TITLE

CAERvest® – A novel endothermic hypothermic device for core temperature cooling – Safety and efficacy testing

RUNNING TITLE

CAERvest® core temperature cooling

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ABSTRACT

Introduction: Cooling of the body is used to treat hyperthermic individuals with heatstroke or to depress core temperature below normal for neuroprotection. A novel chemically activated, unpowered cooling device, CAERvest®, was investigated for safety and efficacy, with the feedback used to inform device development.

Methods: Eight healthy male participants (body mass 79.9±1.9kg and body fat percentage 16.1±3.8%) visited the laboratory (20°C, 40% RH) on four occasions. Following 30min rest, physiological and perceptual measures were recorded. Participants were then fitted with the CAERvest® proof of concept (PoC), prototype 1 (P1), 2 (P2) or 3 (P3) for 60min. Temperature, cardiovascular and perceptual measures were recorded every 5min. After cooling, the CAERvest® was removed and the torso was checked for cold–related injuries.

Results: Temperature measures significantly (p<0.05) reduced pre–to–post in all trials. Larger reductions in *core* and *skin temperature* were observed for PoC (–0.36±0.18 and –1.55±0.97°C) and P3 (–0.36±0.22 and –2.47±0.82°C), compared to P1 and P2. No signs of cold–related injury were observed at any stage.

Conclusion: This study demonstrates the CAERvest® is an effective device for reducing body temperature in healthy normothermic individuals without presence of cold injury. Further research in healthy and clinical populations within controlled and field–settings is warranted.

Key Words

Thermoregulation; Hyperthermia; Heat related illness; Cooling; Targeted temperature management

Abbreviations

Δ change
ANOVA analysis of Variance
BP blood pressure
BMI body mass index
BSA body surface area
CBT core body temperature
CPR cardiopulmonary resuscitation
CV coefficient variation
CWI cold water immersion
HR heart rate
HRI heat related illnesses
M mean
NBM nude body mass
ηp^2 partial eta squared
PoC proof of concept
P1 prototype 1
P2 prototype 2
P3 prototype 3
ROSC return of spontaneous circulation
SD standard deviation
TEM typical error of measurement
T_{arm} arm temperature
T_{calf} calf temperature
T_{chest} calf temperature
T_{thigh} thigh temperature
T_{re} core temperature
TSS thermal sensation
T_{skin} skin temperature
TTM targeted temperature management
U_{osm} urine osmolality
U_{sg} urine specific gravity

1.0 INTRODUCTION

Active cooling treatment is used to reduce an abnormally or dangerously elevated core body temperature (CBT), as in heat related illnesses (HRI). It may also be used to reduce a patient's CBT below normal (e.g. targeted temperature management [TTM]) during cardiac surgery and as neuroprotective treatment to reduce brain damage following a loss of blood supply, as in cases of sudden cardiac arrest with return of spontaneous circulation (ROSC) (1–4).

HRI present on a continuum of pathological states that range from mild to severe (5). If undetected or ineffectively treated, mild HRI can lead to heatstroke, a severe, life–threatening illness (6). Exertional heatstroke (EHS), a consequence of attenuated whole–body heat loss and the inability to dissipate metabolic heat production, can occur while physically active in either temperate or, hot humid conditions (7). Predisposing risk factors include lack of acclimatisation, dehydration, sleep deprivation, low aerobic fitness and diverse biophysical characteristics (6), meaning the onset can be sporadic and unpredictable.

CBT cooling is employed within sporting and occupational health settings prior to and between aerobic exercise or firefighting tasks, which have shown to improve performance in heat stress and reduce physiological and, or perceptual strain (8–10). Methods employed to actively cool vary according to setting and application, while HRI treatment is largely dependent upon the duration and extent to which CBT exceeds critical levels (7). Examples of these modalities include whole–body cold water immersion (CWI) (11), ice slurry ingestion (12), pre–prepared ice packs, evaporative techniques or a combination thereof (13). In contrast, early cooling for post–ROSC patients is difficult pre–admission to hospital due to equipment portability and effectiveness (14), while the precise CBT to be targeted for TTM remains controversial (3).

Currently, available cooling techniques are either external, non–invasive treatments which provide surface heat exchange, or internal, invasive devices that reduce blood temperature through infused cold saline or nasal spray (15,16). Difficulties thus far have been the design of a device that achieves sufficient and extended cooling non–invasively in the field, pre–admission to the hospital and without use of cooling tanks, refrigeration units, or electrical supply. The CAERvest®, a chemically powered, easy to activate, endothermic device that covers the torso, upper abdomen and extends onto the neck, purports to overcome these problems.

We undertook an initial controlled pilot study in healthy normothermic individuals to establish whether CAERvest® prototypes could significantly reduce core and skin temperature effectively over a 60 min period of cooling. Various prototypes were simultaneously assayed to compare efficacy and establish product safety. This testing was also intended to provide data to satisfy regulatory requirements. It was hypothesised there would be no significant difference in core

temperature in a defined group of participants within– and between–data collected over the cooling period in any prototype.

2.0 MATERIALS AND METHODS:

2.1 Participants

Eight moderately active, male participants (mean (*M*) ± standard deviation [*SD*]; age 27±5 years, stature 179±4 cm, nude body mass [NBM] 79.9±1.9 kg, body surface area [BSA] 1.99±0.05 m^2, body mass index [BMI] 24.4±0.2 and body fat percentage 16.1±3.8 %) volunteered for the study having provided written informed consent. Male participants were recruited to control for thermoregulation deviation around the menstrual cycle (17). Participants confirmed they were healthy, taking no medication and had no serious medical history or prior cold–related injuries. The study was approved by the Institution's Research Ethics and Governance Committee and conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2013. Participants refrained from caffeine, alcohol consumption and prolonged strenuous activity for 24 h prior to testing. Participants also abstained from food for 2 h before testing and to arrive in a euhydrated state (18).

2.2 Experimental design

Each participant visited the laboratory on four occasions, separated by >72 h to complete the first three CAERvest® trials (proof of concept [PoC], prototype 1 [P1] and prototype 2 [P2]), which were counterbalanced using a cross–over design. This then informed the product development for the final CAERvest® trial (prototype 3 [P3]), which was completed 21 days after their first visit by all of the participants (Figure 1). Trials were completed in temperate conditions (20°C, 40% relative humidity), with participants wearing only shorts and t–shirt at similar times of the day to minimise circadian rhythm variations (19). Each visit followed the same protocol (Figure 2), although the allocated CAERvest® prototype changed per trial.

2.3 Physiological measures and equipment

Body fat was estimated using skinfold calipers (Harpenden, UK,) across four standard sites (20). Participants provided, in privacy, a fresh mid–flow urine sample which was assessed for osmolality (U_{osm}) (Osmocheck, Vitech Scientific, Japan) and specific gravity (U_{sg}) (hand refractometer, Atago, Japan) to indicate hydration status. Stature and NBM were measured using physician (Detecto scale company Inc., USA) and weighing scales (Adam GFK 150, Equipment Co., UK) respectively, for BMI and BSA calculation (21). Blood pressure (BP*)* was assessed using an automatic monitor (Boso Medicus PC, Cranlea & Company, UK). *Rectal temperature* (T_{re}) was assessed continuously using a rectal probe (4600 thermometer, Henleys medical supplies, UK) inserted 10 cm past the anal sphincter. Although minor delays to rapid transients are associated with T_{re} when compared with esophageal measurement, the equipment's accuracy is ±0.13°C (22). *Heart rate (HR)* (Polar Electro, Finland) monitors were affixed and skin surface

telemetry thermistors (U–type connected to Gen II GD38 transmitter, Eltek, UK) were attached to four sites (mid–belly of the pectoralis major, biceps brachii, rectus femoris and gastrocnemius). Data was transmitted wirelessly from a logging device (RX250AL 1000 series wireless squirrel logger, Eltek, UK), which is accurate to <0.1°C (23). *M weighted skin temperature (T_{skin})* were estimated using the equation of Ramanthan, (24); $M\ T_{skin} = 0{\cdot}3 \times (T_{chest}+T_{arm})+0{\cdot}2 \times (T_{thigh}+T_{calf})$. Where T_{chest}, T_{arm}, T_{thigh} and T_{calf} are *chest*, *arm*, *thigh* and *calf temperature*, respectively.

2.4 Perceptual measures

Participants were familiarised to the perceptual scales on their first visit. These included *thermal sensation* (*TSS*) on an 8–point scale (0 = *unbearably cold* – 8 = *unbearably hot*) (25); *feeling* on a 10–point scale (+5 = *very good* – –5 = *very bad*) (26); *cold discomfort* on a 10–point scale (0 = *comfortable with no experience of cold* – 10 = *unbearably cold*) (27) and *shivering* on a 4–point scale (0 = *absence* – 3 = *severe*) (28).

2.5 CAERvest® devices and development

The CAERvest® devices contain a precise quantity of non–toxic chemical blend (developed by BodyChillz, UK) which, when combined with a defined volume of water from an external reservoir, undergoes an endothermic dissolution process and cools for >1 h. Reservoirs were placed in a water–bath (Fischer Scientific DMU19, UK) to control water temperature (18±1°C), as this represented a reasonable storage temperature for a commercial device. The PoC device comprised three separate compartmentalised, dual layer, polyethylene modules filled with blend and activated by 0.8 L of water. One was placed underneath the participant's back, two were placed across the torso and another smaller module was placed around the neck. A total 4.05 kg of chemical was applied.

The subsequent prototypes (P1, P2 and P3) were larger, single module designs intended to target high blood flow regions in neck, axillae and groins and allow for cardiopulmonary resuscitation (CPR), defibrillation or post resuscitation care. The CAERvest® are also compatible with the LUCAS™ and Autopulse® chest compression systems. The P1 was the first single module design which covered the torso and groins of the participant and the filling mechanism was as per the PoC. A cellulose matrix was introduced in the P2 along with an incorporated neck section to cool the neck vessels preferentially. A solid non–spill quick disconnect coupling was employed to fill this prototype, with the female attached to the module and male to the reservoir. It was concluded after testing the PoC, P1 and P2 prototypes that the polyethylene material was too rigid and insufficiently elastic in nature. Therefore, a further prototype (P3) as displayed in Figure 3, retained the quick–disconnect coupling for filling and used 150 mm micron polyurethane on the inner surface. Nylon coated polyurethane was adopted on the outer portions of the device to improve insulation for the non–contact surface. The P3 design also removed the sections

specifically targeting the neck and groin, which were found to be difficult to position, and increased coverage over the shoulders. The internal channels were redesigned such that fluid entering through the inlet port would push any entrapped air towards newly–introduced one–way valves at the apex of the neck. These valves allowed entrapped air to pass out without causing airlock, fluid loss or points of insulation. The expanding cellulose matrix then caused the device to swell upon fluid introduction and take on a garment–like configuration which improved patient comfort, ensured homogeneity of cooling, minimised movement of the incorporated chemicals in transit and reduced the incidence of cold spots.

2.6 Safety

Signs and symptoms of cold–related injuries were assessed on removal of the CAERvest® device and after the re–warming period. Skin surface was assessed for blistering, oedema and severe erythema, with trial termination if present (zero incidences). Reappraisal of signs and symptoms of cold injury was completed by telephone contact 24 h later.

2.7 Experimental procedures

Hydration status and anthropometric measures were completed on each participant prior to each trial. Temperature and cardiovascular measuring equipment was then attached before a 30 min baseline rest in a supine position. At the end of this, the allocated CAERvest® prototype was applied for 60 min. It was removed early at the participant's request (one incidence at 50 min during the PoC trial), or if T_{re} dropped 1.5°C below resting levels (zero incidences). Cold injury assessments were then completed prior to a re–warming period, where CBT returned naturally, or was aided using extra clothing and light exercise at the participant's discretion. Temperature, cardiovascular and perceptual measures were continuously monitored throughout and recorded at 5 min intervals.

2.8 Safety follow up

Twenty four hours after each trial, follow–up questionnaires and telephone conversations were conducted to account for any adverse effects of cooling (one minor headache).

2.9 Statistical analyses

The trials were an open study of efficacy, assessed by temperature changes over time while using the four CAERvest® prototypes. All data are presented as $M \pm SD$ and were assessed for normality and sphericity prior to statistical analysis. Two way, repeated measure Analysis of Variance (ANOVA) were used to test for differences in temperature, cardiovascular and perceptual responses between and within each trial at 5 min intervals. One way repeated measures ANOVA were used to test for the differences in the lowest point and change (Δ) in temperature and

cardiovascular measures within– and between–trials. Where appropriate, Bonferroni adjusted pairwise comparisons were used to identify where differences occurred. Lowest *M* values and Δ in perceptual scales (non–parametric data) were analysed using a Friedman test, with post–hoc analysis using a Wilcoxon signed–rank test. Data were analysed using SPSS version 20.0, with significance set at $p \leq 0.05$. Effect size for main effects and interactions are presented as partial eta squared (ηp^2), while meaningful differences between related samples during the trials were evaluated using Cohen's *d* (29). Effect size were categorised as small (0.2), moderate (0.5) and large (0.8). Typical error of measurement (TEM) was calculated from the *SD* of the *M* difference during 30 min baseline in T_{re} and T_{skin} between the trials, multiplied by 1 squared, then divided by √2 (30) and expressed as a *M* coefficient variation (CV %). Statistical analysis on resting data within the sample population used within this study presented predefined limits in TEM (CV) of 0.20°C (0.5%) for T_{re} and 0.64°C (2.2%) for T_{skin}. TEM were used to demonstrate clinically relevant trends within changes in T_{re} and T_{skin} when investigating the CAERvest® devices.

3.0 RESULTS:

3.1 Physical characteristics

Participants arrived in similar physiological states across trials with no differences in preliminary measures (all p>0.05) (Table 1), apart from *M* systolic BP, which was elevated ($F(3,21)=3.23$, $p=0.04$, $\eta p^2=0.3$) prior to the PoC trial.

3.2 Baseline measures

No within– or between–participant differences were observed in T_{re} ($F(3,21)=0.48$, $p=0.70$, $\eta p^2=0.1$) or T_{skin} ($F(3,21)=0.03$, $p=0.99$, $\eta p^2=0.0$) across trials. Nor were differences found in *HR* ($F(3,21)=0.47$, $p=0.71$, $\eta p^2=0.1$) or perceptual measures of *TSS* ($F(3,21)=0.30$, $p=0.82$, $\eta p^2=0.0$), *shivering* ($F(3,21)=1.00$, $p=0.41$, $\eta p^2=0.1$), *feeling* ($F(3,21)=1.00$, $p=0.42$, $\eta p^2=0.1$), or *cold discomfort* ($F(3,21)=0.78$, $p=0.56$, $\eta p^2=0.1$) scales (Table 2).

3.3 Cooling measures

Temperature, cardiovascular and perceptual measures within– and between–CAERvest® trials:

A main effect for T_{re} ($F(6,42)=5.35$, $p=0.004$, $\eta p^2=0.4$) and T_{skin} ($F(6,36)=3.46$, $p=0.01$, $\eta p^2=0.4$) occurred in all four trials, with significant pre–to–post reductions (Figure 4 and Table 3). On one occasion the PoC was removed at 50 min upon the participant's request. ΔT_{re} was significantly greater ($p=0.047$) during the PoC trial (–0.36±0.18°C, $d=1$) compared to the P1 (–0.17±0.13°C, $d=0.9$). Moreover, during the P3 trial the ΔT_{skin} (–2.47±0.82°C, $p=0.001$, $d=1$) were significantly greater than the P2 trial (–0.98±0.93°C, $d=0{\cdot}7$) (Table 3).

There was a significantly larger ΔT_{re} ($F(7,49)=5.33$, $p=0.00$, $\eta p^2=0.4$) during the CAERvest® cooling period compared to the ΔT_{re} during baseline rest. This was found within the PoC (p=0.01) and P3 ($p=0.01$) trials, but not the P1 ($p=0.45$) or P2 ($p=0.28$) trials. A similar interaction effect was found for ΔT_{skin} ($F(7,49)=37.24$, $p=0.00$, $\eta p^2=0.8$) within the PoC ($p=0.02$), P1 ($p=0.01$) and P3 ($p=0.00$) trials, but not for P2 ($p=0.09$).

An interaction effect occurred between time and CAERvest® in *shivering* ($F(36,108)=1.55$, $p=0.04$, $\eta p^2=0.3$) and *cold discomfort* ($F(36,108)=2.345$, $p=0.001$, $\eta p^2=0.4$) scales. *Shivering* ($Z=-2.04$, $p=0.04$) and *cold discomfort* ($Z=-2.23$, $p=0.03$) scales were significantly greater during the PoC (1±1 and 5±2, respectively) compared to the P1 trial (0±0 and 4±2, respectively). *Cold discomfort* ($Z=-2.13$, $p=0.03$) scales were also higher during the P3 (5±3) compared to P2 trial (3±2) (Table 4).

An interaction effect between time and CAERvest® occurred in T_{re} (F(36,216)=1.91, p=0.003, ηp^2=0.2) and T_{skin} (F(36,72)=2.60, p=0.001, ηp^2=0.6), as displayed within Figure 4 and 5.

No interactions were present in *HR* (F(36,144)=0.36, p=1.00, ηp^2=0.1), *TSS* (F(36,108)=1.497, p=0.06, ηp^2=0.3), or *feeling* (F(36,108)=1.24, p=0.20, ηp^2=0.3) scales in the same period.

3.4 Device safety analysis

There was no evidence of cold–related injuries across all four CAERvest® prototypes. The only symptoms resulting from the trials were mild skin paleness on removal of the device and one reported headache within 6 h of PoC removal. Neither of these symptoms were considered to represent a serious adverse event. Headaches have been recorded in other cooling garment studies (31).

4.0 DISCUSSION

The aim of this study was to inform the development and investigate the safety and efficacy of a series of CAERvest® prototypes. Therefore, the study was designed to examine the null hypothesis, that there would be no significant difference in CBT in a defined group of participants during the cooling period in any prototype. We found significant reductions in T_{re} and T_{skin} with each device. The PoC and P3 CAERvest® were found to provide greater temperature reductions than the P1 and P2, suggesting improved design. It is postulated that in the PoC this may be because of increased mass and in the P3, despite reduced chemical mass, improved surface area coverage and thermal coupling to the skin. We found no evidence of important cold–related signs or symptoms from the CAERvest® devices during the cooling period, or in the subsequent 24 h. As the CAERvest® was being developed during the study, no comparisons were made with other similar devices, although future studies will address this.

4.1 Comparisons to other cooling modalities

Previous studies investigating surface cooling devices have reported effective (32–39) and ineffective (40–46) physiological responses in athletic performance, and thermoregulatory strain reductions within hyperthermic individuals. As EHS treatment requires a rapid cooling rate of 0.1–0.2°C·min^{-1} (47), Lopez et al. (44), DeMartini et al. (45) and Flouris et al. (11) suggest the continued use of CWI as the standard for hyperthermic individuals, with reported cooling rates of 0.1–0.35°C·min^{-1}. This is opposed to the less effective treatment of ice–wet towels (0.11°C·min^{-1}), ice packs (0.03°C·min^{-1}) and fans (0.02°C·min^{-1}) (48). Within this study the 60 min cooling rate for PoC and P3 were 0.01°C·min^{-1}, while they were 0.003°C·min^{-1} for the P1 and P2, however, the authors acknowledge the normothermic population tested and associated study limitations which are later discussed, although there still remains distinct advantages of a portable, on–site method.

Further, other pre– and in–hospital surface cooling systems which have been used upon hyperthermic or cardiac arrest casualties, include the CritiCool (Curewrap™, MTRE, Yavne, Israel), Blanketrol III (Kool–Kit®, Cincinnati Sub–Zero, OH, USA), EMCOOLS (Flex.Pad®) and Artic Sun® (Medivance, Louisville, CO, USA) have reported cooling rates of 1.5–3.5°C·h^{-1} (49,50). While InnerCool STX (Phillips, Best, Netherlands) and Thermogard XP® (ZOLL) intravascular systems report 2–5°C·h^{-1} (49). Finally, the intranasal device, RhinoChill® (BeneChill, CA, USA) reports 1.75°C reductions in the first hour of cooling (16,51). However, the large variation in cooling suggests product design and function play a key role in achieving clinically important reductions. Although, it is recognised that disparity may also result from alternate methodologies, cooling modalities, aerobic activity and the use of hyperthermic or cardiac arrest patients. These differences make it very difficult to compare across studies. There

are however, disadvantages associated with these pre–hospital methods, including trivial benefits of evaporative fanning or misting (52), unconscious individuals are unable to ingest ice slurries, powered refrigerator requirements and impracticality of CWI, thus failing to provide a portable or flexible solution. Moreover, infusing cold saline intravenously is invasive, requires specialist training and causes additional stress to the circulatory system, often with deleterious effects (53,54). The in–hospital surface cooling devices are effective, but require electrical supply, refrigeration and are sometimes restricted to intensive care units. Finally, the intranasal device, can only be used on unconscious individuals and has large consumable costs (55).

4.2 Physiological responses

T_{re} was shown to reduce significantly pre–to–post while using all four CAERvest® designs, with the largest reported reductions observed in the PoC (–0.36±0.18°C) and P3 (–0.36±0.22°C) trials. Although the PoC implemented a larger surface area of cooling (56), there were no differences compared with the P3 CAERvest®. It is suggested the large range in T_{re} reductions during the PoC (–0.12 – –0.64°C), P1 (–0.12 – –0.41°C), P2 (–0.07 – –0.41°C) and P3 (–0.07 – –0.65°C) trials highlight inter–individual variances within the sample population. Significantly greater ΔT_{re} and ΔT_{skin} were observed during the cooling period compared to the bassline resting period during the PoC and P3 trials, as opposed to no difference during the P1 and P2. Thus, highlighting the greater effect of CBT cooling compared to a no–cooling control state.

The observed T_{skin} reductions (2–3°C) are in line with previously cooled hyperthermic (44) and normothermic (37) individuals in warm conditions. T_{skin} during the P3 trial was significantly lower in the latter stages of the cooling period compared to the PoC and P2 trial, suggesting effective and prolonged cooling. Reportedly, optimal vasodilation, core to skin thermal gradient and therefore, a greater heat flux occurs at T_{skin} ~33–35°C (32). T_{skin} in this study reduced to <33°C in all four trials. Although, this may have appeared as chest and tricep skin thermistors were placed underneath the CAERvest® devices, leading to larger magnitudes of M T_{skin} declines, as similarly observed by Teunissen et al. (57).

While the authors acknowledge the temperature reductions within the study are comparatively modest, it is suggested the limited reductions were observed because the study was performed in a young, asymptomatic healthy population of moderate fitness levels. These individuals may present characteristics similar to those heat–acclimatised, such as lower internal temperature set points (58) and modified thermoregulatory mechanisms, with improved capacity for vasoconstriction (59). Therefore, participants may have been particularly resilient to an external cold induced stimulus and, subsequently, more effective in defending their CBT through homeostasis. Those with predisposing risk factors, exertional heat illnesses or symptomatic clinical populations are expected to be less resistant to cooling due to hypothalamic dysfunction

and CBT regulation disruption after the traumatic event occurs (6,60–65). Extending the evaluation of the CAERvest® to other symptomatic populations warrants further investigation.

4.3 Perceptual responses

While perceptual measures are important for investigating cooling interventions (57), most studies use perceived comfort to assess efficacy prior to and during physical activity in an attempt to enhance performance (12,66), or reduce physiological strain (57). As expected, *TSS* decreased during cooling in all four trials, although no interaction effect occurred. Nor were differences observed in *feeling* scale within– or between–trials, suggesting the PoC and P3 CAERvest® did not make participants feel worse over time, although they felt colder and presented minor shivering responses.

4.4 Limitations and future directions

Aforementioned, the study used healthy, normothermic individuals as opposed to clinical or hyperthermic populations, who are known to be more susceptible to external cold stimulus. Therefore, caution should be used if extending the results of this study to the general population. An additional limitation includes no control trial, although each cooling period was compared against prior resting measures within– and between–trials. Directions for future CAERvest® investigations will include evaluation of product efficacy across a range of exercise–induced hyperthermic individuals, in addition to comparisons against other cooling modalities and normothermic post–cardiac arrest populations.

5.0 Conclusion

This study observed reductions in core and skin temperature without incidence of cold injury in the proof of concept and latter CAERvest® prototype design. The latest P3 CAERvest® is a portable, non–powered, easy–to–use device, which may offer an alternative on–site or pre–hospital strategy for those suffering from HRI or ischemic related events, as a single or combined approach with other modalities, to induce rapid cooling without the prior preparation required. However, further research is warranted in controlled laboratory and field–based settings to continue the evaluation and development of this technology.

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6.1 Conflict of Interest and Funding

Steve Tocker, Dr. Rowland Cottingham and William Simpson, listed as co–authors, are associated with the company that commissioned the product testing, BodyChillz. These individuals were not involved in the data collection or statistical analyses, their involvement was limited to demonstration of CAERvest® prototypes, familiarisation of the study team and the review of this manuscript.

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FIGURE TITLES

Figure 1:

Schematic of experimental design. Prototype 3 (P3) was introduced after the proof of concept (PoC), prototype 1 (P1) and prototype (P2) trials, due to refinements in design following analysis and therefore, were not part of the randomization.

Note: The full colour version of this figure is available online.

Figure 2:

Schematic of experimental design.

A- Body mass, stature, body surface area, body mass index, hydration status, blood pressure.
B- Physiological (*rectal temperature, skin temperature* and *heart rate*) and perceptual (*thermal sensation, cold discomfort, feeling, shivering*) measures monitored continuously and recorded every 5 min.
C- Medical inspection for any associated cold related injuries.

Note: PoC = proof of concept, P1 = prototype 1, P2 = prototype 2 and P3 = prototype 3.

Figure 3.

Photo of prototype 3 on a participant.

Note: The full colour version of this figure is available online.

Figure 4.

Mean rectal temperature changes over the cooling period. Significance ($p<0.05$) is denoted by ‡ between PoC and P1, * between P3 and P1.

Note: PoC = proof of concept, P1 = prototype 1, P2 = prototype 2 and P3 = prototype 3.

Figure 5.

Mean skin temperature changes over the cooling period. Significance ($p<0.05$) is denoted by * between P3 and P2, and ‡ between P3 and PoC.

Note: PoC = proof of concept, P1 = prototype 1, P2 = prototype 2 and P3 = prototype 3.

570 **Tables**

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Table 1. Mean (*SD*) preliminary health measures on the arrival to each trial.

Measure	Trial			
	PoC	P1	P2	P3
NBM (kg)	81.1 ± 15.2	81.2 ± 15.1	76.1 ± 10.2	80.0 ±15.7
BMI	24.6 ± 4.0	246 ± 3.9	23.1 ± 2.8	24.2 ± 3.9
BSA (m^2)	2.01 ± 0.19	2.01 ± 0.19	1.96 ± 0.14	2.00 ± 0.20
Systolic BP (mmHg)	148 ± 18*	144 ± 17	135 ± 5	134 ± 10
Diastolic BP (mmHg)	81 ± 12	79 ± 5	81 ± 6	79 ± 6
U_{osm} (mOsmol·kg^{-1} H_2O)	491 ± 104	524 ± 228	450 ± 157	389 ± 213
U_{sg}	1.013 ± 0.004	1.014 ± 0.008	1.010 ± 0.005	1.010 ± 0.006

Note: * denotes significant difference between other trials, where $p<0.05$. PoC = proof of concept, P1 = prototype 1, P2 = prototype 2 and P3 = prototype 3. BP = blood pressure, BMI = body mass index, BSA = body surface area, NBM = nude body mass, U_{osm} = urine osmolality, U_{sg} = urine specific gravity.

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Table 2. Mean (*SD*) and change in baseline physiological and perceptual measures.

Measure		Trial			
		PoC	P1	P2	P3
T_{re} (°C)	*M*	37.11 ± 0.29	37.10 ± 0.26	37.10 ± 0.27	37.18 ± 0.26
	Δ	–0.13 ± 0.10	–0.14 ± 0.13	–0.09 ± 0.10	–0.11 ± 0.07
T_{skin} (°C)	*M*	31.29 ± 1.01	31.14 ± 1.02	30.92 ± 1.43	30.97 ± 1.18
	Δ	1.08 ± 0.38	1.11 ± 0.76	1.04 ± 0.60	1.04 ± 0.45
HR (bpm)	*M*	63 ± 8	61 ± 9	64 ± 7	63 ± 9
	Δ	–1 ± 6	–2 ± 7	–1 ± 8	–1 ± 4
TSS	*M*	4 ± 1	4 ± 1	4 ± 0	4 ± 1
	Δ	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Shivering	*M*	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	Δ	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Feeling	*M*	2 ± 2	3 ± 2	2 ± 2	2 ± 2
	Δ	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Cold discomfort	*M*	1 ± 1	0 ± 1	0 ± 0	0 ± 1
	Δ	0 ± 0	0 ± 0	0 ± 0	0 ± 1

Note: PoC = proof of concept, P1 = prototype 1, P2 = prototype 2 and P3 = prototype 3. Δ = change, *HR = heart rate, M = mean,* T_{re} *= core temperature,* T_{skin} *= skin temperature,* and *TSS = thermal sensation scale.*

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Table 3. Pre–post mean (*SD*) changes in physiological measures during cooling.

Measure	Trial	Time (min)		
		0 min	60 min	Δ 0–60
T_{re} (°C)	PoC	37.04 ± 0.29	36.68 ± 0.42	–0.36 ± 0.18*$^{+}$
	P1	37.03 ± 0.23	36.86 ± 0.26	–0.17 ± 0.13*
	P2	37.06 ± 0.27	36.87 ± 0.24	–0.19 ± 0.17*
	P3	37.12 ± 0.23	36.76 ± 0.28	–0.36 ± 0.22*
T_{skin} (°C)	PoC	31.76 ± 1.12	30.18 ± 1.38	–1.55 ± 0.97*
	P1	31.59 ± 0.95	29.39 ± 0.62	–2.20 ± 1.04*
	P2	31.33 ± 1.50	30.35 ± 1.22	–0.98 ± 0.93*
	P3	31.42 ± 1.14	28.95 ± 1.10	–2.47 ± 0.82*†
HR (bpm)	PoC	63 ± 10	56 ± 9	–7 ± 12
	P1	60 ± 8	53 ± 7	–7 ± 3
	P2	65 ± 6	60 ± 6	–5 ± 4
	P3	63 ± 9	56 ± 8	–7 ± 8

Note: * denotes significant (p<0.05) difference within trials for pre to post changes, $^{+}$ between PoC and P1, and † between P3 and P2 change. PoC = proof of concept, P1 = prototype 1, P2 = prototype 2 and P3 = prototype 3. Δ = change, T_{re} = *core temperature* and T_{skin} = *skin temperature.*

Table 4. Pre–post mean (*SD*) changes in perceptual measures during cooling.

Measure	Trial	Time (min)		
		0 min	60 min	Δ 0–60
TSS	PoC	4 ± 1	2 ± 1	–2 ± 1*
	P1	4 ± 1	3 ± 1	–1 ± 1*
	P2	4 ± 0	3 ± 1	–1 ± 1*
	P3	4 ± 1	2 ± 1	–2 ± 1*
Shivering	PoC	0 ± 0	1 ± 1	1 ± 1§
	P1	0 ± 0	0 ± 0	0 ± 0
	P2	0 ± 0	0 ± 0	0 ± 0
	P3	0 ± 0	1 ± 1	1 ± 1
Feeling	PoC	2 ± 2	0 ± 3	–2 ± 2
	P1	3 ± 2	1 ± 3	–1 ± 2
	P2	2 ± 2	1 ± 3	–1 ± 1
	P3	2 ± 2	0 ± 3	–1 ± 2
Cold discomfort	PoC	1 ± 1	4 ± 2	4 ± 2*
	P1	0 ± 1	3 ± 3	2 ± 3*
	P2	0 ± 0	3 ± 2	3 ± 2*
	P3	1 ± 1	5 ± 2	4 ± 2*

Note: * denotes significant (p<0.05) difference within trials for pre to post changes, § between P1 and P2. PoC = proof of concept, P1 = prototype 1, P2 = prototype 2 and P3 = prototype 3. Δ = change and *TSS = thermal sensation scale*.

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PoC P1 P2 P3

counterbalanced order

final trial

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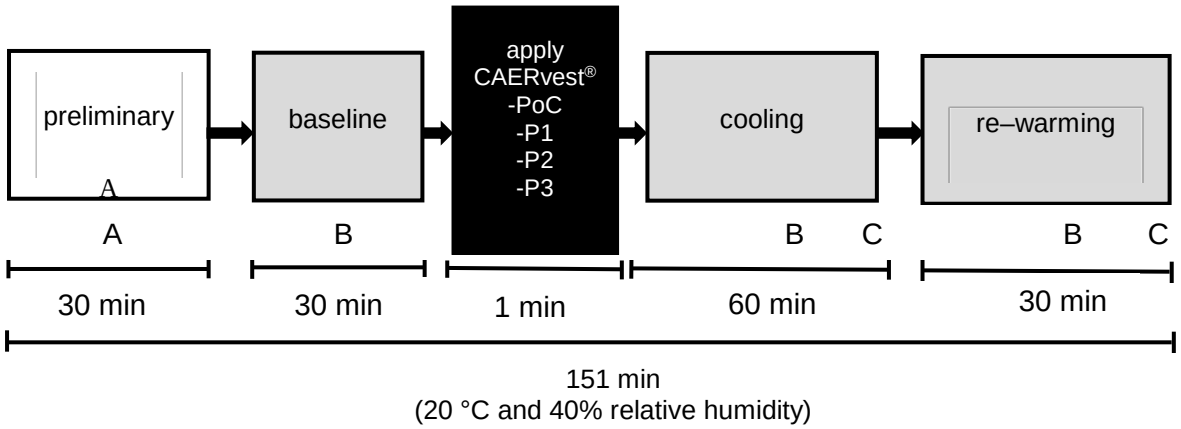
preliminary
A
baseline
apply
CAERvest®
-PoC
-P1
-P2
-P3
cooling
re–warming
A
B
B
C
B
C
30 min
30 min
1 min
60 min
30 min
151 min
(20 °C and 40% relative humidity)

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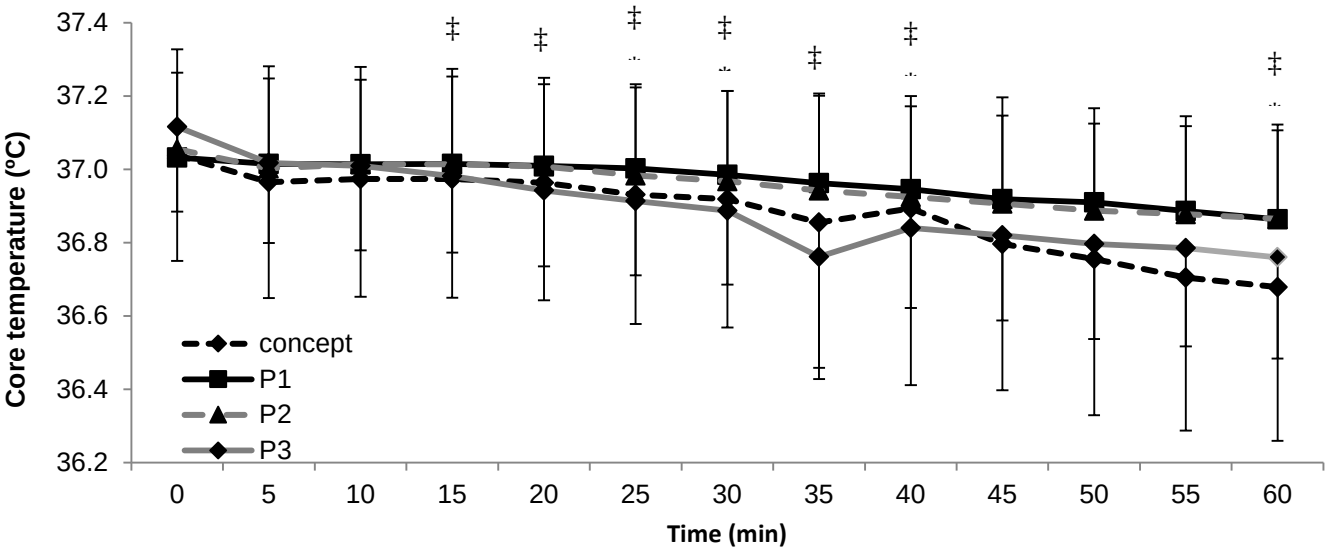
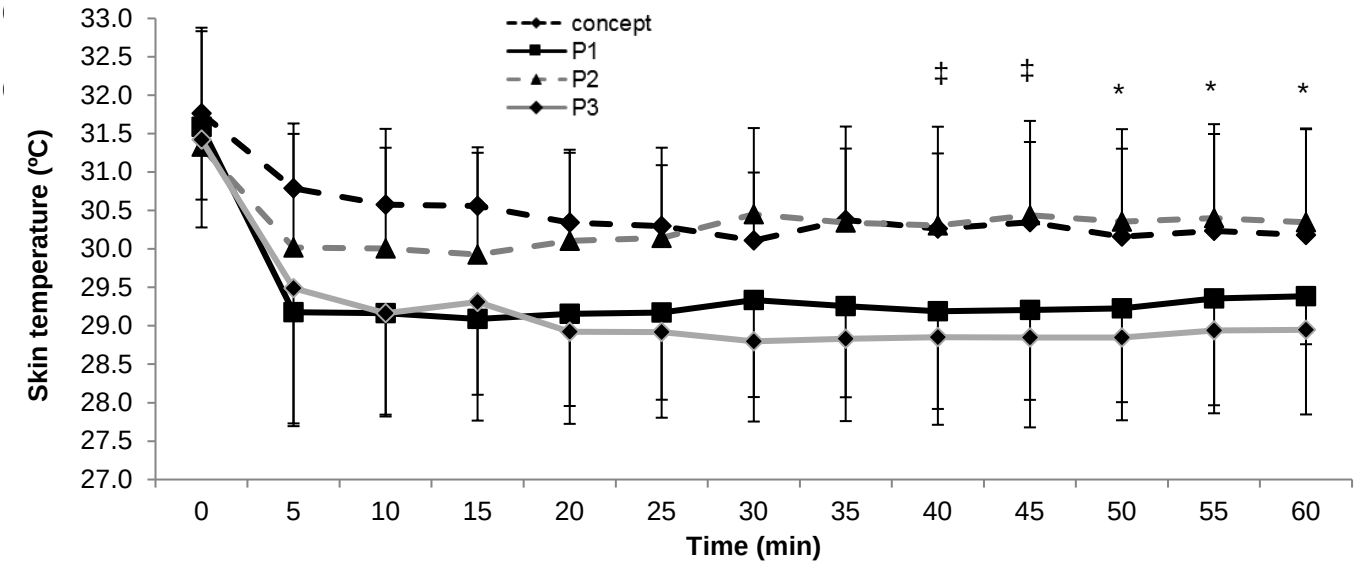

37.4
37.2
37.0
36.8
36.6
36.4
36.2
Core temperature (ºC)
concept
P1
P2
P3
0
5
10
15
20
25
30
35
40
45
50
55
60
Time (min)


concept
P1
P2
P3
Skin temperature (ºC)
Time (min)
33.0
32.5
32.0
31.5
31.0
30.5
30.0
29.5
29.0
28.5
28.0
27.5
27.0
0
5
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