

# Therapeutic hypothermia after cardiac arrest in a Philippine tertiary hospital: a retrospective cohort study

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## Abstract

**Objectives:** To determine the effects of therapeutic hypothermia performed in a Philippine tertiary hospital on hospital survival and favorable neurological outcomes at discharge.

**Design:** Retrospective cohort study.

**Setting:** General ICU in a private, tertiary hospital in the Philippines.

**Patients:** Medical records of all adult (>18 yrs) patients admitted following resuscitation from cardiac arrest from 9/2007 to 12/2008 were reviewed. Inclusion criteria were: Glasgow Motor Score <6 and treatment at the ICU. Exclusion criteria were: patients with arrest times >60 minutes, pre-arrest CPC score >2, severe hemorrhage, or with imposed limitations to intensive care. Patients whose families or attending physicians did not agree to hypothermia induction were classified as controls.

**Interventions:** Therapeutic hypothermia, targeting a core temperature of 32-34 °C, was initiated within 6 hours of

return of spontaneous circulation, and maintained for 12-24 hours. Hypothermia induction methods included combinations of ice packs, ice-water gastric lavage, and cold intravenous fluid boluses.

**Measurements and Results:** Of 49 patients that met final inclusion criteria, 29 were in the intention-to-treat therapeutic hypothermia group. Age, gender, APACHE II scores and initial arrest rhythms were similar between groups. Good neurological outcomes (CPC 1 or 2) were found in 0/20 patients in the control group vs. 9/29 (31%) in patients who received hypothermia therapy ( $p=0.006$ ). However, the difference in hospital survival only approached statistical significance (15% in controls, 41.4% in hypothermia group,  $p=0.06$ ). Exact logistic regression showed that initial pulseless ventricular tachycardia or ventricular fibrillation, and therapeutic hypothermia were independently associated with neurologically favorable survival.

**Conclusion:** Therapeutic hypothermia was associated with favorable neurologic outcomes at hospital discharge.

**Key words:** Induced hypothermia, cardiopulmonary resuscitation, coma, Southeastern Asia, heart arrest, intensive care

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## Introduction

A cardiac arrest is one of the most devastating events that can occur to a patient. Many attempts at resuscitation fail, but even with successful resuscitation, many patients die early from cardiac dysfunction, or later from neurologic dysfunction. (1,2) Comprehensive post-resuscitation care therefore aims to address the complex post-cardiac arrest syndrome and allow neurologically intact survival.

Therapeutic hypothermia (TH) was found to decrease mortality and improve neurologic outcome in initially comatose patients who had been resuscitated from cardiac arrest. (3-6) It has been recommended since 2005 by international consensus resuscitation guidelines to prevent or minimize neurologic complications, and has allowed some patients to resume normal or near-normal lives. (7) While early recommendations focused mainly on patients with out-of-hospital (OOH) pulseless ventricular tachycardia (pVT) or ventricular fibrillation (VF), more recent studies have shown efficacy even in other types of arrest. (2,8) TH has also been used in combination with other therapies, such as percutaneous coronary intervention (PCI) for myocardial infarction. (9,10)

While its efficacy is proven and its safety profile is excellent, (2,5,9,11) induction of hypothermia after cardiac arrest has not yet been adopted universally. Many clinicians have described the challenges of developing and implementing TH protocols. (12,13) Recognizing gaps in our knowledge regarding the optimal patient candidates, methodology and therapeutic targets for post-arrest hypothermia, the critical care community has encouraged the reporting of local series of patients undergoing TH to increase the knowledge base of real-life performance. (6)

This retrospective, non-experimental study describes our early experience in providing therapeutic hypothermia for patients that have suffered a cardiac arrest in a tertiary medical center in a developing country. To our knowledge, it is the first such report from Southeast Asia.

## Materials and methods

### *General*

This is a retrospective cohort study that examined patients who were admitted at The Medical City ICU (Pasig City, Philippines) from September 2007 to December 2008 who remained comatose after a cardiopulmonary arrest. The primary objectives of the study were to determine the effects of therapeutic hypothermia, as performed in our center, on the hospital survival and neurologic outcomes of comatose survivors of cardiac arrests. This study was approved by the hospital Ethics Review Board with a waiver of informed consent.

Consecutive candidates for inclusion were identified from the hospital database of Intensive Care Unit admissions. Patients aged >18 years, who were comatose (Glasgow Motor Score <6) after restoration of spontaneous circulation (ROSC) from any initial arrest rhythm, and who received post-arrest care in the ICU, were included in the study. These included patients with both out-of-hospital (OOH) and in-hospital arrests.

Exclusion criteria were: requested limitations to treatment that could impact optimal ICU care (such as: no vasopressors, limitations to indicated invasive procedures, but excluding simple “do not attempt resuscitation” orders), patients with resuscitation time >60 minutes, patients with gastrointestinal or intracranial bleeding and patients with traumatic arrests, patients known to have a low baseline mental status (CPC >2) prior to the current admission, and patients who were already awake (Glasgow Motor Score 6) within an hour after arrest.

The subjects who met final inclusion criteria were classified into therapeutic hypothermia (TH) and concurrent control groups using the intention-to-treat principle.

### *Patient management and the therapeutic hypothermia protocol*

The Medical City is a Joint Commission International accredited, 500-bed, tertiary private hospital in Metropolitan Manila, the Philippines. (14) Twenty-six beds are allocated to adult critical care. The adult critical care units operate in a semi-closed model of ICU care: patients with more severe illness, including all resuscitated patients, are co-managed by a medical intensivist.

All routine intensive care patient management, including mechanical ventilation, seizure control, hemodynamic stabilization, and any invasive procedures, was performed as per the attending physicians' orders.

Therapeutic hypothermia was recommended for eligible patients without contraindications, but performance of the procedure was dependent upon the agreement of the primary attending physicians and consent from the patients' families.

For those patients who underwent TH, a variety of cooling

techniques to achieve a core temperature of 32-34 °C were started within 6 hours of return of spontaneous circulation (ROSC). These included the infusion of cold intravenous fluid boluses (normal saline at 4 °C, 20 ml/kg volume, only if central venous access was available), repeated nasogastric lavage with ice-cold water (4 °C, 200-250 ml volume, indwelling time of 15 minutes, then drained), the use of an electric cooling blanket (Bair Hugger, Arizant Inc., Eden Prairie, MN), surface cooling with ice, or combinations of the above. Continuous core temperature monitoring was done with an intra-rectal probe (YSI 401 Adult Esophageal/Rectal Probe, Advanced Industrial Systems Inc., Harrods Creek, KY) or with a pulmonary artery catheter (Hands-off Thermodilution Catheter, Arrow International Inc., Milwaukee, WI). Sedation and shiver ablation was achieved with intravenous midazolam, propofol, demerol, or combinations of the above. Refractory shivering was treated with rocuronium. Active temperature management was continued for 12-24 hours after induction per the attending intensivist.

In September 2008, a pre-printed order form was made available for standardizing the induction and maintenance of hypothermia. The order form included the procedures described above in checklist form, stipulated laboratory tests, and clarified rules for stopping (core temperature <32.5 °C, gastrointestinal bleeding, bradycardia with hemodynamic instability) and restarting active temperature management (core temperature >33.5 °C in the absence of contraindications) within the 12-24 hour total duration.

## Data and statistical analysis

Clinical data were extracted from the chart as well as the standard Utstein-style (15) cardiac arrest audit form. All data were entered directly into a secure database by the investigators.

Baseline data gathered included the following: patient's general data, initial arrest rhythm, duration of resuscitation and the location of collapse (in-hospital or out-of-hospital) as well as the location of resuscitation efforts. The presence of shock was defined as the need for vasoactive therapy (dopamine >5 µg/kg/min, or any continuous intravenous infusion of norepinephrine, vasopressin, epinephrine or

dobutamine) or the use of an intra-aortic balloon pump for at least 1 hour during the first 24 hours of ICU stay. The APACHE II score (16) was calculated from parameters measured during the first 24 hours of ICU stay.

The primary outcome variables were hospital survival rate and the rate of good neurologic outcome, defined as a Cerebral Performance Category (CPC) (17) Score 1 or 2, upon hospital discharge. Secondary outcomes included ICU and hospital length of stay, and mechanical ventilator days. For the hypothermia group, the rate of adherence to recommended practice parameters, defined as: induction of hypothermia within 6 hours of arrest, and duration of hypothermia 12-24 hrs, (1) was determined.

Cytel Studio 8.0 with StatXact and LogXact (Cytel Inc, Cambridge, MA) was used for statistical analysis. Results are reported as median (and interquartile range) and odds ratios with 95% confidence intervals when appropriate. The Mann-Whitney-Wilcoxon test, Fisher's exact tests or Pearson's chi-square tests were used, as appropriate, for analysis between groups. For all tests, a p value of <0.05 determined statistical significance. A bivariate analysis of TH and potential factors (including out-of-hospital arrest, initial rhythm, age and presence of shock) thought to have significant positive or negative associations with neurologically favorable survival was performed using exact logistic regression. Factors that were determined to be significant were entered simultaneously into a multivariate exact logistic regression to identify independent associations.

## Results

### *Enrolment and initial characteristics*

Of the 66 records reviewed, 49 met final inclusion criteria (**Figure 1**). Twenty patients were included in the control group, while 29 patients were included in the therapeutic hypothermia group (TH). Baseline characteristics, prognostic variables, and outcomes are presented in **Table 1**.

Gender, age, the presence of shock and the APACHE II scores were similar between groups. The time interval from collapse to ROSC was shorter, and the rate of pVT or VF as an initial cardiac arrest rhythm was higher in the TH

group, but neither of these parameters reached statistical significance. However, more patients in the TH group had out-of-hospital arrests ( $p=0.03$ ).

#### *Outcomes*

Primary outcomes are reported in **Table 1**. All subjects were included in the intention-to-treat analysis. The family of one patient in the TH group chose to withdraw life support during re-warming, while another TH patient was taken home against medical advice with a CPC Score of 4 during the hypothermic maintenance period. One patient in the control group was transferred to a different acute care hospital with a CPC Score of 3.

The association of TH with survival at discharge only approached statistical significance (OR 4.0, 95% CI 1.0 to 16.7,  $p=0.06$ ). However, TH was positively associated with a CPC of Score 1 or 2, with an infinite odds ratio (95% CI, 1.8 - infinity,  $p=0.006$ ), as no patients in the control group were discharged with that level of neurologic function.

ICU and hospital length of stay, as well as days on the mechanical ventilator were similar between the control and TH groups.

In the TH group, there were no instances of premature termination of the hypothermia protocol due to complications. Twenty-one of 29 hypothermia induction attempts (72.4%) were found to be within recommended practice parameters. The median time interval from ROSC to induction of hypothermia was 3.3 hours (IQR 3.0 - 5.0 hrs). Target temperatures were reached 7.0 (IQR 5.0 - 8.3 hrs) after induction. These time intervals are longer than what is reported in other studies of real-life TH use.(2,18) Also, in 10/29 (34.5%), the target temperature (32-34 °C) was not reached.

#### *Factors associated with neurologically intact survival*

The factors that were included in the bivariate exact logistic regression to test for associations with neurologically intact survival were: TH, age <60 years, arrest time  $\leq 25$  min, OOH arrest, and initial rhythm of pVT/VF (**Table 2**).

From these bivariate analyses, only two factors: an initial rhythm of pVT/VF and TH were significant. The adjusted odds ratio for TH was 9.2 (95% CI 1.1 - inf,  $p=0.04$ ). Therefore both an initial rhythm of pVT/VF

and the performance of therapeutic hypothermia were independently associated with neurologically favorable survival.

## **Discussion**

This retrospective study aimed to examine the effects of our existing hypothermia methods under real-life conditions. The efficacy and the basic principles of therapeutic hypothermia for post-cardiac arrest patients have been extensively discussed following its inclusion into international guidelines for resuscitation. (6,19,20)

Therapeutic hypothermia has been recommended mostly for comatose post-cardiac arrest patients with initial rhythms of pVT or VF, (7) and it is generally accepted that patients whose initial rhythms are asystole or PEA still have worse outcomes even with the application of this therapy. (21) However, a recent study demonstrated that when time to ROSC was <25 minutes, hospital survival rate was high, with predominantly good neurological outcomes, notwithstanding the initial rhythm or the presence of shock. (8) In the face of this and other data, (2,19) recommendations for hypothermia are likely to become more inclusive.

The optimal timing of initiation of TH has not been defined, but current consensus is to initiate cooling as early as possible. (1) While inducing TH is generally recommended within 4 to 6 hours of arrest, (7) the therapeutic window, or time after ROSC at which therapeutic hypothermia is still beneficial, is not yet defined. While our TH protocol mandated starting within 6 hours of ROSC, there were 3 patients in the TH group in whom hypothermia was only induced between six and twelve hours after ROSC.

The optimal temperature for TH is also not defined. A core temperature of 32 – 34 °C was targeted in the randomized controlled studies, (3,4) and is the usual target range in published protocols for clinical use. (11,22) About a third of our TH patients did not achieve this target, and in fact our median lowest achieved temperature was only at the accepted targeted upper limit of 34 °C. However, some patients still appeared to derive benefit even with nadir core temperatures >34 °C.

Nine out of 27 (33%) of patients in the TH group were

discharged with a favorable neurological outcome (CPC scores of 1 or 2); compared to 0 out of 20 patients in the control group. The presence of this zero cell imposes an important statistical limitation – and explains the large confidence intervals for the odds ratio.

The majority of patients who were able to recover with good neurological outcome had an initial rhythm of pVT or VF (7 of 9 patients). The logistic regression analysis showed that both TH and an initial arrest rhythm of pVT or VF were independently associated with neurologically favorable survival.

TH was initially offered at our institution (starting in September 2007) mostly, but not exclusively, for post-arrest patients with arrest rhythms of pVT or VF as per the AHA/ILCOR 2005 Guidelines. An unavoidable indication bias is reflected in the distribution of initial arrest rhythms in our study groups (although this only approached statistical significance,  $p=0.11$ ).

The control group represented patients for whom TH was not performed per the family or primary attending physicians' decisions. The reasons for not accepting the recommendation for TH (when specified) included the perceptions of added cost and unfamiliarity with the procedure or the guidelines that support its use.

However, since the release of a pre-printed order form and information sheet for TH in September 2008, early reports of success within the institution, and after educational efforts to promote TH use during in-hospital ACLS courses, most eligible patients in our hospital have undergone TH. In fact, it was in part because of the success of these programs promoting TH that our study had to end in December 2008. We were simply unable to identify concurrent controls after that time.

In this study, in-hospital survival was not associated with the performance of TH. This may well be due to the small sample size, as well as a study population that included both patients with in-hospital and OOH (69.3% of the total population) arrests. The time interval between collapse and the first CPR attempt that is a major determinant of survival

was not known in some patients with OOH arrests. Unlike many countries, the Philippines does not have Emergency Medical Services tasked to provide out-of-hospital ACLS; this surely had a negative influence on OOH arrest outcomes.

Nevertheless, the data from our early experience using TH are encouraging. Available methods to induce and maintain TH have afforded good outcomes without increasing ICU and hospital stay. The applicability of this data to other local hospitals may be questionable though, owing to equipment factors, as well as the unavailability of appropriately trained intensivists operating with high-levels of involvement in local ICUs.

Finally, even after successful implementation of TH, our data still show that our local TH protocol, as well as our management of the other components of the post-cardiac arrest syndrome, will need to be optimized. Early, goal-directed hemodynamic management, as part of a comprehensive package that includes TH, may be the next phase in the evolution of post-resuscitation care. (11,18)

## Conclusions

In this study, therapeutic hypothermia and an initial rhythm of pVT or VF are independently associated with favorable neurologic outcomes in comatose early survivors of cardiac arrests. However, the association of therapeutic hypothermia with in-hospital survival was not statistically significant. While the study has its limitations, it is clear that the performance of therapeutic hypothermia in our setting is feasible, and that. A formal post-resuscitation clinical pathway is recommended to optimize the use of this life-saving therapy, as well as other therapies for the comprehensive critical care of post-arrest patients.

## Acknowledgment

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**Table 1.** Baseline characteristics, prognostic factors and outcomes

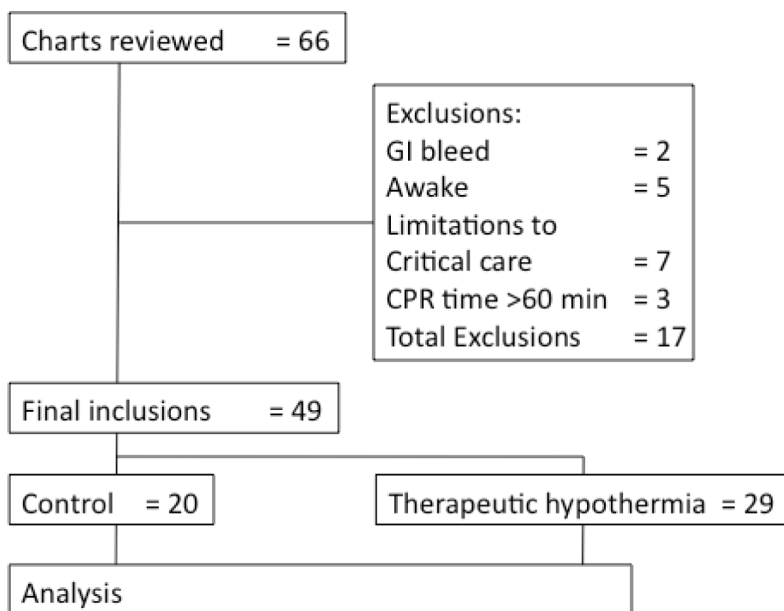
	Control	Hypothermia	OR	95% CI	p value
n	20	29			
Female (%)	8 (40)	9 (31)	0.7	0.2-2.2	0.55 <sup>a</sup>
Age, median (IQR)	69.5 (38-77)	54.5 (43-66)			0.24 <sup>b</sup>
Out-of-hospital arrest (%)	10 (50)	24 (82.8)	4.8	1.3-17.7	0.03 <sup>a</sup>
Time (minutes) from collapse to ROSC, median (IQR) <sup>c</sup>	24 (4-31)	16.5 (5-28)			0.64 <sup>b</sup>
Initial arrest rhythm pVT/VF (%)	3 (15)	10 (34.5)	3.0	0.7-12.7	0.19 <sup>a</sup>
Presence of shock (%)	17 (70.8)	25 (89.3)	1.5	0.3-8.2	0.68 <sup>a</sup>
APACHE II, median (IQR)	30 (24-35.5)	25 (23-34)			0.40 <sup>b</sup>
Hospital survival (%)	3 (15)	12 (41.4)	4.0	1.0-16.7	0.06 <sup>a</sup>
CPC 1 or 2 (%)	0 (0)	9 (31)	inf	1.8-inf	0.006 <sup>a</sup>
ICU length of stay, median (IQR)	3 (1-6.5)	3 (2-12)			0.24 <sup>b</sup>
Hospital length of stay, median (IQR)	3 (1-13)	4.5 (2-32)			0.15 <sup>b</sup>
Ventilator days, median (IQR)	3 (1-13)	5 (2-12)			0.24 <sup>b</sup>

Legend: <sup>a</sup> Two-sided p values from Fisher's exact test; <sup>b</sup> Two-sided p values from Mann-Whitney-Wilcoxon test; <sup>c</sup> Total arrest times not available for 4 patients in each group.

**Table 2.** Bivariate exact logistic regression analysis of factors associated with favorable neurologic survival after cardiac arrest

	OR	Adjusted OR	95% CI	p value
Therapeutic hypothermia	11.6		1.7-inf	0.01
Age <60	9.1	8.0	0.8-419.8	0.1
Initial rhythm pVT/VF	18.0	17.0	2.05-249	0.004
Out-of-hospital arrest	1.7	0.6	0.1-9.1	1
Total arrest time <25 min	0.8	0.6	0.1-3.8	0.73

**Figure 1.** Patient inclusion and exclusion flowchart



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