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# Randomized controlled trial of internal and external targeted temperature management methods in post- cardiac arrest patients

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ABSTRACT

*Background:* Targeted temperature management post-cardiac arrest is currently implemented using various methods, broadly categorized as internal and external. This study aimed to evaluate survival-to-hospital discharge and neurological outcomes (Glasgow-Pittsburgh Score) of post-cardiac arrest patients undergoing internal cooling verses external cooling.
*Methodology:* A randomized controlled trial of post-resuscitation cardiac arrest patients was conducted from October 2008–September 2014. Patients were randomized to either internal or external cooling methods. Historical controls were selected matched by age and gender. Analysis using SPSS version 21.0 presented descriptive statistics and frequencies while univariate logistic regression was done using R 3.1.3.
*Results:* 23 patients were randomized to internal cooling and 22 patients to external cooling and 42 matched controls were selected. No significant difference was seen between internal and external cooling in terms of survival, neurological outcomes and complications. However in the internal cooling arm, there was lower risk of developing overcooling ($p = 0.01$) and rebound hyperthermia ($p = 0.02$). Compared to normothermia, internal cooling had higher survival (OR = 3.36, 95% CI = (1.130, 10.412), and lower risk of developing cardiac arrhythmias (OR = 0.18, 95% CI = (0.04, 0.63)). Subgroup analysis showed those with cardiac cause of arrest (OR = 4.29, 95% CI = (1.26, 15.80)) and sustained ROSC (OR = 5.50, 95% CI = (1.64, 20.39)) had better survival with internal cooling compared to normothermia. Cooling curves showed tighter temperature control for internal compared to external cooling.
*Conclusion:* Internal cooling showed tighter temperature control compared to external cooling. Internal cooling can potentially provide better survival-to-hospital discharge outcomes and reduce cardiac arrhythmia complications in carefully selected patients as compared to normothermia.



## 1. Introduction

In the USA, the incidence of out-of-hospital cardiac arrest (OHCA) is estimated at 1.89/1000 person-years [1], with an estimated 400–460,000 people that die every year from OHCA [2]. In Singapore, over 1800 people suffer out-of-hospital cardiac arrest (OHCA) every year and the average chance of survival is a dismal 2.7% [3]. Survival rates in other Asia-Pacific countries are also low ranging from 0.5% in Malaysia to 8.5% in Korea [4]. Targeted temperature management is a treatment recommended by the American Heart Association as part of post-cardiac arrest management guidelines [5]. The guidelines include

*Abbreviations:* TTM, targeted temperature management; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; ED, emergency department; MICU, medical intensive care unit; CCU, coronary care unit; R2TH, ROSC to initiation of TTM; R2TT, ROSC to target temperature; T2TT, time from initiation of TTM to target temperature; CPR, cardiopulmonary resuscitation; PEA, pulseless electrical activity; VF/VT, ventricular fibrillation/ventricular tachycardia; OR, odds ratio; CI, confidence interval; PCI, percutaneous coronary intervention; AICD, automatic implantable cardioverter defibrillator; CPC, cerebral performance category; OPC, overall performance category; IQR, interquartile range.

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achieving target temperature of 32–36 °C in as short as possible a time and maintained over 24 h. This recommendation stemmed from 2002 randomized controlled trials that showed decreased mortality and improved neurological outcomes in comatose patients after successful resuscitation with TTM compared to standard therapy [6,7]. TTM has been shown to decrease inflammation, reduce cerebral, myocardial and cellular metabolism and promote heart epicardial flow [8]. Proposed mechanisms for the protective effect of hypothermia include reduced cerebral oxygen metabolism and ischemia [9-13], suppression of reperfusion injury [11,14-16] and by suppression of inflammatory mediators [17,18].

However a recent trial involving OHCA with TTM of 33 °C compared to 36 °C showed no difference in outcomes [19]. The main difference in this trial and the 2002 trials was in the active prevention of hyperthermia in the control group. This offers a possible interpretation that in temperature management post-cardiac arrest, prevention of hyperthermia may be more important than an induced hypothermia.

Published results of randomized trials comparing between methods of TTM after cardiac arrest in terms of mortality and neurological morbidity outcomes are lacking. Invasive/internal cooling methods such as endovascular cooling catheter have been proposed to have better temperature control during the therapy compared to external cooling methods [20-21]. There have been other observational studies between internal and external cooling which did not find any difference in neurological outcomes and further suggested that it might be worth looking at rewarming phase as contributor to outcome [21,22]. In this study, we aimed to evaluate survival-to-hospital discharge and neurological outcomes (Glasgow-Pittsburgh Score) of post-cardiac arrest patients undergoing TTM with internal cooling verses external cooling. The secondary objective was to compare survival outcomes for TTM (either method) and normothermia (historical controls). Other secondary outcomes included looking at each TTM method's performance and complications.

## 2. Methods

The study was designed as a single-centre phased, prospective, clinical study with a nested, randomized controlled comparison between external and internal cooling for post cardiac patients. The patients in the intervention arm were randomized in 1:1 ratio to receive either internal cooling using an endovascular catheter or external cooling using gel pads with water-based circulating system.

Study participants were consecutive patients who suffered out-of-hospital or in-hospital cardiac arrest achieving return of spontaneous circulation (ROSC) for >30 min, admitted to one of two intensive care units capable of providing TTM. Other inclusion criteria included patients aged between 18 and 80 years old who remained comatose or unresponsive post-resuscitation but otherwise hemodynamically stable (systolic blood pressure above 90 mm Hg with or without inotropic support).

Exclusion criteria included patients who had traumatic causes of arrest, cardiac arrest due to intracranial hemorrhage, remained hemodynamically unstable despite fluid and/or vasopressor support, female aged below 50 years with positive pregnancy test or patients with known poor premorbid status (bedbound and uncommunicative).

Patients were recruited from the Emergency Department (ED), Coronary Care Unit (CCU) and Medical Intensive Care Unit (MICU) from October 2008 to September 2014. Informed consent was obtained from all patients enrolled in the prospective interventional trial.

25 retrospective (2006–2008) and 17 contemporary controls (2012–2014) were chosen from cardiac arrest patients who did not receive TTM (they received conventional normothermia treatment), but who would otherwise have met all criteria for TTM treatment. Besides the retrospective controls, the contemporary controls had not been enrolled into the prospective trial either because they had not been identified for enrollment or they had been admitted into an overflow ICU where nursing staff were unable to support TTM. These controls were matched by age and gender to intervention cases.

The protocol and consent procedures were approved by the ethics committee of a public tertiary hospital and also registered under ClinicalTrials.gov registry (NCT00827957). Delayed consent had to be sought from relatives as participants enrolled were in a life-threatening situation, unconscious and unable to provide consent for trial enrollment.

Post-resuscitated cardiac arrest patients that met all the inclusion criteria in the ED were randomized to either TTM arm by sealed opaque envelopes. ED physicians would then initiate hypothermia treatment by cold saline infusion and cold ice packs around the patient's groin and axilla. A Foley or esophageal temperature probe was also inserted to monitor and chart temperature. Cooling treatment by either surface or internal cooling device was then continued at the MICU or CCU. Consent was taken from relatives either at the ED if they were present or subsequently at the MICU/CCU. Eligible post-resuscitation patients from MICU/CCU after in-hospital cardiac arrest were also randomized to either arm of therapy by contacting the study coordinator.

Prior to commencement of the therapy, patients were first sedated and paralyzed to avoid shivering and then crash-cooled to target temperature of 34 °C. After which, they were maintained at that temperature for 24 h before rewarming passively at 1 °C every 4 h (0.25 °C/h) to 36.5 °C.

Internal cooling was achieved with the Alsius Thermogard XP™ Intravascular Temperature Management System (ZOLL Medical Corp), which requires a triple lumen catheter to be inserted into the central venous system of the patient via the femoral approach. The thermal regulation system controls the temperature of saline and circulates cool or warm saline through the catheter balloons without infusing saline into the patient's body. External cooling and rewarming was achieved with the Arctic Sun® 2000 Temperature Management System (Medivance Pte Ltd.) which uses ArcticGel gel-coated pads to maintain contact with the patient's skin throughout the treatment.

Only physicians with experience and skills in central venous cannulation were allowed to insert the internal cooling catheter. Only MICU/CCU physicians and nurses who were trained in the usage of both temperature management systems by completing the manufacturer's training program and who were familiar with the protocol were allowed to use the devices.

Definition of outcomes and other variables collected followed the Utstein recommendations for reporting [23-25]. The primary outcome assessed in this study was survival-to-hospital discharge and neurological outcomes. Survival to hospital discharge was defined as patient surviving the primary event and discharged from the hospital alive. Return of spontaneous circulation (ROSC) was defined as the presence of any palpable pulse, which was detected by manual palpation of a major artery. Neurological status on discharge was assessed using the Glasgow-Pittsburgh outcome categories to evaluate quality of life after successful resuscitation. The cerebral performance categories evaluate only the cerebral performance capabilities while the overall performance categories reflect both cerebral and non-cerebral status.

The primary outcome of the study was survival-to-hospital discharge and neurological outcomes on discharge between the internal cooling arm and external cooling arm. The secondary objective was to compare survival outcomes for TTM (either method) and normothermia (historical controls). Other secondary outcomes included looking at each TTM method's performance and complications. Time and temperature data were collected in the data-logger of each TTM device by a bladder-temperature probe (Foley catheter temperature sensor, Smiths Medical) or esophageal probe (Smiths Medical). Incidents of overcooling <33 °C and undercooling >34.2 °C after target temperature was achieved and post-rewarming rebound hyperthermia ≥38 °C were noted. Time data correlated with temperature curves were used to determine the time from ROSC to initiation of TTM (R2TH), time from ROSC to target temperature (R2TT) and time from initiation of TTM to target temperature (T2TT).

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