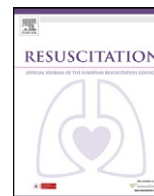




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Clinical paper

## Rapid induction of therapeutic hypothermia using convective-immersion surface cooling: Safety, efficacy and outcomes<sup>☆</sup>

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### ABSTRACT

Therapeutic hypothermia has become an accepted part of post-resuscitation care. Efforts to shorten the time from return of spontaneous circulation to target temperature have led to the exploration of different cooling techniques. Convective-immersion uses a continuous shower of 2 °C water to rapidly induce hypothermia. The primary purpose of this multi-center trial was to evaluate the feasibility and speed of convective-immersion cooling in the clinical environment. The secondary goal was to examine the impact of rapid hypothermia induction on patient outcome.

24 post-cardiac arrest patients from 3 centers were enrolled in the study; 22 agreed to participate until the 6-month evaluations were completed. The median rate of cooling was 3.0 °C/h. Cooling times were shorter than reported in previous studies. The median time to cool the patients to target temperature (<34 °C) was 37 min (range 14–81 min); and only 27 min in a subset of patients sedated with propofol. Survival was excellent, with 68% surviving to 6 months; 87% of survivors were living independently at 6 months.

Conductive-immersion surface cooling using the ThermoSuit® System is a rapid, effective method of inducing therapeutic hypothermia. Although the study was not designed to demonstrate impact on outcomes, survival and neurologic function were superior to those previously reported, suggesting comparative studies should be undertaken. Shortening the delay from return of spontaneous circulation to hypothermic target temperature may significantly improve survival and neurologic outcome and warrants further study.

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### 1. Introduction

Mild therapeutic hypothermia reduces mortality and morbidity after cardiac arrest. Two large multi-center randomized controlled trials<sup>1,2</sup> have shown that reducing a patient's core temperature to a target range of 32–34 °C following resuscitation from cardiac arrest can improve important intermediate and long-term outcomes compared to supportive therapy without cooling. A third trial showed improvements in metabolic endpoints for patients who present with pulseless electrical activity or asystole. Experimenten-

tal studies<sup>3–13</sup> suggest that the period of therapeutic hypothermia reduces neuronal damage by minimizing oxygen consumption, reducing inflammation and edema, and possibly by stimulating the release of protective proteins.

The clinical benefits of therapeutic hypothermia are thought to be greatest when administered early after return of spontaneous circulation. The 2005 AHA/ILCOR Guidelines<sup>14</sup> recommend that therapeutic hypothermia be considered early after a cardiac arrest (class 2). The European Council on Resuscitation recommends that "cooling should be started as soon as possible"<sup>15</sup> and the Canadian Association of Emergency Physicians recommends that for selected patients "cooling should begin as soon as the clinical situation allows."<sup>16,17</sup>

The challenge of cooling patients rapidly is a difficult one. Commonly employed cooling methods include cold saline infusion, ice-packs, and fan-and-misting techniques. There are a variety of

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approved devices available that offer both whole body and partial body cooling using external or intravascular methods, all developed in an effort to speed and simplify the cooling process.<sup>15</sup> The interval from the return of spontaneous circulation (ROSC) to achieving target temperatures of therapeutic hypothermia is highly variable. If cooling strategies require complex or invasive equipment, require transfer to higher levels of care, or if they incur delays because of slow cooling rates, the therapeutic benefit achieved may be suboptimal.<sup>16</sup>

Ice water immersion has previously been demonstrated to produce very rapid cooling in humans,<sup>18,19</sup> particularly when the water is circulating and providing an additional convective heat loss. We refer to this method of hypothermia induction as convective-immersion surface cooling. The ThermoSuit® System (TSS) (Life Recovery Systems) is a whole body cooling device which has been described previously.<sup>20</sup> It uses convective-immersion by circulating ice water from a perforated top-sheet and an under-blanket across the skin surface at a rapid rate (14 L/min).

The primary purpose of this trial was to observe the feasibility and speed of cooling of the ThermoSuit® System in the clinical environment. The secondary goal was to examine the impact of rapid hypothermia induction on patient outcome.

## 2. Methods

This was a multi-center observational study. Patients were recruited from the Vienna General Hospital, Vienna, Austria; St. Michael's Hospital, Toronto, Canada; and Kingston General Hospital, Kingston, Canada. The study protocol received ethical approval from each institutional review board. Study monitoring and database management was performed by i3 Innovus (Burlington Ontario, Canada).

We included patients who had a cardiac arrest of presumed cardiac origin who were successfully resuscitated to a spontaneous rhythm but had persistent neurological dysfunction (Glasgow Coma Score <8). We excluded patients with an estimated or known age < 18 years, patients who could not have an oesophageal temperature probe successfully inserted, patients for whom the resuscitation lasted longer than 60 min, patients with a core temperature less than 35 °C after return of spontaneous circulation (ROSC), patients with a comatose state prior to the cardiac arrest, pregnant patients, patients with a known terminal illness, patients with known enrollment in another study, patients requiring urgent surgery, patients with a coagulopathy and active bleeding, patients more than 4 h after ROSC and patients with haemodynamic instability (SBP < 90 mmHg or MAP < 60 mmHg for > 30 min after ROSC despite vasopressors). Patients with a height greater than 188 cm or elbow-to-elbow length greater than 60 cm were excluded due to size limitations of the cooling device.

Study patients meeting inclusion/exclusion criteria were placed in the device (Fig. 1) in accordance with the product's instructions for use (Life Recovery Systems, Waldwick, NJ, USA). In accordance with the local ethics committee requirements and regulations a waiver of consent was used to prevent delays in patient care, with confirmation of consent for use of study data from the patient or patient's substitute decision-maker when they became available. Sedation, analgesia, and paralysis (if used) were administered prior to the start of cooling according to standard institutional procedure for post-resuscitative therapeutic hypothermia. Medications and their dosages were recorded from the medical record. Adhesive defibrillation pads were applied to the patient in the conventional locations and an esophageal temperature probe was inserted for continuous temperature monitoring. Wounds, catheterization sites and defibrillation electrodes were covered with occlusive dressings prior to activating the device. Defibrillation was provided if required without discontinuation of the cooling process.



Fig. 1. The Life Recovery Systems ThermoSuit® System, which uses convective-immersion to cool patients.

Cooling was initiated by circulating ice-cold water ( $2.0 \pm 2.0^\circ\text{C}$ ) through the TSS. The clinician was prompted to purge the fluid from the suit when the patient's oesophageal temperature reached  $34.5^\circ\text{C}$ . This was intended to produce a final patient oesophageal temperature of  $32\text{--}34^\circ\text{C}$ , which we used to define our target temperature. Cooling time was defined as time from activation of water flow over the patient to core temperature reaching the target range.

Patients were removed from the device and maintained at  $32\text{--}34^\circ\text{C}$  using warming or cooling techniques at the discretion of the treating physician for 12–24 h. The patients were then re-warmed at a target rate of  $0.2\text{--}0.5^\circ\text{C/h}$  using passive blankets or a conventional heating blanket.

Patient data collected included time of start of cooling, time of purging of the TSS, temperature of water infused through the suit, oesophageal temperature, blood pressure, heart rate and rhythm, and electrocardiogram (ECG). Episodes of shivering and drugs administered to control shivering or discomfort were recorded.

The primary outcome measure was time from collapse to a core temperature of  $34.0^\circ\text{C}$ . Other data collected included cardiac arrest time, drug administration, operator interaction with the device, and adverse events. Safety parameters measured included survival at 24 h, hospital discharge, 30 days, and 6 months. Mini-Mental Status Exam (MMSE), Modified Rankin Score (MRS) and Cerebral Performance Category (CPC) were collected  $30 \pm 7$  days and 6 months  $\pm 15$  days post-event. MMSE was also collected at hospital discharge  $\pm 3$  days. Information was collected at 6 months regarding whether the surviving patients were living independently or required long-term care.

**Table 1**  
Patient characteristics.

Height	175(172–180) cm <sup>a</sup>
Age	65(50–80) years
Presenting rhythm	
VF/VT	14/22(63.6%)
PEA	7/22(31.8%)
Asystole	1/22(4.5%)
Duration of resuscitation	18.0(15.3–25.0) min <sup>a</sup>
Starting temperature	36.1(35.5–6.8) °C <sup>a</sup>

<sup>a</sup> Median (interquartile range).

### 3. Results

A total of 24 patients with post-resuscitative coma were enrolled. Two patients were excluded after declining to give consent for neurological assessments. Table 1 shows the characteristics of the patients enrolled, while Table 2 shows the cooling time and rate, survival, and neurologic outcomes.

The median time from initiation of cooling to the target core temperature (34 °C) was 37 min. 87% of the patients reached target temperature in less than 60 min, and 33% reaching target in 30 min or less. A subgroup of patients who received propofol as their sedating agent had a significantly shorter cooling time. The median rate of cooling for all patients was 3 °C/h, with the propofol group achieving a median rate of 4.2 °C/h. Fig. 2 demonstrates the mean esophageal temperature change in the first 30 min of cooling.

There were no serious adverse patient events related to the device. There was one reported device malfunction that did not alter the care of the patient. Thirteen patients had core temperatures that dropped below 32 °C, and the median time spent below 32 °C was 180 min (75% quartile 317 min). There was no association between the minimum patient temperature and patient outcome in this study.

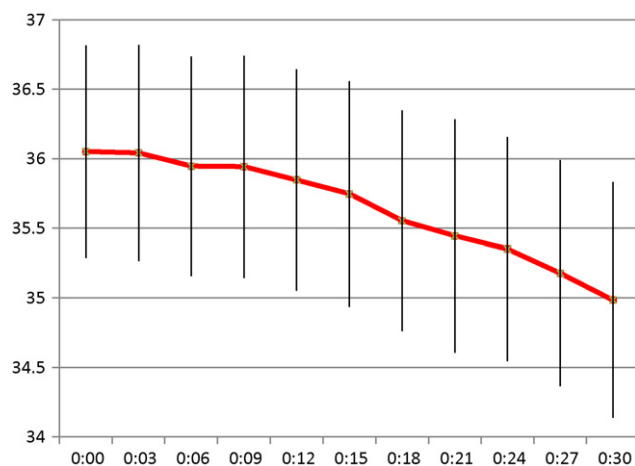
Only five of the study patients required additional cooling to maintain them in the therapeutic range for the entire 24 h of therapy, the remaining 17 patients remained in the target core temperature range passively.

Of the 22 patients who consented to follow-up, 68% survived to 6 months. 87% of these survivors were living independently. Time from ROSC to target temperature was significantly lower in survivors than non-survivors (Table 3).

**Table 2**  
Outcomes.

Cooling time (min)	All patients (n: 22)	Sedated with propofol (n: 7)	Sedated with other agents (n: 15)
Minimum	14.0	14.0	21.0
Maximum	81.0	39.0	81.0
Median (interquartile range)	37.0(27.25–48.75)	27.0(22.5–32.5)	46.0(31.0–57.5)
Mean (std. dev.)	40.0(17.3)	27.1(8.4)	45.9(17.0)
Cooling rate (°C/h)			
Minimum	1.3	2.5	1.3
Maximum	8.8	8.8	7.9
Median (interquartile range)	3.0(2.3–3.9)	4.2(2.9–5.9)	2.7(2.0–3.5)
Mean (std. dev.)	3.5(2.0)	4.7(2.5)	3.0(1.6)
Patient outcomes (n: 22)			
Survival to 6 months	15(68.1%)		
Living independently	13(59.1%)		
Neurologic testing (at 6 months)			
	CPC	MMSE	MRS
Median (interquartile range)	1(1–1)	28(28–29)	0(0–1)
Mean (std. dev.)	1.23(.60)	27.9(2.23)	0.61(1.12)

Std. dev.: standard deviation; CPC: Cerebral Performance Category; MMSE: Mini-Mental Status Exam; MRS: Modified Rankin Score.



**Fig. 2.** Mean esophageal temperature with standard deviations for the first 30 min of cooling.

### 4. Discussion

Convective-immersion cooling resulted in significantly shorter cooling times than previously reported. There was no control group in this study using an alternative cooling device, but this method appears to be much better than those reported in previous trials. The cooling rate of 3.0 °C/h achieved with the device compares quite favorably to the rate of 0.9 °C/h reported in the Bernard trial.<sup>2</sup> In the HACA trial,<sup>1</sup> which used a combination of methods, had a median time to target temperature of 480 min, while the Bernard trial<sup>2</sup> achieved 120 min—still more than three times the 37 min achieved with conductive-immersion using the ThermoSuit® System.

In 2007 Hoedemaekers et al. published a prospective comparison of methods of hypothermia induction (Table 4). The most rapid cooling rate they achieved was with an intravascular cooling device at 1.46 °C/h, half the rate achieved by the ThermoSuit.<sup>20</sup>

Skin surface cooling using water slightly above the freezing point produces mild cutaneous vasodilatation. This phenomenon has been described as the “Lewis Reaction” or “hunting effect”, a reversal of the normal vasoconstrictive response to cold in part due to reduced contractility of the walls of the arterioles at temperatures below 8 °C.<sup>21–23</sup> This enhances the rate of heat transfer

**Table 3**  
Survival and time to 34 °C.

Time from ROSC to 34 °C <sup>a</sup> (min)	All patients (22)	Survivors (15)	Non-survivors (7)
Minimum	109	109	114
Maximum	422	348	422
Median (interquartile range)	204(145–246)	184(145–234)	220(155–256)
Mean (standard deviation)	210(85)	196(73)	232(101)

ROSC: return of spontaneous circulation.

<sup>a</sup> Time interval includes time to stabilize patient, transfer to definitive care, set-up and induction of therapeutic hypothermia.

through the skin and accelerates core cooling. Use of propofol as a sedating agent seemed to shorten cooling times further, possibly due to the vasodilatory effect of the drug.

Although the study is too small to make conclusions about outcome, there is an apparent correlation between shorter time to target temperature and survival on subgroup analysis within the study (Table 3). Wolff et al.<sup>24</sup> had a similar finding when they studied 49 patients cooled with intravascular catheters and concluded that a 1-h delay in reaching target temperature tended to worsen the likelihood of a favorable outcome by 31%. Direct evidence of survival benefit from more rapid induction of therapeutic hypothermia in a controlled human study may no longer be possible due to a loss of clinical equipoise but the results of this study support the commonly held belief that the sooner therapeutic hypothermia is achieved, the better the patient's neurologic outcome.

Time from ROSC to target temperature involves a number of system issues in addition to the effectiveness of the cooling methods. Stabilization of the patient, interfacility and interdepartmental transfers can significantly delay the initiation of cooling and the time to target temperature. As more rapid cooling methods are developed, these delays will comprise a greater proportion of the overall time interval. As we move the time it takes to cool patients from 8 h toward 30 min, a 1-h delay in cooling initiation becomes much more significant. Issues of who will initiate cooling and where it will be initiated may need to be reexamined in some systems.

The high survival rates achieved in this study were accompanied by a high percentage of patients living independently at 6 months. Although survival is often considered the ultimate outcome measure, consideration of quality of life will continue to be of concern to clinicians and patients alike. In addition to objective, numeric neurologic assessments like the MMSE, MRS and CPC, the ability to live independently is a very meaningful measure that should continue to be a part of the long-term evaluation of these interventions.

Once the patients were cooled to the target temperature they tended to remain in the target range when left exposed to room air. Only 5 of the study patients required any additional cooling to maintain them in the therapeutic range for the entire 24 h of therapy. Those that did require temperature maintenance could be maintained at the desired level with simple means such as conventional cooling blankets or temperature-controlled air. This is in contrast to studies that used the application of cold fluids, where

**Table 4**  
Comparison of available cooling methods.

Cooling method	Rate of cooling (°C/h)
ThermoSuit with propofol sedation	4.2 <sup>a</sup>
EmcoolPads	3.3 <sup>b</sup>
ThermoSuit	3.0 <sup>a</sup>
Intravascular catheter	1.46 <sup>c</sup>
Water-circulating blanket	1.33 <sup>c</sup>
Gel-coated external device	1.04 <sup>c</sup>
Conventional (cold saline and ice-packs)	0.32 <sup>c</sup>
Air-circulating device	0.18 <sup>c</sup>

<sup>a</sup> Median rate of cooling, from this trial.<sup>b</sup> Median rate of cooling, data from Uray et al.<sup>26</sup><sup>c</sup> Mean cooling, data from Hoedemaekers et al.<sup>20</sup>

most of the patients re-warmed spontaneously and needed additional cooling.<sup>25</sup> This might be explained by the higher heat mass that can be removed by conductive-immersion cooling.

The study has a number of limitations. As a feasibility study, there was not a comparison group using another method of cooling. Comparison to historical controls is always difficult due to variations in patient populations and other treatment provided. The study is too small to make conclusions about outcomes, although the results are hypothesis generating.

This study was designed primarily to assess the feasibility of cooling with the ThermoSuit and secondarily to assess outcomes. Convective-immersion surface cooling by the ThermoSuit was rapid and effective. The measured outcomes are among the best reported, despite the inclusion of patients who presented with pulseless electrical activity and asystole. Further efforts to shorten the time from ROSC to therapeutic hypothermia, and further study of the impact of this simple, effective cooling method are essential.

## 5. Conclusion

Conductive-immersion surface cooling using the ThermoSuit® System is a rapid, effective method of inducing therapeutic hypothermia. Although the study was not designed to demonstrate impact on outcomes, survival and neurologic function were superior to those previously reported, suggesting comparative studies should be undertaken. Shortening the delay from return of spontaneous circulation to hypothermic target temperature may significantly improve survival and neurologic outcome and warrants further study.

## Conflict of interest

Drs. Howes, Dorian and Holzer received research grants for this study. Drs. Freedman, Ohley, and Schock are co-inventors of the ThermoSuit® System and own stock in Life Recovery Systems HD, LLC (LRS). Dr. Freedman is employed by Freedman Memorial Cardiology, Alexandria, LA, and serves as President of LRS. Dr. Ohley is employed by the University of Rhode Island (URI), Kingston, RI, and is a part-time employee of LRS. Dr. Schock is employed by LRS. Dr. Klock received financial assistance from LRS while a student at URI and is now employed by Northern Arizona University, Flagstaff, AZ. Danica Krizanac worked as scientific collaborator and received honoraria for this study by Life Recovery Systems. Michael Holzer has received honoraria for lectures from KCI Medical and Medivance, he worked as medical advisor for KCI Medical and Emcools, he received travel grants for scientific conferences from Alsius, KCI Medical, Emcools and Life Recovery Systems. The Department of Emergency Medicine received research grants from Alsius, KCI Medical, Medivance Inc., Life Recovery Systems, Benechill Inc. and Medcool Inc.

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