studies in mice have identified a TRP Plet of ion channels, involving overlapping set expression of TRPV1, TRPA1, and TRPM3 channels, which mediate current (summed increase in discharge frequency of impulses of nerve fibers) causing a maximal noxious heat-sensing response [3,5]. In a more delicate DKO (DKOV1/M3 and DKOV1/A1) study, the TRPV1 channel was identified as the most abundant and most sensitive heat sensor of the three [5], with a channel current activity threshold of ∼ 42 °C [13,14]. This observation led to the hypothesis that in healthy humans, whole-body immersion in noxious hot 45 °C (vs. innocuous warm 37 °C) water would evoke a respiratory heat shock response, as manifested by increases in heart rate (HR), minute ventilation (Vt), breathing frequency (BF), tidal volume (Vt), oxygen uptake/consumption...
(VO$_2$), carbon dioxide washout/production (VCO$_2$), and respiratory exchange ratio (RER).

**Materials and methods**

**Participants**

Eighteen male volunteers were assessed for eligibility. Participants were excluded if they smoked or had Raynaud’s syndrome, asthma, a neurological pathology, or another condition that could be worsened by acute exposure to hot (45°C) water. The inclusion criteria were as follows: (i) between 20 and 30 years old; (ii) no excessive regular sport activities (i.e., < 3 times per week and 150 min of moderate intensity or 75 min of vigorous intensity activity per week); (iii) no involvement in any temperature-manipulation program or extreme temperature exposure for 3 months; (iv) no medications or dietary supplements that could affect experimental variables; (v) no needle phobia; and (vi) had a regular sleep schedule (7–9 h of sleep per night). Fifteen men met the inclusion criteria and agreed to participate in this study. The physical characteristics of the participants are presented in Table 1. Written informed consent was obtained from all participants after explanation of all details of the experimental procedures and the associated discomforts and risks. All procedures were approved by the Regional Human Research Ethics Committee (No. BE-2–30) and were conducted according to the guidelines of the Declaration of Helsinki, with the exception of registration on a clinical trials database. The participants were in self-reported good health, which was confirmed by a medical history and physical examination.

**Experimental design**

**Rationale for the experiment**

Mainly because water is > 800 times denser than air [15], heat transfer (thermal conductivity) by water is 25 times greater than by air alone [16,17]. Considering that the change in skin temperature (T$_sk$) in the first 20 s of immersion is essential to evoke a maximal respiratory shock response [6], we used 5-min whole-body naked immersion in noxious hot water to evaluate the effects in terms of acute respiratory (heat shock) parameter response. In the current study, we chose to apply noxious 45°C water [1], but within safe time limits and with no risks in scalding [18]. The evoked responses were compared with those induced by immersion in innocuous warm (37°C) water in order to evaluate the hydrostatic pressure effect and with those induced by transition to an empty bath at thermoneutral conditions in order to evaluate the acute postural change effect.

**Familiarization session**

One week before the experiment, the participants were familiarized with the laboratory setting and test procedures. They were instructed to sleep for 7–9 h the night before the experiment and to refrain from strenuous exercise, alcohol, and caffeine for at least 24 h before the experiment. Thus, any participants who mentioned that they had slept less than 6 h the night before the experiment were excluded from participation. To avoid the effect of diet-induced thermogenesis, the participants fasted for 10 h before the onset of each trial [19]. To standardize the conditions of hydration and the feeling of thirst, subjects could drink water up to 60 min before the first body mass measurement [20].

**Experimental protocol**

The study consisted of experiments with (i) a brief (5-min) immersion of whole body in 37°C water (WI-37°C trial); (ii) a brief (5-min) immersion of whole body in hot 45°C water (HWI-45°C trial); and (iii) a brief (5-min) control trial in an empty bath in thermoneutral conditions at an ambient temperature of 24°C and 60% relative humidity (CON). These trials were performed in a balanced random order (cross-over design) at least 1 week apart. We used the IBM Statistical Package for the Social Sciences (SPSS) for Windows version 22.0 (IBM Corp., Armonk, NY, USA) to determine which trial each participant underwent first.

Experiments began in November and continued for 4 months, with average atmospheric temperatures of 5.4°C in autumn and 0.5–2.8°C in winter. The acute heat-stress procedure was performed in the morning (08:00–10:00 a.m.). On arrival, participants voided their bladders to estimate the level of hydration based on the specific gravity (SG) of urine (PocketChem UA PU-4010, Arkray Factory Inc., Kyoto, Japan). All subjects were found to be well hydrated (SG, 0.010–0.020). Next, each subject was weighed unclothed. The participant donned swimming briefs covering the genitals and buttocks (7% of body surface area [BSA]) [21] and self-inserted a rectal probe, after which the strap used for recording HR was attached to the chest. The participant was then asked to lie in a semi-recumbent position for 20 min and to stand for 5 min at an ambient temperature of 24°C and 60% relative humidity. The resting baseline pulmonary ventilatory (V$_E$, V$_T$, BF) values, pulmonary gas exchange (VO$_2$, VCO$_2$, RER) values, and HR were recorded during the last 2 min of the standing position. Baseline pre-immersion values of skin (T$_sk$), muscle (T$_mu$), and rectal (T$_re$) temperatures were then measured, and the CON, WI, or HWI procedure began. The participant was fully immersed within a period of 5 s in a semi-recumbent position up to the level of the manubrium in a 37°C (WI-37°C trial), 45°C (HWI-45°C trial) stirred water bath, or underwent CON trial in an empty towel-covered bath under thermoneutral conditions. Pulmonary ventilatory values, pulmonary gas exchange values, and HR were

Table 1. Physical characteristics of the participants in the study.

| Number of participants | 15 |
|------------------------|----|
| Age, yr                | 25 ± 2 |
| Height, cm             | 187.40 ± 1.59 |
| Mass, kg               | 88.69 ± 2.01 |
| Body mass index, kg m$^{-2}$ | 25.28 ± 0.56 |
| Body fat, %            | 17.93 ± 1.13 |
| Mean skinfold thickness, mm | 11.85 ± 1.40 |
| Body surface area, m$^2$ | 2.15 ± 0.11 |

Values are expressed as the mean ± standard error of the mean.
recorded continuously throughout CON, WI-37°C, and HWI-45°C trials. Each participant was asked to evaluate his subjective perception at the end of CON, WI-37°C and HWI-45°C. After 5 min, the participant exited the bath and within 1 min Tsk, T.re, and T.mu were measured. Finally, the participant was weighed unclothed once again.

Experimental measurements

Anthropometric measurements

Body mass and body fat were measured using a body composition analyzer (TBF-300, Tanita, Arlington Heights, IL, USA) and the body mass index was calculated. BSA was estimated according to the formula: 

\[ \text{BSA} = 128.1 \times \text{weight}^{0.44} \times \text{height}^{0.60} \]  

[22]. Skinfold thickness was calculated as the average thickness of 10 skinfold sites (chin, subscapular, chest, side, suprailium, abdomen, triceps, thigh, knee, and calf) [23] using a medical skinfold caliper (SH5020, Saehan, Masan, South Korea). The bodily sweat loss was calculated by subtracting the body mass measured after the CON, WI and HWI from that measured before the CON, WI and HWI [24].

Body temperature measurements

\( T_{\text{re}} \), \( T_{\text{sk}} \), and \( T_{\text{mu}} \) were measured before and immediately (within 1 min of leaving the bath) after CON, WI-37°C, and HWI-45°C trials. \( T_{\text{re}} \) was measured using a thermocouple (accuracy, ± 0.01°C. Rectal Probe, Ellab, Hvidovre, Denmark) inserted to a depth of 12 cm past the anal sphincter [25]. The rectal thermistor sensor was placed by each participant. \( T_{\text{sk}} \) was measured with thermistors (accuracy, ± 0.01°C, Skin/ Surface Probe, DM852, Ellab) at three sites: midlines of the anterior surface of the right scapula (back), the anterior surface of the right thigh (thigh), and midline of posterior surface of the right forearm (forearm). The mean \( T_{\text{sk}} \) was calculated using the equation as 

\[ T_{\text{sk}} = 0.5_{\text{back}} + 0.36_{\text{thigh}} + 0.14_{\text{forearm}} \]  

[26] was measured with a needle microprobe (accuracy, ± 0.01°C, Intramuscular Probe, MKA, Ellab) inserted to a depth of 3.5 cm under the skin covering the largest bulk of the lateral gastrocnemius muscle in the right leg. For skin preparation before each \( T_{\text{mu}} \) measurement, the skin was shaved and disinfected before and after insertion of the microprobe using a cotton wool pad soaked with medicinal alcohol. No local anesthesia was administered before insertion. After the first measurement, the insertion area was marked with a circle with a diameter of 0.5 cm to ensure that the same insertion point was used in later measurements [27].

Spirometry and HR measurements

A mobile spirometry system (Oxycon Mobile, Jaeger/VIASYS Healthcare, Hochberg, Germany) was used to measure changes in \( V_{\text{E}} \), \( V_{\text{r}} \), BF, \( V_{\text{O}_2} \), and \( V_{\text{CO}_2} \) on a breath-by-breath basis with a sampling rate of 0.2 Hz. The RER was calculated as 

\[ \text{RER} = \frac{V_{\text{CO}_2}}{V_{\text{O}_2}} \]  

Automatic calibration of the gas analyzer and delay time was performed before the measurements, as described by the manufacturer. A calibration gas at 180 kPa (15.2% \( \text{O}_2 \), 5.02% \( \text{CO}_2 \), and 79.62% \( \text{N}_2 \)) was supplied to attain gain, offset, and delay times within 1%. HR was measured before and throughout CON, WI-37°C, and HWI-45°C trials using an HR monitor (V800, Polar Electro OY, Kempele, Finland).

Subjective ratings

The method described by Cernych et al. [28] was used to measure subjective ratings for thermal and sweating sensations. Thermal sensation ratings ranged from 1 (very cold) to 9 (very hot), with 5 being neutral. Sweating ratings ranged from 4 (being neutral) to 1 (heavily sweating). Subjective ratings were recorded at the end of 5-min for CON, WI-37°C, and HWI-45°C trials.

Statistical analysis

The number of participants was selected based on the calculated sample effect size, following the use of the data involving the first five subjects who completed the study. At an \( \alpha \) value of 0.05 and \( \beta \) (power) value of 80%, our power analysis indicated that 15 participants in a within-condition comparison would be required to detect a large effect (\( p < .05; \eta^2 > 0.25 \)) for hypothesized parameters.

The data were tested for normality using the Shapiro–Wilk test before parametric statistical analyses, and all data were found to be normally distributed. Differences between the three trials (CON vs. WI-37°C vs. HWI-45°C) for the baseline states of body weight, body temperatures, and spirometry indices were analyzed by one-way repeated-measures analysis of variance (ANOVA) using Tukey’s adjustment for within-subject factors.

Two-way repeated-measures ANOVA was used to analyze the effects of the three temperature conditions (CON, WI-37°C, and HWI-45°C) and time (pre- vs. post- CON, WI-37°C, and HWI-45°C; pre vs. 0–1 min vs. 1–5 min) on the dependent body temperature, HR, and spirometry variables. Two-way repeated-measures ANOVA was also performed to study the effects of the three temperature conditions (CON, WI-37°C, and HWI-45°C) and time kinetics (baseline (start) value vs. values obtained at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, and 60s) during the immersion or condition in a thermoneutral empty bath with respect to dependent variables (HR and spirometry indices). When significant main effects were found, Sidak’s post hoc adjustment was used for multiple comparisons across a set of conditions within each repeated-measures ANOVA. A dependent-sample t test was used to locate the difference in time points and condition. The non-parametric Wilcoxon’s signed-rank test for two related samples (CON vs. WI-37°C vs. HWI-45°C) was used to compare changes in subjective ratings of perception (thermal sensation and sweating). The partial eta squared (\( \eta^2 \)) was estimated as a measure of the temperature condition and time effect size.

Statistical significance was defined as \( p < .05 \). Descriptive data are presented as mean ± standard error of the mean.
(SEM). Statistical analyses were performed using IBM SPSS (v. 22; IBM Corp., Armonk, NY, USA).

Results

Body temperature response

No differences in baseline $T_{re}$ (Figure 1A), $T_{mu}$ (Figure 1B), and $T_{sk}$ (Figure 1C) were observed among conditions ($p > .05; \eta^2_p < 0.1$). There was no significant change in $T_{re}$ from before to after CON and WI-37°C conditions ($p > .523$ and $p = .491$, respectively), whereas HWI at 45°C temperature resulted in a significant $0.21 \pm 0.05$°C $T_{re}$ increase ($p < .001; \eta^2_p = 0.32$), with a significant time x trial interaction ($p < .01; \eta^2_p > 0.4$).

There was no significant change in $T_{mu}$ and $T_{sk}$ from before to after CON trial ($p > .05; \eta^2_p < 0.05$). Whole-body head-out immersion at both 37°C and 45°C water temperatures resulted in significant $T_{mu}$ and $T_{sk}$ increase ($p < .01; \eta^2_p > 0.3$). As expected, the $T_{mu}$ $0.59 \pm 0.09$°C vs. $0.18 \pm 0.04$°C, mean change from the pre-immersion value; $p < .001; \eta^2_p = 0.46$ and $T_{sk}$ $7.13 \pm 1.25$°C vs. $2.37 \pm 0.98$°C, mean change from the pre-immersion value; $p < .001; \eta^2_p = 0.52$) increased more in the HWI-45°C trial condition than in the HWI-37°C trial condition, with a significant time x trial interaction ($p < .001; \eta^2_p > 0.4$).

HR response

No difference in baseline HR (Figure 2B) was observed between conditions ($p > .85; \eta^2_p < 0.04$). The initial first minute (0–1 min) of whole-body immersion in 45°C water resulted in a significant HR increase ($19.85 \pm 4.74$ bpm, mean change from the pre-immersion value) (trial effect: $p = .009; \eta^2_p = 0.425$). There was no significant mean value change in HR during the initial first minute of whole-body transition to an empty bath compared with baseline value ($0.39 \pm 0.24$ bpm, mean change from the pre-transition value) ($p = .821; \eta^2_p = 0.041$). During the remaining (1–5 min) immersion time, HR continued to increase only in HWI-45°C trial ($p = .032; \eta^2_p = 0.261$, compared with 0-to-1 min point), whereas in WI-37°C and CON trials, HR decreased below the baseline value ($p < .001; \eta^2_p > 0.5$). The decrease in HR was significantly greater in CON trial than in WI-37°C trial (trial effect: $p = .031; \eta^2_p = 0.261$). For all described effects, a significant trial x time interaction was found ($p < .05; \eta^2_p > 0.25$).

In more detailed time-course (slope) kinetic analyses (Figure 2A), we found that on immersion in 45°C water, HR abruptly (within initial 5–10 s) increased ($p < .001; \eta^2_p > 0.4$) and then decreased gradually within the remaining 30–40 s of the initial first minute without reaching the baseline (start) value ($p = .009; \eta^2_p = 0.289$). On the other hand, on immersion in 37°C water as well as on whole-body transition to an empty bath, HR abruptly (within initial 10–15 s) increased ($p < .001; \eta^2_p > 0.45$) and then declined gradually to the baseline (compared with start value, $p = .421; \eta^2_p = 0.071$) or even below the baseline level (compared with start value, $p = .0141; \eta^2_p = 0.272$), respectively, within the remaining 30 s of the initial first minute. The peak value of HR during the initial first minute was significantly higher in HWI-45°C conditions than in WI-37°C and CON conditions ($p < .01; \eta^2_p > 0.29$). There was no difference between WI-37°C and CON trial conditions for peak HR ($p = .748; \eta^2_p = 0.067$). For all described effects, a significant trial x time interaction was found ($p < .05; \eta^2_p > 0.3$).

Pulmonary $V_E$, $V_T$, and BF responses

As shown in Figure 3, no differences in baseline $V_E$ (Figure 3D), $V_T$ (Figure 3E), and BF (Figure 3F) were observed between conditions ($p > .05; \eta^2_p < 0.09$). Whole-body immersion in water at both temperatures as well as control thermoneutral condition in an empty bath induced a significant increase in $V_E$ ($p < .01; \eta^2_p > 0.3$), $V_T$ ($p < .01; \eta^2_p > 0.25$), and BF ($p < .01; \eta^2_p > 0.4$) compared with baseline values, with a significant time x trial interaction ($p < .05; \eta^2_p > 0.2$). More detailed post-hoc analyses revealed a significantly greater increase in $V_E$ ($p < .05; \eta^2_p > 0.35$) and $V_T$ ($p < .05; \eta^2_p > 0.25$) during the initial first minute (0–1 min) of immersion in 45°C water than in 37°C water or transition to an empty bath. Moreover, we found a significantly greater increase in initial $V_E$ in the WI-37°C than in the CON.
Figure 2. Time-dependent changes in heart rate (HR) (A) during whole-body immersion at 37°C (WI-37°C) and 45°C (HWI-45°C) water temperature and during the control thermoneutral condition of an empty bath (CON). Mean and individual values of HR (B), before (pre), during the first minute (0–1 min), and during the remaining 4 min (1–5 min) of WI-37°C, HWI-45°C, and CON conditions. Values are expressed as the mean±standard error of the mean. *p < .05, **p < .01, ***p < .001, significant difference between two indicated (line above) values; †p < .05, compared with the start value at HWI-45°C trial; ‡p < .05, compared with the start value at WI-37°C trial; §p < .05, compared with the start value at CON trial; †p < .05, compared with the HWI-45°C condition; ‡p < .05, compared with the CON condition. Symbols indicate first detected significant difference by dependent-sample t test.

condition (p = .042; ηp² = 0.241). No significant difference between the two temperature conditions (45°C vs. 37°C) was found for BF responses (p = .854; ηp² = 0.032). However, in the CON trial, we found a significantly lower increase in initial BF response compared with immersions in 37°C and 45°C water (p < .001; ηp² > 0.5). During the remaining (1–5 min) water immersion time, VE, VT, and BF values did not differ between 37°C and 45°C water temperature conditions (p > .05; ηp² < 0.1). In addition, the values of VE, VT, and BF at 45°C, and the values of VE and BF at 37°C remained significantly higher during the remaining (1–5 min) immersion time compared with the pre-immersion baseline values (p < .05; ηp² > 0.2; Figure 3D, 3E, and 3F). Moreover, the values of VE, VT, and BF at CON condition were significantly lower during the remaining (1–5 min) time compared with the 37°C and 45°C water temperature conditions (p < .05; ηp² > 0.3).

Pulmonary VO₂, VCO₂, and RER responses

There was no significant difference in baseline VO₂ (Figure 4D), VCO₂ (Figure 4E), and RER (Figure 5F) values between the different conditions (p > .05; ηp² < 0.09). The initial first minute (0–1 min) of whole-body immersion in 37°C and 45°C water resulted in ∼2-fold increase in VO₂ (p < .001; ηp² = 0.697) and VCO₂ (p < .001; ηp² = 0.721), with a significant time × trial interaction (p < .001; ηp² > 0.6). As shown by a more detailed post-hoc analysis, VO₂ and VCO₂ responses did not differ significantly between the two water-immersion temperature conditions (p > .05; ηp² < 0.1). Although the CON condition resulted in a significant increase in VO₂ and VCO₂ compared with the baseline value (time effect: p < .01; ηp² > 0.4), this increase was significantly smaller compared with the other two conditions (trial effect: p < .01; ηp² > 0.3). The values of VO₂ and VCO₂ at 37°C and 45°C conditions remained significantly higher during the remaining (1–5 min) immersion time compared with the pre-immersion values (p < .001; ηp² > 0.4).

Interestingly, the initial (0–1 min) immersion at 37°C as well as the initial control thermoneutral condition in an empty bath resulted in an abrupt decrease in RER (compared with baseline and HWI-45°C values, p < .001; ηp² > 0.5; Figure 4C), whereas immersion in 45°C water did not change the RER level (compared with the pre-immersion value, p = .986; ηp² = 0.009), with a significant time × trial interaction (p < .05; ηp² > 0.3). During the remaining (1–5 min) time, RER increased gradually under all experimental conditions (Figure 5F) and returned to baseline value in CON (p = .65; ηp² = 0.059) and increased above the pre-immersion and 0-to-1 min value in WI-37°C and HWI-45°C conditions (p < .001; ηp² > 0.3). For this result, a significant time × trial interaction was found (p = .0189; ηp² = 0.339).

In more detailed time-course (slope) kinetic analyses, we found that under CON, WI-37°C, and HWI-45°C trial conditions the abrupt VO₂ (Figure 4A), VCO₂ (Figure 4B), and RER (Figure 4C) change to the peak value manifested within the initial 5–15 s of immersion or transition to an empty bath (time effect: p < .01; ηp² > 0.35), with a significant time × trial interaction (p < .001; ηp² > 0.4). The peak value of VO₂ and VCO₂ was found to be significantly greater in WI-37°C and HWI-45°C than in
the CON condition ($p < .01; \eta_p^2 > 0.3$), and the peak value of RER was significantly lower in CON and WI-37 °C than in the HWI-45 °C condition ($p < .001; \eta_p^2 > 0.7$). There was no significant difference in the peak value of RER between CON and WI-37 °C conditions ($p = .61; \eta_p^2 = 0.062$).

**Perception score responses and body weight loss**

In CON trial, the subjects felt “neutral” (Figure 5B) and “being neutral” (Figure 5A) for thermal and sweating perception, respectively. At the end of HWI-37 °C, the subjects felt somewhere between “neutral” and “slightly warm,” whereas at the end of HWI-45 °C, the subjects felt somewhere between “warm” and “hot” (trial effect: $p < .05$). Moreover, the subjects indicated “slightly sweating” only in the HWI-45 °C trial condition (trial effect: $p < .05$). The latter result coincided with the 0.156 ± 0.092 kg body weight loss found from before to after HWI-45 °C and the body weight maintenance from before to after CON (87.82 ± 1.98 vs 87.81 ± 1.96) and WI-37 °C (88.59 ± 2.08 vs 88.56 ± 2.05) conditions.

**Discussion**

In the present study, we examined whether short-duration whole-body immersion (for 5 min) in noxious hot water (45 °C) is a sufficient stimulus to induce a respiratory acute
shock response. Our results indicated that short-duration immersion in noxious 45°C water produced a significantly greater body temperature, HR, and perceptual and respiratory strain than immersion in innocuous warm 37°C water, and a greater respiratory response than in control thermoneutral conditions of an empty bath. The initial first minute of HWI-45°C (vs. WI-37°C or CON) caused a cardiorespiratory shock response, which was manifested as acute hyperventilation (increase in $V_\text{E}$), and increased $V_{\text{t}}$, RER, and HR. Participants adjusted to this initial cardiorespiratory heat shock response within a minute of immersion, as shown by a lower respiratory activity response during the remaining (1–5 min) HWI time. Intriguingly, the time-course kinetics of BF, $V_{\text{O}_2}$, and $V_{\text{CO}_2}$ did not differ during whole-body immersion between the two trial conditions but were higher than in the control thermoneutral conditions of an empty bath.

In cerebrate and decerebrate cats, stimulation of cutaneous nociceptors by heating the skin alone to 46°C caused respiration to increase, while respiration did not increase when the skin was heated to 41°C. Previous studies in humans have not shown any respiratory shock response during the first minute of innocuous warm (25–42°C) whole-body immersion [11,12]. These two previous studies in humans were mostly limited to a relatively low immersion water temperature ($\leq 41^\circ$C), low participant numbers (n = 7), and separate respiratory (gas mixing box) and spirometry (rotameter) techniques, with a recording interval of...
immersion conditions, but to a greater extent at 45°C and as indicated in our present study, do not illustrate the respiratory changes observed in the first minute of whole-body immersion. Such an analysis would require breath-by-breath measurement of CO2 and O2 upon immersion in 37°C water.

VCO2 and VO2 are negligible. A thermal noxious pain stimulus raises alveolar PaCO2 and thereby the drive to breathe. In fact, the afferent neural pathway for pain and temperature are anatomically and physiologically distinct. Both pain and heat perceptions are initiated in a subpopulation of peripheral sensory nerve fibers (nociceptors) that have cell bodies in the trigeminal and dorsal root ganglia. Both pain and heat perceptions are initiated in a subpopulation of peripheral sensory nerve fibers (nociceptors) that have cell bodies in the trigeminal and dorsal root ganglia. The nociceptors are excited by noxious stimuli and transmit nociceptive information to higher centers.

We showed that respiration increased upon both water immersion conditions, but to a greater extent at 45°C than at 37°C. We also showed that acute postural change from vertical to semi-recumbent position was a contributing but not primary factor causing abrupt cardiorespiratory change. On whole-body immersion, there must be an increase in the amount of oxygenated blood from the legs and viscera. This momentary increase in venous return to the right side of the heart forces an increased passage of blood through the heart and lungs. This results in a brief increase in oxygen uptake by the blood as the volume of oxygenated arterial blood is increased and that of the deoxygenated venous blood is decreased. Immersion-induced respiration can result from hydrostatic pressure or water temperature, or both. Discriminating between hydrostatic pressure and water temperature mechanisms that trigger respiratory responses is complicated because it is not known which mechanism is more stressed upon immersion.

In the present study, hydrostatic pressure (mechanical stimulus) upon immersion was the same between WI-37°C and HWI-45°C trials, suggesting that the greater VE, V̇r, HR, and RER responses found at 45°C water immersion may be exclusively because of the temperature factor. Furthermore, despite a modest increase in core temperature, the values of V̇CO2 and VO2 upon immersion in 37°C and 45°C baths were not significantly different, which may indicate that the temperature contribution to the hydrostatic component for V̇CO2 and VO2 is negligible.

Our results showed that the initial first minute of whole-body immersion in 37°C and 45°C water resulted in an abrupt ~2-fold increase in mean and ~4–5-fold increase in peak VO2 and V̇CO2 values. A thermal noxious pain stimulus via the sympathetic nervous system results in increases in heart rate, stroke volume, peripheral resistance, muscle tone, and blood pressure, which in turn cause an instantaneously greater venous return to the heart and lungs. Differently to cardiorespiratory heat shock, cold shock responses mediate cutaneous vasoconstriction and represent a crucial ‘first line of defense’ against excessive reduction in body temperature thus increasing greater CO2 elimination in respect to O2 uptake by the lungs. Taken together, these results suggest the volume-dependent venous return to the lungs and RER value. That is, the greater the momentary venous return, the greater the RER value. Thus, in the present study, the higher HR in HWI-45°C (vs. WI-37°C) paralleled higher RER values, a sign of excess ventilation. Evidence indicates that acute increase in VE washes out CO2 stores and increases O2 uptake. At the beginning of hyperventilation, there is a dramatic reduction of partial pressure of CO2 in arterial blood (PacO2). CO2 elimination at the lungs increases initially but drops within a few minutes and eventually returns to normal as balance is restored between washout from the lungs and tissues. In addition to CO2 washout, the immediate increase in VO2 occurs independently of the water temperature. In addition to the hydrostatic force on pressure sensors, activation of warm TRP-channels per se enhances vasodilation of peripheral blood vessels, causing greater blood pooling in the extremities. Peripheral blood pooling consequently results in a greater volume of blood being displaced caudally for an identical hydrostatic force induced with the onset of head-down immersion.

The consequent increase in cardiac output via increased HR raises alveolar and PacO2, and a rise in PacO2 then increases VO2. Thus, a brief initial increase in VO2 upon immersion may not be evidence of an increased rate of oxygen consumption, but rather, it may reflect an increase in the uptake of oxygen by the blood.

Normally, humans perceive temperatures ≤17°C (cold) and ≥43°C (hot) as painful. The capacity to feel pain is normally advantageous, providing a powerful motivation to withdraw from noxious stimuli and to avoid dangerous environments, such as contact with dangerously hot or cold materials. The sensation of pain has been shown to affect the respiratory cycle through a mixture of behavioral response and a direct effect on medullary respiratory centers. Any increase in ventilation due to pain will decrease PacO2 and thereby the drive to breathe. In fact, the afferent neural pathway for pain and temperature are anatomically very close and extremes of heat activate hot nociceptors. Both pain and heat perceptions are initiated in a subpopulation of peripheral sensory nerve fibers (nociceptors) that have cell bodies in the trigeminal and dorsal root ganglia and extend their sensory endings in the skin, mucosa, and internal organs.

Nociceptive information can be transmitted directly to bulbar respiratory nuclei without involving higher centers. It is therefore possible that part of the initial first ~30 s of the greater ventilatory response to 45°C water immersion in our present study was (in addition to acute postural change, temperature and hydrostatic pressure) initiated by heat associated pain. Most likely, the greater ventilatory response arises because of direct stimulation at the spinal level of α-motor neurons innervating the intercostal muscles.
muscles and diaphragm [41]. Participants adjusted to this initial cardiorespiratory heat shock response within a minute of immersion, which can be explained by a gradual thermoregulatory activation shift via a decrease in discharge frequency of heat-sensitive fibers to a less stressful physiological condition [42]. Pain raises blood pressure acutely, which in turn causes increased stimulation of baroreceptors that consecutively activate the descending inhibitory pathways of pain, restoring initial homeostasis [31].

In conclusion, we have shown that short-duration (5 min) whole-body immersion in noxious 45 °C water produces greater rises in body temperature, HR, and perceptual and respiratory strain than immersion to innocuous warm 37 °C water, and a greater respiratory strain than the thermoneutral condition of an empty bath. The initial first minute of HWI-45 °C caused an acute cardiorespiratory shock response, which manifested as acute hyperventilation, and increased tidal volume, RER, and HR. Participants adjusted to this initial cardiorespiratory heat shock response within a minute of immersion, as shown by a lower HR and respiratory activity response during the remaining immersion time. Intriguingly, the time-course kinetics of breathing frequency, V̇O₂, and V̇CO₂ did not differ during whole-body immersion between the two trial conditions, but were higher than in the control thermoneutral trial of an empty bath. This may be a result of events initiated not only by the water temperature alone but also by the change in the hydrostatic pressure acting upon the body when immersed in water.

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