Scand J Med Sci Sports 2015: 25 (Suppl. 1): 229–239
doi: 10.1111/sms.12317

SCANDINAVIAN JOURNAL OF
MEDICINE & SCIENCE
IN SPORTS

Effectiveness of cold water immersion for treating exertional heat stress when immediate response is not possible

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Accepted for publication 10 August 2014

Immediate treatment with cold water immersion (CWI) is the gold standard for exertional heatstroke. In the field, however, treatment is often delayed due to delayed paramedic response and/or inaccurate diagnosis. We examined the effect of treatment (reduction of rectal temperature to 37.5 °C) delays of 5, 20, and 40 min on core cooling rates in eight exertionally heat-stressed (40.0 °C rectal temperature) individuals. We found that rectal temperature was elevated above baseline ($P < 0.05$) at the end of all delay periods (5 min: 40.08 ± 0.32; 20 min: 39.92 ± 0.40; 40 min: 39.57 ± 0.29 °C). Mean arterial pressure was reduced ($P < 0.05$) below baseline (92 ± 1.8 mm Hg) after all delay periods (5 min: 75 ± 2.6; 20 min: 74 ± 1.7; 40 min: 70 ± 2.1 mm Hg; $P > 0.05$). Rectal core cooling rates were similar among conditions (5 min: 0.20 ± 0.01; 20 min: 0.17 ± 0.02; 40 min: 0.17 ± 0.01 °C/min; $P > 0.05$). The rectal temperature afterdrop following CWI was similar across conditions (5 min: 35.95; 20 min: 35.61; 40 min: 35.87 °C; $P > 0.05$). We conclude that the effectiveness of 2 °C CWI as a treatment for exertional heat stress remains high even when applied with a delay of 40 min. Therefore, our results support that CWI is the most appropriate treatment for exertional heatstroke as it is capable of quickly reversing hyperthermia even when treatment is commenced with a significant delay.

Exertional heatstroke is the second leading cause of death in sports besides cardiac conditions (Mueller & Cantu, 2009). Early recognition of exertional heatstroke and rapid on-site cooling of the individual with exertional heatstroke to a near-normal resting core temperature is paramount to their survival and to minimize heat-related injury (Casa et al., 2007a, 2012; Flouris et al., 2014). To ensure patient well-being, it has been suggested that the treatment of exertional heatstroke must achieve a rectal temperature (T_{re}) cooling rate exceeding 0.1–0.2 °C/min when cooling begins immediately and no less than 0.15 °C/min if cooling is delayed (Casa et al., 2007b).

The survival of exertional heatstroke victims is largely dependent on the length of time that T_{re} is maintained above critical levels (Zeller et al., 2011). This is because the severity and reversibility of multisystem organ failure associated with exertional heatstroke is related to the duration of temperature elevation (Hubbard et al., 1977; Zeller et al., 2011; Casa et al., 2012). This is also supported by the greater number of fatalities reported when treatment is delayed (Zeller et al., 2011; Casa et al., 2012) as well as the greater organ dysfunction, longer hospitalizations, and/or longer return to play/work period in exertional heatstroke victims who survive despite delays in treatments (Costrini et al., 1979; O'Connor et al., 2010; Stearns et al., 2011; Zeller et al., 2011; Casa et al., 2012). As such, all relevant guidelines highlight that the cooling of exertional heatstroke patients should commence as soon as possible. In field settings, however, more than often treatment may be delayed due to considerable wait for first responders (Carr et al., 2006; Marom et al., 2011; Casa et al., 2012) and/or inaccurate diagnosis or recognition of the condition (Casa et al., 2007a, 2012). Nevertheless, the effectiveness of treating exertional heatstroke when immediate response is not possible has not been studied to date.

Cold water immersion (CWI) is considered the gold standard treatment for victims of exertional heatstroke as it has been shown to produce the highest core cooling rates to date (0.35 °C/min) (Proulx et al., 2003; Casa et al., 2007b; Flouris et al., 2014). However, these rates are based on measurements performed in individuals immersed within 5 min of achieving an exercise-induced elevated state of hyperthermia (core temperature ≥40 °C). It remains unclear if CWI remains equally effective in treating hyperthermic victims when

treatment is delayed for an extended period. This is important because victims of exertional heatstroke typically experience a rapid deterioration in cardiovascular (i.e., precipitous decrease in arterial blood pressure) and thermoregulatory (e.g., marked reduction in heat dissipation that can progress to complete thermoregulatory system failure) functions with delays in treatment (Casa & Roberts, 2003; Epstein & Roberts, 2011). Indeed, previous reports using exertional heat stress (EHS) as a model (which is not exertional heatstroke *per se*, but can lead to it) showed that when recovery is extended following a dynamic exercise bout, heat is gradually transferred to the core region and the inactive muscle tissue (Kenny et al., 2003). Combined with a decrease in skin perfusion (and sweating), the gradual decrease in the muscle-to-core and core-to-skin temperature gradients can increase the insulator effect of muscle and adipose tissue (Kenny & Jay, 2007; Kenny et al., 2008). As a consequence, this can reduce the rate of heat transfer during subsequent CWI (Scott et al., 2004). However, it remains unclear whether these changes in tissue heat distribution can influence core cooling rates when the treatment of EHS is delayed. Previous studies examining the benefit of CWI in the treatment of exertional heatstroke have been limited to the examination of core cooling rates following only a brief 5-min delay period (Proulx et al., 2003, 2006; Casa et al., 2007b; Lemire et al., 2009).

The aim of the current study was to examine the effect of treatment delays of 5-, 20-, and 40-min duration on core cooling rates in EHS individuals (i.e., T_{re} of 40.0 °C). The delay periods used are representative of the delays in treatment that result from an inaccurate diagnosis, lack of recognition of the condition and/or transport to treatment facilities (~20 min) (Casa et al., 2007a, 2012), as well as a considerable wait for first responders and treatment (~40 min) (Carr et al., 2006; Marom et al., 2011; Casa et al., 2012). We evaluated the hypothesis that longer treatment delay would result in a decrease in core cooling rate during subsequent CWI (and, thus, more time required to treat EHS) due to changes in tissue heat distribution and sustained cardiovascular disturbance (post-exercise hypotension). In turn, the greater immersion times required to treat EHS would result in a greater post-immersion core temperature afterdrop and longer subsequent recovery times following CWI.

Methods

The current experimental protocol was approved by the University of Ottawa Health Sciences and Science Research Ethics Board in accordance with the Declaration of Helsinki. Written informed consent was obtained from all volunteers prior to their participation in the study.

Participants

Following appropriate determination of sample size (see Statistical Analysis section), eight healthy (nonsmoking, free of any known cardiovascular, respiratory, or metabolic diseases) physically active (exercised at a minimum of 30 min, 3–5 times/week) males participated in the study. Their physical characteristics were as follows (mean ± SD): age: 30 ± 6 years; height: 180 ± 6 cm; mass: 79.6 ± 9.1 kg; maximum oxygen consumption: 59.8 ± 4.2 mLO_2/kg/min; percentage of body fat: 13.4 ± 3.0%; body surface area: 1.99 ± 0.14 m^2.

Experimental protocol

All participants completed one preliminary and three experimental sessions separated by a minimum of 48 h. During the preliminary session, informed consent was obtained followed by measurements of participants' nude body mass, height, body density, and maximum oxygen consumption. Nude body mass was measured using a calibrated digital high capacity scale (IND560, Mettler Toledo Inc., Mississauga, Ontario, Canada) while body height was determined using a stadiometer (model 2391; Detecto, Webb City, Missouri, USA). Body density was measured by hydrostatic weighing and used to calculate lean body mass and percent body fat with the Siri equation (Siri, 1956). Maximum oxygen consumption was measured by indirect calorimetry (MOXUS system, Applied Electrochemistry, Pittsburgh, Pennsylvania, USA) during a graded exercise test performed on a treadmill (Woodway Desmo, Woodway USA, Inc., Waukesha, Wisconsin, USA) in thermoneutral conditions [22 °C, 30% relative humidity (RH)] (Canadian Society for Exercise Physiology, 1986). Participants were instructed to refrain from alcohol and the use of nonsteroidal anti-inflammatory drugs for 48 h, severe or prolonged exercise for 24 h, and caffeine for 12 h, as well as food consumption for 2 h prior to each session. Water consumption was not restricted prior to or during the conduct of each session. Experimental sessions were conducted at the same time of day for each participant to avoid circadian variations in core temperature.

Upon arrival at the laboratory, participants voided their bladder, inserted a temperature probe in their rectum, and weighed themselves nude. Subsequently, they donned standardized athletic clothing (shorts and running shoes) and sat quietly outside the temperature-controlled chamber (ambient temperature: 23 °C) while being instrumented. Following instrumentation, they remained resting for 20 min for baseline resting measurements. Participants then moved into a thermal chamber (Can-Trol Environmental Systems Ltd, Markham, Ontario, Canada) regulated at 40 °C and 20% RH where they remained seated for an additional 20 min during which time pre-exercise resting values were recorded. Participants subsequently donned a nylon rain poncho covering the entire upper body and head to minimize evaporative heat loss and accelerate the heating process. Participants then ran continuously on a treadmill (Desmo HP, Woodway USA, Inc.) at ~ 65% of their predetermined maximal oxygen consumption until T_{re} reached 40.0 °C. Following the cessation of exercise, the nylon poncho was removed and was replaced with a sleeveless nylon running jacket. The participants were then required to sit in an upright seated resting position for either a short (5 min), moderate (20 min), or prolonged (40 min) post-exercise recovery period to simulate treatment delay in the temperature-controlled chamber at 40 °C (20% RH) (Note: For the purposes of this presentation, this post-exercise recovery period will be referred to as the treatment delay period). Following the treatment delay, participants donned neoprene boots (DuPont, Wilmington, Delaware, USA) and entered a circulated ice-water (2 °C) bath (S-110-SL, Whitehall Manufacturing, City of Industry, California, USA) located in the temperature-controlled chamber. During the CWI, participants were immersed to the nipples while in an upright seated position with the legs extended with both arms out of the bath (for the purpose of measuring blood pressure and to keep the intravenous catheter out of the water) until T_{re} was reduced to 37.5 °C. Upon reaching a T_{re} of 37.5 °C, participants exited the cold water bath and

sat upright in the thermal chamber (40 °C, 20% RH) while they were towel dried. To ensure the safety of each participant, T_{re} was monitored until it returned to 36.5 °C. After the completion of the trial, a nude body weight measurement was completed to assess fluid loss which was corrected for water consumption during each condition.

Measurements

Esophageal (T_{es}) and T_{re} were measured with general purpose thermocouple temperature probes (Mallinckrodt Medical Inc., St. Louis, Missouri, USA). The T_{es} probe was inserted 40 cm past the entrance of the nostril while the participants sipped water through a straw. The T_{re} probe was inserted to a depth of 15 cm past the anal sphincter. Skin temperature and dry heat loss (H_D) were measured at nine sites using T-type (copper/constantan) thermocouples integrated into heat flow sensors (Concept Engineering, Old Saybrook, Connecticut, USA) attached to the skin with surgical tape (3M™, Transpore™, St. Paul, Minnesota, USA). The area-weighted mean skin temperature (MT_{sk}) and H_D were subsequently calculated using a 9-point weighting of the regional proportions determined by Hardy and Dubois (1938). These were as follows: forehead 9.39%, upper arm 9.39%, upper back 11.75%, chest 11.75%, lower back 11.75%, abdomen 11.75%, quadriceps 12.75%, hamstring 12.75%, and front calf 8.72%. Because the head, chest, upper back, upper arm, and forearm were not entirely immersed during CWI, they were not used to calculate MT_{sk} and H_D as no weighting has been validated for such conditions (where the upper body regions are exposed to a hot-dry environment while the central and lower body regions are immersed in 2 °C water). As such, the following weightings were used to calculate MT_{sk} and H_D during water immersion: lower back 20.35%, abdomen 20.35%, quadriceps 22.09%, hamstring 22.09%, and front calf 15.12%. Temperature and heat flow data were collected every 15 s using a HP Agilent data acquisition module (model 3497A) and simultaneously displayed and recorded in spreadsheet format with LabVIEW software (version 7.0, National Instruments, Texas, Austin, USA).

Metabolic heat production was measured as the difference between metabolic energy expenditure and the work, in watts, required to run on the treadmill. Rate of metabolic energy expenditure (M) was calculated from 30 s average values for expired O_2 and CO_2 concentrations (AMETEK models S-3A/1 and CD 3A, respectively, Applied Electrochemistry) according to the following equation:

$$M\,(\text{watts}) = \text{VO}_2 \cdot [(\text{RER} - 0.7/0.3 \cdot e_c) + (1 - \text{RER}/0.3 \cdot e_f)]/60$$

where RER is the respiratory exchange ratio (CO_2 exhaled/O_2 inhaled), e_c is the caloric equivalent of a liter of O_2 when carbohydrates are oxidized (21.116 kJ), and e_f is the caloric equivalent of a liter of O_2 when fat is oxidized (19.606 kJ) (Nishi, 1981).

Cardiac output (CO) was measured using a noninvasive inert gas (0.5% nitrous oxide and 0.1% sulfur hexafluoride) re-breathing technique (Innocor™, DK-5260 Innovisions, Odense, Denmark) that has been previously validated against the direct oxygen Fick method and thermodilution (Peyton & Thompson, 2004). In brief, with their nose plugged, participants breathed through a mouthpiece into the closed re-breathing system, comprised of a three-way respiratory valve connected to an antistatic rubber bag and an infrared photo acoustic gas analyzer. The time points at which measurements of CO were taken were as follows: (a) end of the 20-min baseline resting period in thermoneutral conditions; (b) at the end of the 20-min pre-exercise rest period in the heat; (c) at 5 min post-exercise (note: this was the only measurement point for the short delay period); (d) at the end of the treatment delay period (i.e., at 20- and 40-min post-exercise for the moderate and prolonged treatment delay conditions); and (e) at the end of post-immersion recovery (i.e., when T_{re} returned to 36.5 °C). Values for total peripheral resistance (TPR) and stroke volume (SV) were calculated as TPR = MAP/CO and SV = CO/HR, respectively. No shivering or hyperventilation was observed during the CO measurements (i.e., at the end of the post-immersion recovery).

Heart rate (HR) was monitored continuously using a Polar coded transmitter combined with a Polar heart rate monitor (Model FS1, Polar Electro Oy, Kempele, Finland), and measurement samples were documented every 5 min during the trial. Blood pressure was measured by auscultation of the brachial artery every 5 min during the baseline resting periods in thermoneutral and hot ambient conditions as well as during the treatment delay periods. Measurements were performed every 2 min during the CWI period. Mean arterial pressure (MAP) was calculated using the formula: 1/3 systolic pressure + 2/3 diastolic pressure. Oxygen consumption was measured during the resting and CWI periods on a breath-by-breath basis and averaged over 15 s using a portable metabolic measurement system (Oxycon Mobile, Viasys HealthCare Inc., Hoechberg, Germany). Measurements of nude body weight were obtained prior to and following each experimental session using a digital high-performance scale (IND560). Results were recorded to the nearest 0.01 kg.

Venous blood was collected via an indwelling intravenous catheter (BD Insyte™ Autoguard™, 18G, BD, Franklin Lakes, New Jersey, USA) in a superficial vein. Blood samples were drawn at the end of each time period (i.e., baseline, rest, 5-min post-exercise, end of treatment delay, and end of recovery) similar to CO as noted above. In every measurement, approximately 5 mL was drawn into a sterile plastic syringe and transferred immediately into plasma K_2EDTA 5.4 mg BD Vacutainer® tubes for immediate hematologic analyses. Hematocrit and hemoglobin concentrations were analyzed in duplicate and determined using the Coulter method (Coulter® A^c•T diff 2™ analyzer, Beckman Coulter, Miami, Florida, USA). Changes in plasma volume (PV) and blood volume (BV) from baseline levels were estimated from changes in hemoglobin and hematocrit using a standardized formula (Dill & Costill, 1974). Values are reported as means for duplicate measures.

Data processing

For each trial, T_{re} T_{es}, and MT_{sk} values for the baseline resting (i.e., thermoneutral ambient conditions) period were averaged over the final 5 min. The rates for whole-body heating during exercise [change in (Δ) temperature/exercise time] and core cooling during CWI (Δ temperature/immersion time) were calculated for both T_{re} and T_{es}. The core cooling rates were calculated from pre-immersion temperature ($T_{pre\text{-}imm}$) (i.e., the core temperature value immediately prior to the start of immersion) values for both T_{re} and T_{es}. They were evaluated by examining: (a) the overall cooling rates as calculated by the time it took for each core temperature measure to reach 37.5 °C, and (b) the rate of cooling measured for the first-degree Celsius reduction in temperature ($T_{pre\text{-}imm}$ – 1 °C) and second-degree Celsius reduction in temperature [($T_{pre\text{-}imm}$ – 1 °C) – 1 °C] for each condition, respectively. During the immersion period, MT_{sk} and H_D were calculated in minute averages. The break point or delay (lag) period (in minutes) at which T_{re} cooling started to decrease following the start of immersion was determined by segmental linear regression analysis using GraphPad Prism software v5.0 (GraphPad Software Inc., La Jolla, California, USA). The lowest T_{re} and T_{es} values (nadir) measured following CWI, the time to reach the nadir for both T_{re} and T_{es}, as well as the time to recovery (T_{re} of ~ 36.5 °C) were also determined.

Statistical analysis

The minimum required sample size was determined using data from a previous study (Leicht et al., 2009) where thermal variables

were recorded during exercise in the heat (until core temperature reached 40 °C) and a subsequent recovery using different cooling treatments. Sample size calculations were conducted using G*Power 3.0 (Faul et al., 2007). The A.R.E. method of the "Wilcoxon signed-rank test" incorporated in the "t tests" family with "a priori" as the type of power analysis was used to calculate the power of the within effect. A two-tailed test was selected. Statistical power and α error probability were set to 0.95 and 0.05, respectively. The minimum required sample size was determined by calculating the effect size *d*. Using the aforementioned published data (Leicht et al., 2009), the resulting minimum required sample size was seven participants. In order to confidently detect a reasonable departure from the null hypothesis, we recruited a total of eight participants.

A common time point relative to all conditions (i.e., 5-min post-exercise) was used to make comparisons. Comparisons were made between baseline resting values (i.e., rest in the thermoneutral ambient temperature), 5-min post-exercise, end of treatment delay, and end of post-immersion recovery (i.e., when T_{re} returned to 36.5 °C) for all experimental conditions. A two-way repeated measures analysis of variance (ANOVA) with the repeated factors of time (5-min post-exercise; end of treatment delay) and condition (short, moderate, and prolonged delays) was used to analyze the effects of treatment delay on the dependent variables [thermal (T_{re}, T_{es}, and MT_{sk}), cardiovascular (CO, MAP, TPR, HR, and SV), as well as BV and PV]. In separate analyses, we determined the effects of treatment delay relative to baseline resting values as well as end of post-immersion recovery in each group using repeated measures ANOVA. A two-way repeated measures ANOVA was used to analyze H_D, MT_{sk}, and rates of metabolic heat production during every minute of the immersion period with the repeated factor of time (0, 1, 2, 3, 4, 5, 6, 7, 8, 9 min, etc. to the last common immersion point) and the repeatable factors of experimental condition (short, moderate, and prolonged). Comparisons for heating and cooling rates (overall, first, and second degree), time to cool, time to reach core temperature nadir, time to end recovery, and changes in body mass between experimental conditions were performed utilizing a one-way repeated measures ANOVA. When a significant main effect was observed, post-hoc comparisons were conducted using paired samples *t*-tests. All analyses were performed using the statistical software package SPSS 20 for Windows (SPSS Inc., Chicago, Illinois, USA) and the level of significance was set at $P \leq 0.05$. During multiple comparisons, the alpha level was adjusted to maintain the rate of type I error at 0.05 using the Bonferroni ($P \leq 0.05/N$; N = number of comparisons) correction.

Results

There were no statistically significant differences in baseline resting values for thermal (T_{re}, T_{es}, and MT_{sk}) and cardiovascular (CO, HR, SV, MAP, and TPR) variables ($P > 0.05$; Table 1).

Table 1. Baseline values (mean ± SE) for thermal and cardiovascular parameters and their corresponding changes from baseline at 5-min post-exercise, end of treatment delay, and end of post-immersion recovery

	Baseline	5-min post-exercise	Treatment delay	Post-immersion recovery
T_{re} (°C)				
Short	36.91 ± 0.10	+3.16 ± 0.13*	+3.16 ± 0.13*	−0.42 ± 0.09§
Moderate	36.86 ± 0.07	+3.29 ± 0.08*	+3.09 ± 0.11*	−0.41 ± 0.14§
Prolonged	36.84 ± 0.09	+3.25 ± 0.11*	+2.77 ± 0.09*†‡	−0.33 ± 0.13§
T_{es} (°C)				
Short	36.82 ± 0.10	+2.97 ± 0.20*	+2.97 ± 0.20*	−0.11 ± 0.10§
Moderate	36.88 ± 0.05	+3.23 ± 0.13*	+2.63 ± 0.18*†	+0.20 ± 0.12§
Prolonged	36.72 ± 0.10	+3.03 ± 0.20*	+1.86 ± 0.10*†‡	+0.28 ± 0.20§
CO (L/min)				
Short	6.0 ± 0.3	+5.2 ± 0.9*	+5.2 ± 0.9*	+1.9 ± 0.5*§
Moderate	5.8 ± 0.4	+4.8 ± 0.6*	+4.1 ± 0.4*	+1.5 ± 0.4§
Prolonged	5.8 ± 0.3	+5.3 ± 0.7*	+3.8 ± 0.4*†	+1.7 ± 0.2*§
HR (beats/min)				
Short	60 ± 3.6	+77 ± 5.5*	+77 ± 5.5*	+17 ± 3.2*§
Moderate	61 ± 3.6	+81 ± 2.5*	+76 ± 3.7*	+13 ± 2.8*§
Prolonged	61 ± 3.5	+79 ± 4.7*	+60 ± 2.8*†	+19 ± 4.9*§
SV (mL)				
Short	100 ± 8.8	−16 ± 9.7*	−16 ± 9.7*	+7 ± 7.8
Moderate	96 ± 5.5	−21 ± 3.3*	−24 ± 3.9*	+5 ± 7.5
Prolonged	95 ± 4.7	−15 ± 5.1*	−16 ± 3.4*	+1 ± 8.0
MAP (mmHg)				
Short	92 ± 1.6	−17 ± 2.4*	−17 ± 2.4*	−11 ± 1.4*
Moderate	92 ± 1.8	−17 ± 2.3*	−18 ± 2.4*	−7 ± 2.9*§
Prolonged	92 ± 4.3	−20 ± 11.8*	−22 ± 4.1*	−6 ± 4.9*§
TPR (mmHg/L/min)				
Short	15.2 ± 0.7	−8.5 ± 0.6*	−8.5 ± 0.6*	−5.6 ± 0.9*§
Moderate	15.0 ± 0.7	−8.2 ± 0.3*	−7.1 ± 0.5*	−4.1 ± 0.9*§
Prolonged	15.4 ± 0.8	−9.1 ± 0.8*	−8.2 ± 0.8*	−4.5 ± 0.5*§

*Significant difference from baseline ($P \leq 0.05$).

†Significant difference from 5-min post-exercise ($P \leq 0.05$).

‡Significant difference from the short condition ($P \leq 0.05$).

§Significant difference from treatment delay ($P \leq 0.05$).

T_{re}, rectal temperature; T_{es}, esophageal temperature; CO, cardiac output; HR, heart rate; SV, stroke volume; MAP, mean arterial pressure; TPR, total peripheral resistance.

Exercise period

Exercise time taken to reach the experimental criterion end point (i.e., T_{re} of 40.0 °C) was similar between conditions (short: 37.8 ± 10.7 min; moderate: 41.4 ± 5.0 min; prolonged: 42.8 ± 13.7 min) ($P = 0.602$). In parallel, end-exercise T_{re} and T_{es} were similar between conditions (Fig. 1). As such, the core heating rates during exercise were not different for T_{re} (short: 0.09 ± 0.02 °C/min; moderate: 0.08 ± 0.01 °C/min; prolonged: 0.08 ± 0.02 °C/min; $P = 0.418$) or T_{es} (short: 0.09 ± 0.02 °C/min; moderate: 0.09 ± 0.01 °C/min; prolonged: 0.08 ± 0.03 °C/min; $P = 0.378$), respectively. Moreover, there were no differences in rates of metabolic heat production between conditions prior to exercise (short: 123 ± 9 W; moderate: 123 ± 11 W; prolonged: 120 ± 11 W; $P = 0.753$).

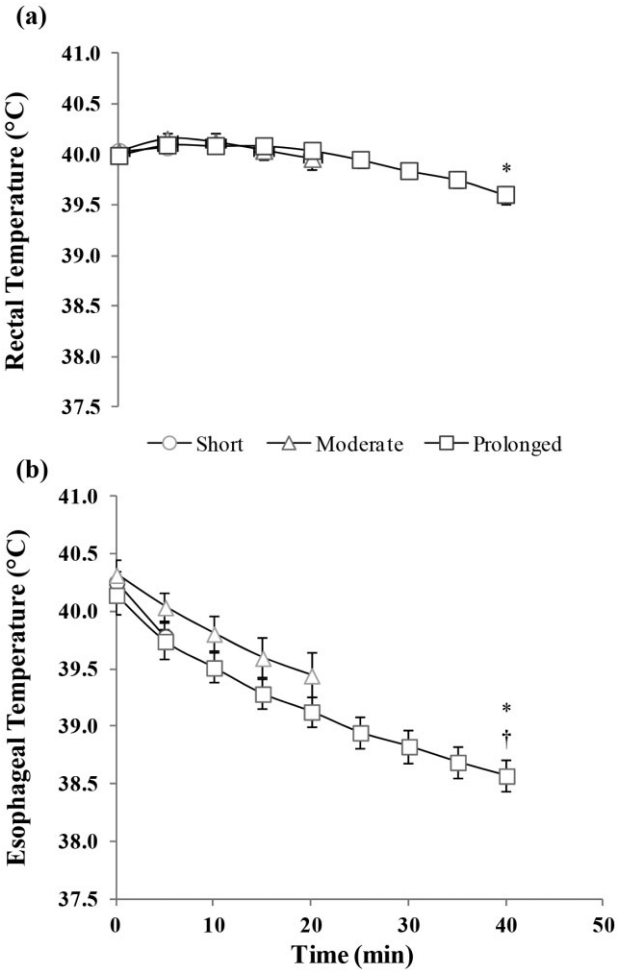

Fig. 1. Rectal temperature (a) and esophageal temperature (b) responses during the treatment delay periods after exertional heat stress. Values are presented as mean ± SE for the short (5 min) (○), moderate (20 min) (Δ), and prolonged (40 min) (□) treatment delay conditions. The values at the 0 time point are the values at the end of exercise for each condition. Values are also presented for the end of each respective delay period. *Significantly different from the short delay condition ($P < 0.05$). †Significantly different from the moderate delay condition ($P < 0.05$).

Delay of treatment period

Both T_{re} and T_{es} remained significantly elevated from baseline values at 5-min post-exercise and the end of treatment delay for all conditions ($P < 0.001$; Fig. 1). No differences between conditions were measured in thermal responses at 5-min post-exercise ($P > 0.05$; Table 1). Whereas a significant reduction in T_{es} was measured for both the moderate and prolonged conditions at end of treatment delay relative to 5-min post-exercise, T_{re} differed only for the prolonged condition (all $P < 0.05$).

While CO and HR were significantly elevated from baseline values following exercise at 5-min post-exercise, MAP, TPR, and SV were significantly reduced ($P \leq 0.05$). No differences between conditions were measured at 5-min post-exercise ($P > 0.05$); however, both CO and HR were significantly reduced at the end of the prolonged treatment delay relative to 5-min post-exercise ($P < 0.01$) while MAP, TPR, and SV remained unchanged ($P > 0.05$; Table 1).

PV was significantly reduced to similar extent for all treatment conditions at 5-min post-exercise (short: −9.0 ± 1.3%, moderate: −10.8 ± 2.3%; prolonged: −10.4 ± 2.2%; $P < 0.05$). However, a significantly greater reduction was measured at the end of treatment delay for the moderate (−14.5 ± 1.6%; $P = 0.025$) and prolonged (−14.0 ± 1.8%; $P = 0.022$) conditions relative to the short condition (−9.0 ± 1.3%). The reductions in BV measured at 5-min post-exercise were not different between the short (−5.4 ± 0.9%), moderate (−6.6 ± 1.2%), and prolonged (−6.4 ± 1.3%) conditions ($P = 0.497$). Further, a similar reduction in BV was measured at the end of the treatment delay period across conditions (i.e., short: −5.4 ± 0.9%, moderate: −9.1 ± 0.9%; prolonged: −8.6 ± 0.9%; $P = 0.06$).

The CWI period

The overall cooling rates and time required to reduce both T_{re} and T_{es} to 37.5 °C were similar among all conditions ($P > 0.05$; Table 2). Similarly, there were no differences in the cooling rates or the time required to reduce T_{re} and T_{es} by the first-degree or the second-degree Celsius between conditions ($P > 0.05$).

Reductions in MT_{sk} at the beginning of CWI became gradually less evident as a function of time ($P < 0.001$; Fig. 2) and were comparable between all conditions ($P > 0.05$). Increases in the rate of dry heat exchange (H_D) reduced as a function of time ($P < 0.01$) at similar rates between conditions ($P > 0.05$). No differences in the rates of metabolic heat production between conditions were observed at the start of immersion (short: 217 ± 301 W; moderate: 222 ± 21 W; prolonged:

Table 2. Core cooling rates (mean ± SE) for rectal and esophageal temperatures for different core temperature intervals during cold water immersion after delays in treatments

	Pre-immersion (°C)	Core cooling rates (°C/min)		
		First °C cooling (T – 1 °C)	Second °C cooling [(T – 1 °C) – 1 °C]	Immersion period (until T = 37.5 °C)
Rectal temperature (T_{re})				
Short delay	40.08 ± 0.32	0.18 ± 0.02	0.24 ± 0.02*	0.21 ± 0.03
Moderate delay	39.92 ± 0.40	0.14 ± 0.01	0.21 ± 0.01*	0.17 ± 0.01
Prolonged delay	39.57 ± 0.29†	0.15 ± 0.02	0.23 ± 0.01*	0.17 ± 0.01
Esophageal temperature (T_{es})				
Short delay	39.58 ± 0.25	0.45 ± 0.06	0.55 ± 0.07	0.47 ± 0.03
Moderate delay	39.30 ± 0.39	0.40 ± 0.06	0.53 ± 0.06	0.45 ± 0.01
Prolonged delay	38.51 ± 0.41†‡	0.43 ± 0.06	0.45 ± 0.09	0.41 ± 0.03

The pre-immersion ($T_{pre\text{-}imm}$) rectal and esophageal temperatures are the temperature values following the short (5 min), moderate (20 min), and prolonged (40 min) treatment delay periods immediately prior to cold water immersion. The first-degree Celsius drop in core temperature is the $T_{pre\text{-}imm}$ – 1 °C for each respective condition for both rectal and esophageal temperatures. Further, the second-degree Celsius drop in core temperature is the ($T_{pre\text{-}imm}$ – 1 °C) – 1 °C.

*Significant difference from first-degree Celsius cooling ($P < 0.05$).

†Significant difference from the short condition ($P < 0.05$).

‡Significant difference from the moderate condition ($P < 0.05$).

220 ± 40 W) as well as at the end of immersion (short: 180 ± 37 W; moderate: 219 ± 25 W; prolonged: 257 ± 36 W; $P > 0.05$), respectively.

Post-CWI recovery period

No differences were measured in T_{re} (short: 37.55 ± 0.02 °C; moderate: 37.54 ± 0.03 °C; prolonged: 37.50 ± 0.03 °C), T_{es} (short: 35.54 ± 0.25 °C; moderate: 35.28 ± 0.26 °C; prolonged: 35.29 ± 0.29 °C), and MT_{sk} (short: 10.95 ± 0.85 °C; moderate: 8.67 ± 1.00 °C; prolonged: 8.79 ± 0.78 °C) at the end of CWI ($P > 0.05$). Upon exiting the CWI, T_{re} and T_{es} continued to decrease for all conditions reaching a similar point of nadir across the short (T_{re}: 35.95 ± 0.22 °C; T_{es}: 35.12 ± 0.20 °C), moderate (T_{re}: 35.61 ± 0.27 °C; T_{es}: 34.97 ± 0.23 °C), and prolonged (T_{re}: 35.87 ± 0.20 °C; T_{es}: 35.02 ± 0.26 °C) conditions, respectively (Fig. 3). The time to reach nadir as defined by T_{re} response was significantly different between the short (17.5 ± 3.0 min) and prolonged (26.7 ± 2.8 min) conditions only ($P = 0.008$). In contrast, the time to reach the T_{es} nadir was not different among conditions (short: 3.8 ± 0.7 min; moderate: 4.4 ± 1.0 min; prolonged: 3.2 ± 0.9 min; $P = 0.715$). The post-immersion recovery time as defined by the time required for T_{re} to return to 36.5 °C was similar among all conditions (short: 49.4 ± 20.2 min; moderate: 58.8 ± 19.1 min; prolonged: 56.5 ± 19.7 min) ($P = 0.158$).

No differences in cardiovascular responses (i.e., CO, HR, SV, MAP, and TPR) were found between conditions at the end of the post-immersion recovery ($P > 0.05$) (Table 1). Values for CO and HR were significantly reduced relative to the end of the treatment delay period for all conditions; however, they were still elevated relative to baseline values ($P \leq 0.05$). Values for MAP, TPR, and SV were similar between conditions at the end of the post-immersion recovery. Whereas SV returned to baseline resting values, MAP and TPR remained significantly reduced albeit attenuated compared with end of treatment delay values with the exception that MAP remained significantly reduced for the short condition relative to the moderate and prolonged conditions ($P < 0.05$).

The percent changes in PV were significantly greater for the moderate (–13.4 ± 1.6%; $P = 0.020$) and prolonged (–14.4 ± 2.4%; $P = 0.024$) conditions relative to the short (–7.4 ± 1.4%) condition. A similar pattern of response was measured for BV with significantly greater reductions recorded in the moderate (–8.2 ± 0.9%; $P = 0.015$) and prolonged (–8.4 ± 1.1%; $P = 0.023$) conditions compared with the short (–4.2 ± 1.1%) condition. The reductions in body mass observed for the moderate (–2.2 ± 0.3 kg) and prolonged (–2.4 ± 0.5 kg) conditions were significantly greater relative to the short (–1.6 ± 0.3 kg) condition ($P < 0.01$).

Discussion

It is well accepted that immediate treatment with CWI is the gold standard for EHS and exertional heatstroke (Casa et al., 2007b, 2012; Flouris et al., 2014). In this study, we examined the effectiveness of CWI (core cooling rates during immersion and core temperature afterdrop following immersion) for treating EHS when delays of 5, 20, and 40 min are present. Contrary to our hypothesis, we show no effect of delay periods on core cooling rates during subsequent CWI. Indeed, despite the increased dehydrated state during the moderate and prolonged conditions (i.e., significantly greater reductions in PV, BV, and body mass), we observed similar marked elevations in

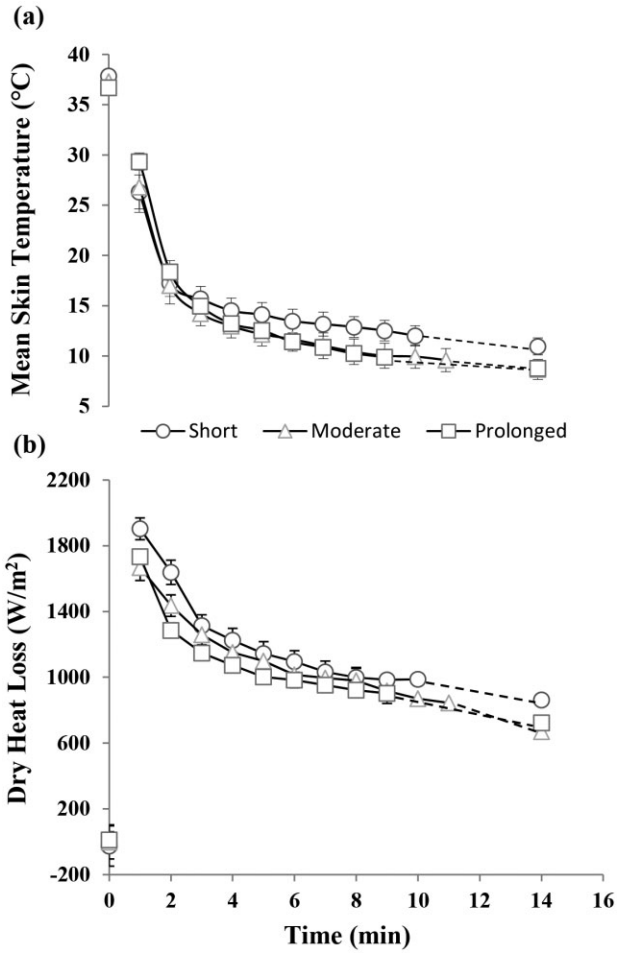

Fig. 2. Mean skin temperature (a) and rate of dry heat loss (b) during cold water immersion (2 °C) after exertional heat stress followed by subsequent treatment delays. Values are mean ± SE for the short (5 min) (○), moderate (20 min) (△), and prolonged (40 min) (□) treatment delay conditions. The values at the 0 time point are the values at the end of each treatment delay (i.e., pre-immersion values). Data are presented for the immersion time periods common to all conditions and at end immersion. The dashed lines represent mean values for the end of immersion for each participant.

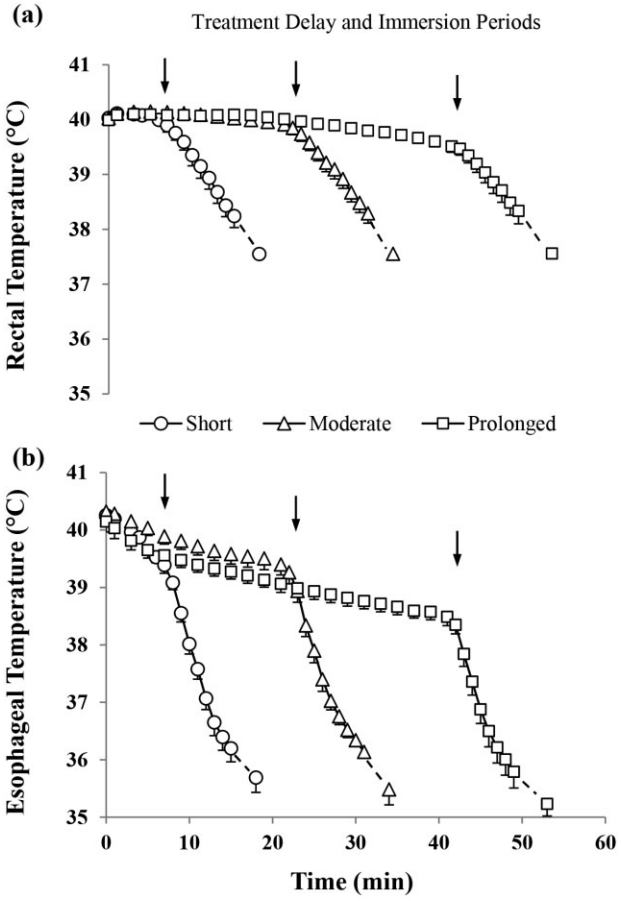

Fig. 3. Rectal (a) and esophageal (b) temperatures during post-exercise recovery [i.e., treatment delay periods and subsequent cold water immersion (2 °C)] after exertional heat stress. Values are mean ± SE for the short (5 min) (○), moderate (20 min) (△), and prolonged (40 min) (□) treatment delay conditions. The values at the 0 time point are the values at the end of exercise for each condition. Data are presented for the immersion time periods common to all participants in each condition as well as at the mean core temperature value (i.e., both rectal and esophageal) at end immersion. The mean core temperature value at the end of immersion is identified at the average immersion time for each condition and is joined by a dashed line. The arrow (↓) indicates the start of immersion for each respective treatment delay condition.

thermal (i.e., T_{re} of 40.1 °C, 39.9 °C, and 39.6 °C for delay periods of 5, 20, and 40 min, respectively) and cardiovascular strains (i.e., attenuated SV and sustained decreases in MAP of ~ 20 mmHg) in all three conditions prior to CWI, while core cooling rates and therefore immersion times were similar (~15 min) between conditions. Furthermore, we showed no effect of delay period on the post-immersion afterdrop (rectal temperatures of 35.9 °C, 35.6 °C, and 35.9 °C for delay periods of 5, 20, and 40 min, respectively). Taken together, our findings demonstrate that CWI remains an effective and safe treatment modality despite the marked prolonged elevated states of thermal and cardiovascular strains observed during the delay periods.

In real-life situations, delays in treating exertional heatstroke victims are not uncommon. This can be the result of a failure to recognize the presence or seriousness of exertional heatstroke and/or the absence of medical personnel to care for the victim (Casa et al., 2012). Even if exertional heatstroke is promptly recognized at the time of the incident, an individual can still succumb to exertional heatstroke if the high level of hyperthermia is not rapidly reduced (Hubbard et al., 1977; Armstrong et al., 2007; Casa et al., 2010; Zeller et al., 2011). This is the first study to show that the effectiveness of CWI as a treatment for EHS remains high even when applied with a delay of 40 min. This is important because the length of time T_{re} remains above critical values (i.e., core temperature of ≥40 °C) is a key criterion determining the survival of exertional heatstroke victims (Hubbard et al., 1977; Armstrong et al., 2007; Casa et al., 2010). In fact, studies show that

survival rate is negatively impacted when duration of severe hyperthermia extends beyond 15–30 min (Hubbard et al., 1977; Heled et al., 2004; Armstrong et al., 2007; Casa et al., 2007b, 2010). In this light, our data support the use of CWI for treating EHS even when treatment is commenced with a significant delay.

Effects of treatment delays on thermal and cardiovascular responses

The participants in the current study suffered from severe levels of exercise-induced hyperthermia (i.e., T_{re} of 40.0 °C), yet they did not experience exertional heatstroke, a much more complicated condition in which a T_{re} of 40.0 °C is accompanied by multi-organ dysfunction. Nevertheless, by design, in the present study we were able to maintain T_{re} at near end-exercise values for the duration of each delay period (i.e., ~40 °C) and elicit a significant cardiovascular strain (i.e., attenuated SV and reduction in MAP of ~20 mmHg). These responses are consistent with those observed in victims of exertional heatstroke (O'Donnell & Clowes, 1972; Zeller et al., 2011). Under a hyperthermic state, effective heat dissipation is facilitated by elevated levels of skin perfusion and sweating; however, whole-body heat loss can be severely compromised in victims of exertional heatstroke, resulting in a sustained elevation in core temperature (Armstrong et al., 2007; Epstein & Roberts, 2011; Casa et al., 2012). In the present study, we showed that the use of an impermeable jacket to restrict heat dissipation during recovery in the heat coupled with the time-dependant convective transfer of residual heat from previously active muscle to the central core (Kenny et al., 2003) was sufficient to maintain an elevated state of hyperthermia typically observed in exertional heatstroke victims (Costrini et al., 1979; Shapiro & Seidman, 1990; Epstein et al., 1999; Rav-Acha et al., 2004; Zeller et al., 2011).

In parallel to the elevated level of hyperthermia recorded in our participants, we showed a pronounced level of cardiovascular strain. Participants were required to remain upright seated during recovery which resulted in marked sustained reductions in arterial blodd pressure in the early stages of post-exercise recovery (i.e., −17 mmHg at 5 min) that persisted throughout the delays in treatment (i.e., −18 and −22 mmHg for the 20- and 40-min recovery periods, respectively). The magnitude of decrease in MAP was similar to levels previously reported in victims of exertional heatstroke. For example, O'Donnell and Clowes (1972) reported MAP reductions of 20 mmHg coupled with increments in HR as high as 100 beats/min prior to field treatment consisting of ice-water immersion of seven marines suffering from acute exertional heatstroke. Similarly, in a retrospective study of 27 patients admitted to the hospital and diagnosed with exertional heatstroke from 1995 to 2007, Sithinamsuwan et al. (2009) reported MAP attenuation of 22 mmHg combined with an elevation of HR by 69 beats/min on arrival at the hospital prior to treatment. Further, in addition to a markedly reduced MAP, we observed a reduced TPR (−8.5 ± 0.6 mmHg/L/min, −7.1 ± 0.5 mmHg/L/min, and −8.2 ± 0.8 mmHg/L/min for short, moderate, and prolonged delay periods, respectively) and SV (−16 ± 9.7 mL, −24 ± 3.9 mL, and −16 ± 3.4 mL for short, moderate, and prolonged delay periods, respectively) relative to baseline values that remained unchanged throughout the delay period. By comparison, the reduction in TPR was comparable to that reported by O'Donnell and Clowes (1972) who observed a TPR of ~7.5 mmHg/L/min (603 dynes/s^5/cm^2) in victims of exertional heatstroke.

Effect of treatment delays on core cooling rates during CWI

Despite the prolonged exposure of our participants to a sustained and elevated state of thermal and cardiovascular strains lasting up to 40 min following cessation of exercise, CWI resulted in similar core cooling rates and immersion times measured for all treatment conditions. Similarly, there were no differences between conditions in the time taken for the first and second degrees of core temperature reduction as measured from the start of immersion. The second degree of cooling was significantly greater compared with the first degree for T_{re} which is consistent with a previous study (Proulx et al., 2003). These differences are attributed to a greater lag time associated in tissue heat transfer observed between the start of immersion and initiation of T_{re} cooling, thereby resulting in slower temporal response of T_{re} in the early stages of cooling. It is important to note that Proulx et al. (2003) reported an ~1.9-fold greater overall core cooling rate (0.35 °C/min) relative to the overall core cooling rate observed in the present study (0.17–0.20 °C/min) for a similar exercise-induced state of hyperthermia (i.e., T_{re} of 40 °C). This disparity can be attributed to methodological differences between the two studies. Whereas Proulx et al. (2003) immersed their participants up to the clavicles (which included the arms and hands), we immersed our participants to the nipples only with arms out of the water to accommodate our physiological measurements (i.e., continuous blood pressure monitoring, access to intravenous catheter on forearm). Furthermore, the immersion tub employed in the present study did not permit our participants to be placed in a supine posture similar to the posture employed in the study by Proulx et al. (2003). Rather, our subjects were immersed in the upright seated posture with legs extended. Finally, we applied the CWI treatment inside the thermal chamber (40 °C and 20% RH) in contrast to Proulx et al. (2003) who applied CWI outside the thermal chamber. While the former approach used in the current study results in a more accurate simulation of field settings where an exertional heatstroke may be experienced, it may have affected our calculations

because body regions that were not entirely immersed (due to safety reasons; see *Perspectives*) were not used to calculate MT_{sk} and H_D. Nevertheless, the impact of applying CWI in a hot environment and excluding non-immersed regions, if any, was systematic across sessions and did not influence our findings regarding the impact of treatment delay on core cooling rates. Taken together, the above suggests that the differences in absolute core cooling rates between our study and that of Proulx et al. (2003) are attributed to differences in posture and surface area exposed. Interestingly, Lemire et al. (2009) reported T_{re} cooling rates of 0.12 °C/min for hyperthermic males (39.5 °C) immersed in 2 °C water using a similar posture to the present study. Moreover, the T_{re} cooling rates observed in our study are similar to or greater than those reported in other studies that employed 2 °C to cool hyperthermic individuals (Costrini, 1990; Armstrong et al., 1996; Lemire et al., 2009). In addition, our observed core cooling rates exceed current recommendations for a cooling rate of 0.10 °C/min when cooling begins immediately (i.e., within 5 min), and not less than 0.15 °C/min when cooling is delayed by 20–30 min (Casa et al., 2007a). Finally, while the skin temperatures recorded may have been partly influenced by the cold water, the fact that a 14-min period was necessary for MT_{sk} to reach a nadir – which was 8–12 °C higher than the water temperature – confirms that the direct effect of water temperature was minimal. Moreover, recording skin temperature during CWI is a standardized technique that has been employed in a number of previous studies (Proulx et al., 2003, 2006; Flouris & Cheung, 2009; Lemire et al., 2009; Carrillo et al., 2011, 2013; Flouris et al., 2014).

Core temperature afterdrop following CWI

A key challenge associated with the use of CWI in the treatment of exercise-induced hyperthermia is reducing the risk of a core temperature afterdrop that typically occurs following the removal of the patient from the cold water bath (Proulx et al., 2003, 2006; Gagnon et al., 2010). The core temperature afterdrop has been attributed to conductive and convective heat transfer of cooler blood from the periphery to the core (Gagnon et al., 2010), as well as the transfer of excess amounts of heat above and beyond that which was gained during exercise (Proulx et al., 2006). In order to avoid excessive afterdrop following CWI, safe cooling limits have been proposed whereby individuals should be removed from the water bath when T_{re} reaches 38.6 °C (Proulx et al., 2006). This procedure has been used to ensure the removal of 100% of the heat gained by exercise while reducing the risk of hypothermia (Proulx et al., 2006; Gagnon et al., 2010; Flouris et al., 2014). With respect to the latter, in contrast to our hypothesis, we observed a similar nadir [nadir for the short (35.9 °C), moderate (35.6 °C), and prolonged (35.9 °C) delay conditions, respectively] to that reported by Proulx et al. (2003) following 2 °C CWI (35.7 °C). Thus, we confirm the previous recommendations (Proulx et al., 2006; Gagnon et al., 2010; Flouris et al., 2014) that a similar exit temperature should be used even if cooling of the exertional heatstroke victim is delayed by as much as 40 min.

Conclusion

In conclusion, this study shows that the effectiveness of CWI as a treatment for EHS remains high even when applied with a delay of 40 min. Specifically, treatment delay causes no changes in core cooling rates and similar post-immersion core temperature afterdrop. Therefore, our results are compatible with the conclusion that CWI is the most appropriate treatment for exertional heatstroke as it is capable of quickly reversing the hyperthermic state of the individual even when treatment is commenced with a significant delay.

Perspectives

When CWI treatment is commenced within 5 min of collapse, survival rate has been reported to be 100% (Casa et al., 2010). Despite the proven clinical benefits of CWI in the treatment of hyperthermic individuals (Casa et al., 2010), there remains an unwillingness by some to use this treatment modality. This is due in part to the misconception that CWI can potentially invoke dangerous and undesirable physiological responses that could compromise the health of the patient [i.e., cold shock response (sudden immersion in cold water inducing potentially lethal responses including hyperventilation, cardiac arrhythmias, elevated blood pressure, and reduced cerebral blood flow; Tipton, 1989) and an elevated shivering response reducing the rate of core cooling, etc.] while being perceived as generally uncomfortable for the patient (Casa et al., 2007b, 2010, 2012; Taylor et al., 2008). Further, it has been speculated by some that the deterioration in the health status of the exertional heatstroke victim when treatment is delayed suggests against the use of an aggressive cooling strategy such as CWI immersion (Mazerolle et al., 2011). With respect to the former point, in the current study that used EHS as a model (and not exertional heatstroke *per se*), we found that (a) the short immersion time produced by the CWI treatment minimized the effect of increased heat production via shivering thermogenesis, thereby eliciting a rapid decrease in core body temperature, and (b) the rapid skin vasoconstriction induced by the CWI helped reestablish normal cardiovascular function. Moreover, we did not observe any negative physiological responses associated with the cold shock response. With respect to the latter

point, the pattern of response in our study was unaffected by delays in treatment. Despite the fact that our participants showed signs of syncope and elevated levels of physical discomfort during the 20- and 40-min extended delay periods, CWI proved to be an equally effective treatment strategy. Finally, we recommend not immersing the arms during CWI treatment despite the minor reduction in core cooling rate. Allowing access to the patient's arms is beneficial as it allows better monitoring and prevents the patient from slipping down into the tub if he/she loses consciousness.

Key words: Cold water immersion, cardiovascular strain, heat stress, exercise recovery.

Acknowledgements

This research was supported by the Natural Sciences and Engineering Research Council (Discovery grant RGPIN-298159-2009 and RGPIN-06313-2014, and Discovery grants Program Accelerator Supplements RGPAS-462252-2014) and Leaders Opportunity Fund from the Canada Foundation for Innovation (22529, held by Dr. Glen Kenny). Dr. Glen Kenny was supported by a University of Ottawa Research Chair Award. The provision of financial support does not in any way infer or imply endorsement of the research findings by either agency. The authors thank all of the participants who volunteered for this study as well as Mr. Mike Carter for his technical assistance and Mr. Michael Sabino of Can-Trol Environmental Systems Limited (Markham, ON, Canada) for his support.

Conflicts of interest: The authors of this study declare that they have no conflicts of interest.

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