

## Review of the Clinical Evidence and Controversies in Therapeutic Hypothermia for Survivors of Sudden Cardiac Death

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### ABSTRACT

Sudden cardiac arrest constitutes a major public health burden in both developed and developing countries. In those successfully resuscitated from cardiac arrest, subsequent mortality is still high (~75%) and is due to a combination of ischaemia and reperfusion injury. The purpose of this review is to describe the experimental and clinical evidence supporting therapeutic hypothermia in survivors of sudden cardiac arrest. We also discuss controversies and unresolved issues in therapeutic hypothermia, including the optimum target temperature for therapeutic hypothermia, and the role of pre-hospital induction of hypothermia. We conclude with a perspective on therapeutic hypothermia as it applies to the Singapore context.

**Keywords:** Resuscitation, Targeted temperature management, Sudden cardiac arrest, Singapore, Therapeutic hypothermia

### INTRODUCTION

In recent prospective studies from the United States<sup>1,2</sup>, Netherlands<sup>3</sup>, Ireland<sup>4</sup>, China<sup>5</sup> and Singapore (Pan-Asian Resuscitation Outcomes Study Group, unpublished data, 2014), the annual incidence of sudden cardiac death (SCD) ranges from 30 to 100 per 100,000 in the general population<sup>6</sup>. It therefore represents a major public health burden. In spite of advances in cardiopulmonary resuscitation and post resuscitation care, survival rates of those who present with either in- or out-of-hospital cardiac arrest are poor. In the US, the Resuscitation Outcomes Consortium Cardiac Epistery and Get With The Guidelines®-Resuscitation data showed survival to hospital discharge was only 9.5% in 2013<sup>7</sup>. For in-hospital cardiac arrest, survival to discharge was only 23%<sup>7</sup>.

Analysis of survival at different time points after arrest shows that a substantial portion (~75%) of those initially resuscitated successfully by emergency

services do not survive to hospital discharge<sup>8</sup> (Fig. 1). It is believed this mortality represents a combination of injury not solely from anoxia during the period of no- or low-flow preceding resuscitation, but also as a consequence of reperfusion. Although reperfusion is clearly necessary, there is no doubt that it also induces an inflammatory response that is harmful. This combination of initial ischaemic insult followed by subsequent reperfusion injury is now termed ischaemia-reperfusion injury, and it is a key component of post-cardiac arrest syndrome<sup>9,10</sup>.

Clinically, the most important residuum of whole-body ischaemia following cardiac arrest is brain injury (Fig. 2). Myocardial injury is also important, but to a lesser extent. In all reported series, the commonest cause of death or withdrawal of life-sustaining therapy (WLST) is brain injury<sup>11,12</sup>. Accordingly, most efforts have been directed at ameliorating neurological injury following return of spontaneous circulation.

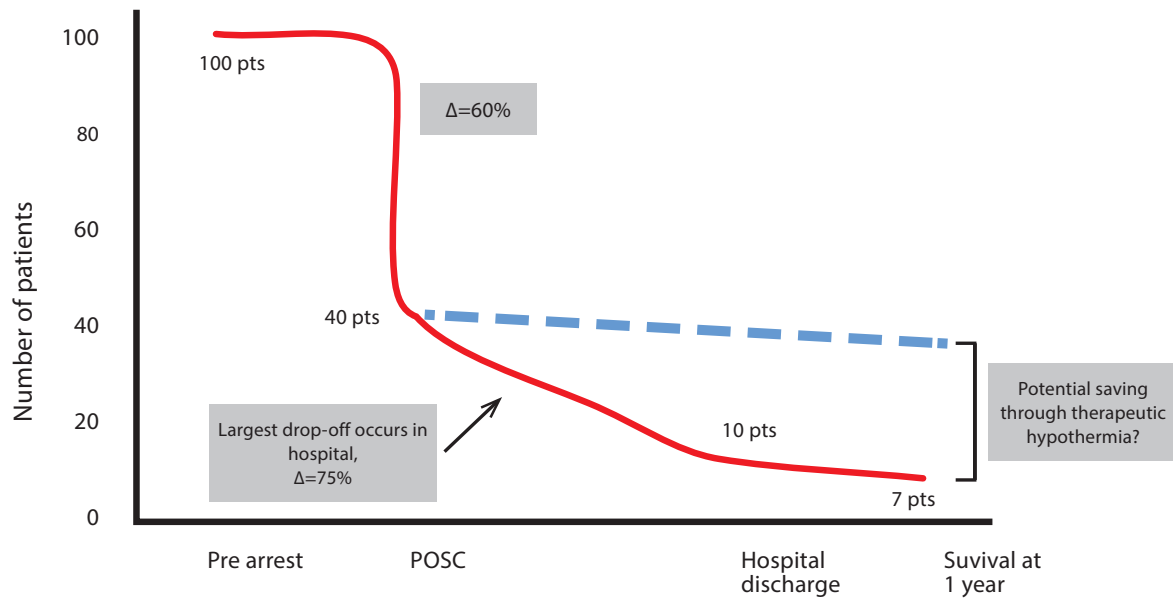


Fig. 1. Idealised survival curve after out-of-hospital cardiac arrest (adapted from Kern, 2012<sup>10</sup>). Even after return of spontaneous circulation, there is subsequent mortality due to a combination of damage from ischaemia, together with injury from reperfusion (see text). It is likely that hypothermia can favourably influence ischaemia-reperfusion injury.

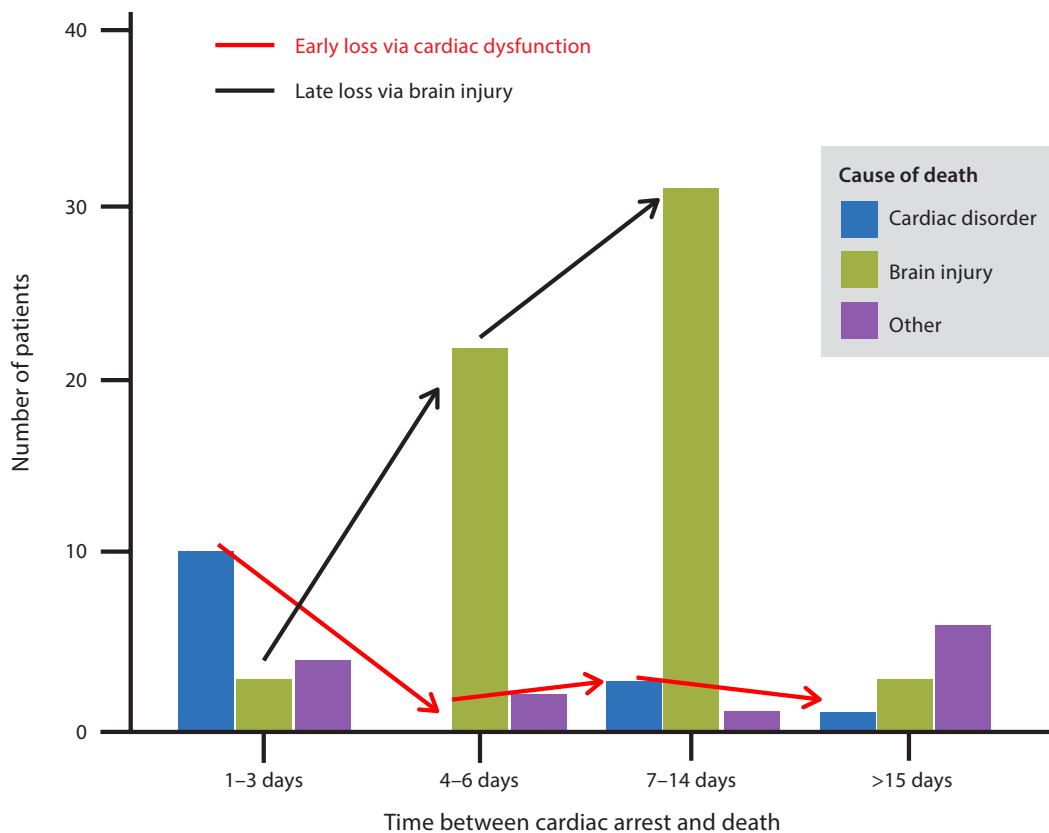


Fig. 1. Mode of death after cardiac arrest (adapted from Dragancea *et al.*, 2013<sup>11</sup>). Early mortality is often from cardiac dysfunction (days 1-3), but subsequent mortality is largely due to brain injury.

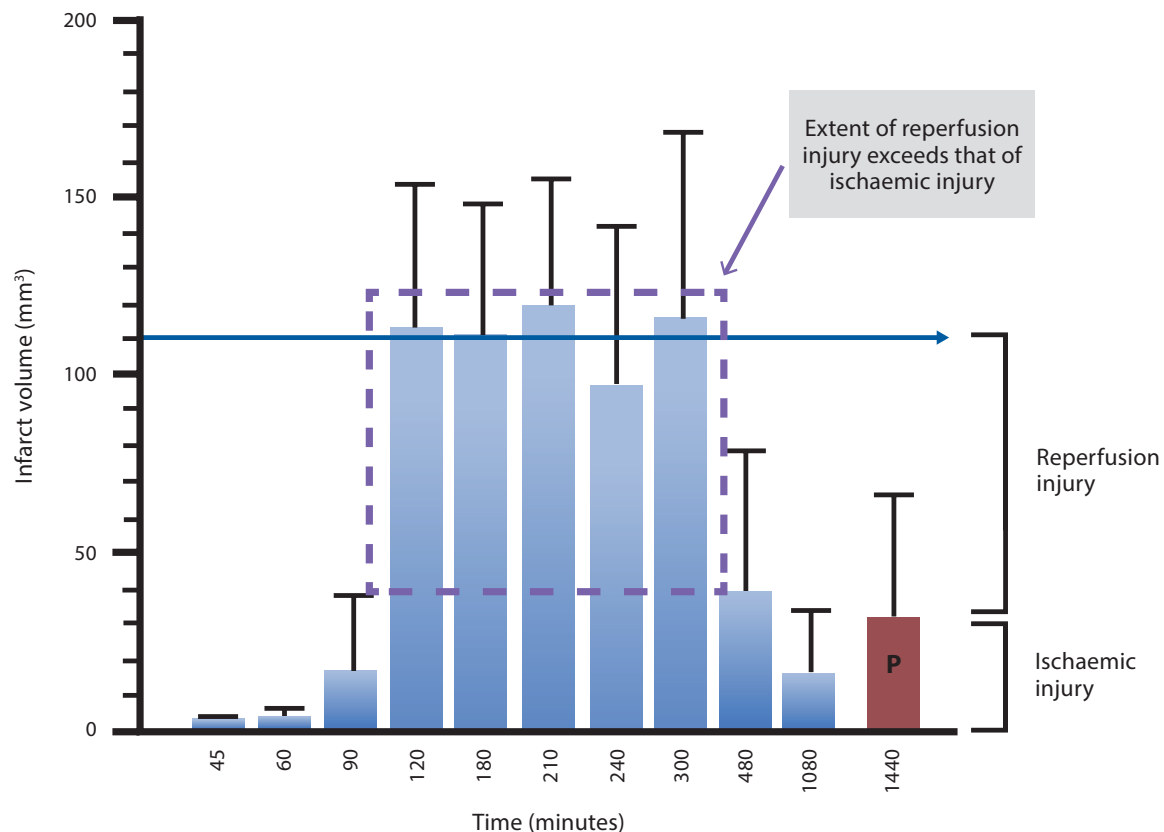


Fig. 3. Average infarct volume at 24 hours of maturation after variable duration of reversible (blue bars) or permanent (brown bar, P) left unilateral MCA/CCA occlusion in Long Evans rats (adapted from Aranowski *et al.*, 1997<sup>32</sup>). Note that unilateral occlusion of the MCA/CCA between 120 and 300 minutes leads to a significant increase in infarct volume compared to permanent occlusion, indicating that reperfusion itself is injurious.

One of the most promising therapies in this respect has been therapeutic hypothermia (also referred to as induced hypothermia, controlled hypothermia and targeted temperature management). The purpose of this article is to review the clinical evidence and controversies surrounding this specific therapy as it applies to the post-cardiac arrest setting. (Note that therapeutic hypothermia has also been applied following ST-segment elevation myocardial infarction, stroke, traumatic brain or spinal cord injury, neonatal encephalopathy and acute liver failure, but therapeutic hypothermia for these indications will not be reviewed here.)

### HISTORICAL BACKGROUND

The impact of hypothermia on survival following injury has been appreciated since antiquity<sup>13</sup>, but in modern times, hypothermia was first described as a therapy for acute brain injury in the 1940s<sup>14</sup>. The experimental and clinical foundation supporting therapeutic hypothermia arose in the following decades. Functional and survival benefits were demonstrated in both rodent<sup>15,16</sup> and canine<sup>17,18</sup> models of asphyxial cardiac arrest in the 1990s. The

first human clinical study enrolled 22 patients<sup>19</sup> and was reported in 1997, but it was not until 2002 that the two landmark clinical trials that led to widespread acceptance and adoption of controlled hypothermia post-cardiac arrest were published<sup>20,21</sup>.

### PATHOPHYSIOLOGICAL MECHANISMS

#### Ischaemia-reperfusion Injury

The cellular mechanisms underlying ischaemia-reperfusion injury are only now being unraveled<sup>22-4</sup>. Cessation of blood flow to mammalian brains under normothermic conditions results in disappearance of the electroencephalogram (EEG) within 20 seconds, probably reflecting failure of high-energy metabolism. Within five minutes of anoxia, adenosine triphosphate (ATP) levels are depleted. Intracellular ion gradients are maintained by ATP-requiring pumps, and ATP depletion sets in place a cascade of cellular changes, including potassium efflux, sodium and calcium influx, mitochondrial calcium overload, activation of membrane protein kinases and phospholipases. Activation of the latter enzymes leads to cell membrane damage, and also promotes arachidonic acid formation — a

Table 1. Landmark randomised controlled trials of therapeutic hypothermia in out-of-hospital cardiac arrest.

	Bernard et al., 2002 <sup>21</sup>	HACA, 2002 <sup>20</sup>
<b>Design</b>	Randomised clinical trial with blinded assessment of endpoint	Randomised clinical trial with blinded assessment of endpoint
<b>Chief inclusion</b>	<ul style="list-style-type: none"> <li>Initial rhythm VF</li> <li>Successful ROSC</li> <li>Persistent coma after ROSC</li> </ul>	<ul style="list-style-type: none"> <li>Witnessed cardiac arrest</li> <li>Initial rhythm VF or nonperfusing ventricular tachycardia</li> <li>Age 18–75 years</li> <li>Estimated 5–15 minutes from collapse to first attempt at resuscitation</li> <li>≤60 minutes from collapse to ROSC</li> </ul>
<b>Chief exclusion</b>	<ul style="list-style-type: none"> <li>Age &lt;18 (men)</li> <li>Age &lt;50 (women)</li> <li>Cardiogenic shock</li> <li>Possible causes of coma other than cardiac arrest</li> </ul>	<ul style="list-style-type: none"> <li>Tympanic membrane temperature &lt;30°C on admission</li> <li>Pregnancy</li> <li>Response to verbal commands after ROSC and before randomisation</li> <li>Cardiogenic shock</li> <li>Significant hypoxemia after ROSC</li> </ul>
<b>Total enrollment</b>	77	275
<b>Outcome: favourable neurology at discharge</b>	49% (hypothermia) vs. 26% (normothermia) p=0.046, ARR 23%, NNT 4.3	41% (hypothermia) vs. 55% (normothermia) p=0.02, ARR 14%, NNT 7

potent prostaglandin inducer. Excitatory neurotransmitters, which are released during ischaemia, also play a role in both ischaemic and reperfusion phases of injury, through both calcium-dependent and calcium-independent mechanisms<sup>25,26</sup>.

Following reperfusion, a complex series of events occurs. A full description of this is beyond the scope of this article but has recently been reviewed elsewhere<sup>27</sup>. Briefly, some of the key events include ATP repletion allowing mitochondrial calcium uptake, but this in turn leads to massive calcium overload in mitochondria and their subsequent destruction<sup>27,29</sup>. Generation of highly damaging reactive oxygen species (ROS) also occurs, leading to further loss of cell membrane integrity. A pro-inflammatory milieu is set up, both locally and systemically. This leads to local activation of neutrophils, platelets and the coagulation cascade, and both local and systemic cytokine release<sup>27,30</sup>. Other important mechanisms include cerebral oedema, loss of blood-brain barrier integrity, haemorrhagic transformation and vascular plugging<sup>27,28,30</sup>.

### Modification of Response to Ischaemia-reperfusion by Hypothermia

Experimental animal work shows that hypothermia favourably influences the biochemical processes following ischaemia-reperfusion. It may limit ischaemic injury through a reduction in metabolic demand; early on, it was demonstrated in dogs that cerebral metabolism decreases by 6–10% per degree reduction in core body temperature<sup>31</sup>.

However, another important mechanism is likely to be modification of the response to reperfusion. Two lines of evidence support this.

First, in at least some circumstances, extent of reperfusion injury can exceed the injury induced by initial ischaemia. In an experimental rat model where anoxic brain injury was induced by occlusion of the middle cerebral artery/common carotid artery, occlusion for 120 to 300 minutes was associated with a more than two-fold increase in infarct volume compared to permanent occlusion<sup>32</sup> (Fig. 3). Second, therapeutic hypothermia can clearly attenuate reperfusion injury. In a Mongolian gerbil model, 24 hours of hypothermia at 32°C prevented 70% of delayed hippocampal CA1 neuronal cell death following brief global forebrain ischaemia<sup>33</sup>.

### LANDMARK CLINICAL STUDIES

This foregoing experimental work has been translated to the clinical arena. It is worth emphasising early on that the clinical evidence base supporting controlled hypothermia can be divided among patients where the initial rhythm is ventricular fibrillation or non-perfusing ventricular tachycardia, and patients with all other rhythms (asystole, pulseless electrical activity). This division is not necessarily rooted in pathophysiology, but because both landmark studies in support of controlled hypothermia enrolled almost exclusively survivors of witnessed cardiac arrest where the initial rhythm was ventricular fibrillation or non-perfusing ventricular tachycardia

### **Group 1: Initial Presentation with Ventricular Fibrillation or Non-perfusing Ventricular Tachycardia**

**Bernard et al., 2002<sup>21</sup>**

The first landmark study in humans was a randomised controlled trial performed in Melbourne, Australia. The chief inclusion criteria were: initial rhythm of ventricular fibrillation at time of arrival of ambulance, successful return of spontaneous circulation (ROSC) and persistent coma after ROSC (Table 1).

For patients assigned to hypothermia, paramedics began measures in the field by removing patient clothing and applying cold packs to the patient's head and torso. This was continued in hospital; ice packs were removed when the core temperature reached 33°C and this temperature was maintained for 12 hours while the patient was sedated and paralysed. Beginning at 18 hours, patients were actively rewarmed for the next 6 hours by external warming with a heated-air blanket. Patients assigned to normothermia were also sedated and paralysed initially, but otherwise received usual care. No specific measures to control hyperthermia were stipulated.

A specialist in rehabilitation medicine who was unaware of the treatment group assessed outcome. On the basis of this evaluation, patients were discharged home, to a rehabilitation facility or to a long term nursing facility. Good outcomes corresponded to discharge to home or to a rehabilitation facility, whereas poor outcomes corresponded to death or discharge to a long term nursing facility, whether the patient was conscious or unconscious.

A total of 77 patients were enrolled (43 assigned to hypothermia, 34 to normothermia). Baseline clinical data were well matched between groups. After adjustment for baseline differences in age and time from collapse to ROSC, hypothermia was clearly associated with favorable neurological outcomes, with an odds ratio of 5.25 for a good outcome as compared with normothermia (95% confidence interval 1.47–18.76;  $p=0.011$ ; Table 1). There was no difference in either mortality or the frequency of adverse events.

#### ***Hypothermia after Cardiac Arrest<sup>20</sup>, 2002***

Nine centres from five European countries participated in this randomised controlled trial, which was significantly larger than the study

by Bernard *et al.*<sup>21</sup> but otherwise similar in design (Table 1).

The hypothermia group was cooled to 32–34°C with external cooling within four hours after ROSC. This temperature was maintained for 24 hours from the start of cooling, followed by passive rewarming over a period of 8 hours. No specific protocol to control temperature in the control group was stipulated.

The primary outcome was favourable neurology within 6 months, defined as a Pittsburgh cerebral-performance category of 1 (good recovery) or 2 (moderate disability). Neurologic outcome was determined without knowledge of the patient's treatment assignment. Secondary end points were overall mortality at 6 months and rate of complications during the first seven days after cardiac arrest.

The total number of patients enrolled was 275. Baseline data were well matched between groups. The outcome of good neurologic recovery strongly favoured hypothermia (risk ratio 1.40, 95% confidence interval 1.08–1.81,  $p=0.009$ ), consistent with the data by Bernard *et al.*<sup>21</sup>. In addition, the secondary outcome of mortality was also significantly in favor of hypothermia (Table 1). No significant difference in the complication rates between groups was noted.

#### ***International Liaison Committee on Resuscitation (ILCOR) recommendations<sup>34,35</sup>, 2003***

These two randomised clinical trials together enrolled 352 patients. In addition, several thousand patients in observational studies and registries have reported improved survival compared with historical controls. A systematic review and individual patient data meta-analysis found a summary risk ratio of 1.68 (95% confidence interval 1.29, 2.07) for favourable neurological recovery in patients treated with hypothermia<sup>18</sup>. On this basis, in October 2003, ILCOR recommended therapeutic hypothermia to 32–34°C for 12–24 hours in unconscious adults with spontaneous out-of-hospital cardiac arrest<sup>34,35</sup>. The important proviso is that the initial rhythm should be VF or non-perfusing (pulseless) VT.

### **Group 2: Initial Presentation with Rhythms Other than Ventricular Fibrillation or Non-Perfusing Ventricular Tachycardia**

In contrast, evidence for therapeutic hypothermia in this setting is much weaker and mostly observational with substantial risk of bias<sup>34–36</sup>. Pooled data suggests

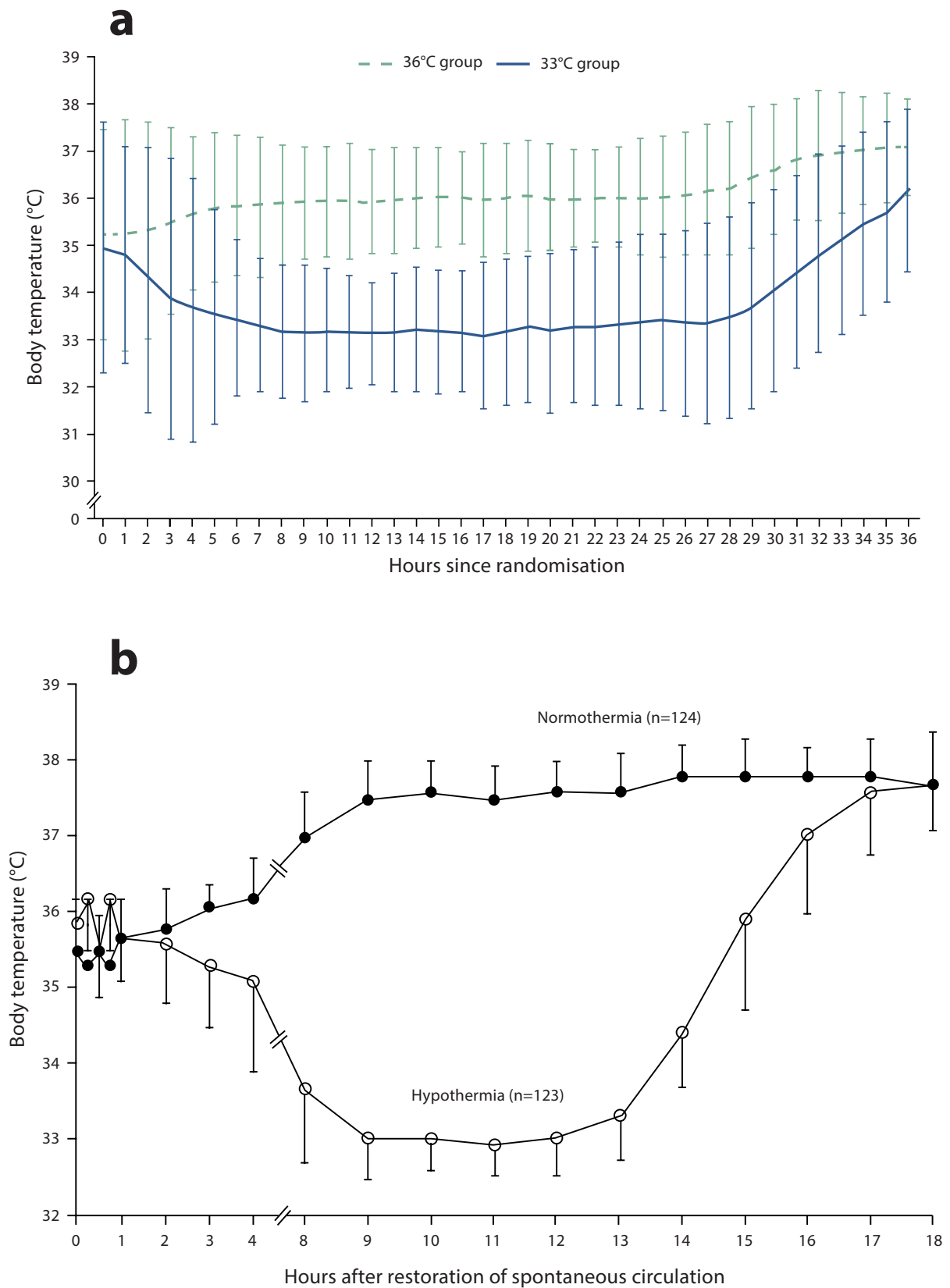


Fig. 4. Temperature curves of treatment and control arms from indicated studies: (a) TTM<sup>33</sup> trial temperature curves: 33°C vs 36°C; (b) HACA<sup>20</sup> trial temperature curves: hypothermia vs "normothermia". Reproduced from Nielsen *et al.*, 2013<sup>37</sup> and HACA Study Group, 2002<sup>20</sup> respectively.

that mild therapeutic hypothermia for 24 hours in this setting may be associated with a 15% reduction in hospital mortality and a minimal, albeit significant improvement in neurological outcome at discharge. Consequently, the level of recommendation by ILCOR for initial rhythms other than VF or nonperfusing VT is much weaker.

### FRESH CONTROVERSIES IN THERAPEUTIC HYPOTHERMIA

It is worthy to point out that the randomised evidence base that led to the 2003 ILCOR recommendation was based on a total of only 352 patients, just half of whom were randomised to therapeutic hypothermia. More than 95% had witnessed cardiac arrest, and the enrolment criteria stipulated either VF or pulseless VT as the presenting rhythm.

In 2013, two large notable studies were published<sup>37,38</sup>, raising fresh questions regarding therapeutic hypothermia post cardiac arrest.

- The Targeted Temperature Management study<sup>37</sup> evaluated induced hypothermia to a target temperature of 33°C versus 36°C, and failed to find a difference in outcome (neurological grade and mortality) between the two groups.
- Kim *et al.*<sup>38</sup> studied the effect of pre-hospital induction of mild hypothermia using infused cold saline by paramedics in the field on survival and neurological status, and found that this intervention also did not improve either of these endpoints.

#### **Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest<sup>37</sup>**

This was a well-conducted, randomised controlled trial with blinded assessment of endpoint. Thirty-six intensive care units in Europe and Australia were involved. Eligibility criteria differed from the Bernard *et al.*<sup>21</sup> and HACA<sup>20</sup> trials in that all initial rhythms were permitted; in other respects, inclusion and exclusion criteria were similar. Subjects were randomised 1:1 to target temperatures of either 33°C or 36°C.

The treatment protocol mandated all patients were sedated and mechanically ventilated. The goal in both treatment groups was to achieve the target temperature as rapidly as possible using ice-cold fluids, ice packs and intravascular or surface

temperature-management devices. After 28 hours, gradual rewarming to 37°C was commenced in both groups. At 36 hours, mandatory sedation was discontinued or tapered. After the intervention period, body temperature for unconscious patients was maintained below 37.5°C for 72 hours after the cardiac arrest using fever-control measures at the discretion of each site. This was a key difference compared to the Bernard *et al.*<sup>21</sup> and HACA<sup>20</sup> trials (in which no specific temperature management strategy was mandated in the control arm).

The primary outcome was all cause mortality. The main secondary outcome was a composite of poor neurologic function or death, as well as predefined serious adverse events.

In total, 950 patients were enrolled, making this the largest trial of therapeutic hypothermia to date. However, no difference in either neurological outcome or mortality was found between the two treatment arms. The rate of serious adverse events was also similar between groups. The overall conclusion was that among unconscious survivors of out-of-hospital cardiac arrest of presumed cardiac origin, hypothermia at a targeted temperature of 33°C did not confer benefit as compared to a targeted temperature of 36°C.

Commentary from the press and on the internet shortly after publication of this trial included the suggestion that therapeutic hypothermia post cardiac arrest may not be efficacious after all, despite the earlier randomised studies. However, it is immediately evident that the TTM trial was not a trial of therapeutic hypothermia versus no hypothermia, but rather a trial of therapeutic hypothermia at two different temperatures. The temperature curves from the TTM study and the HACA study differ fundamentally (Fig. 4) and show that patients with out-of-hospital cardiac arrest not receiving active cooling measures have a strong tendency to develop fever. This difference of around 1.5 to 2 degrees between the HACA control group and the TTM 36°C group could be sufficient to account for the loss of apparent benefit of cooling to 33°C seen in the TTM trial. Essentially, the postulate would be that avoidance of fever leads to better outcome in such patients. The incidence of fever (defined as a core temperature of >38°C) in patients with out-of-hospital cardiac arrest is estimated at between 20% and 80%, and in multiple earlier studies has been associated with poorer outcome<sup>39</sup>.

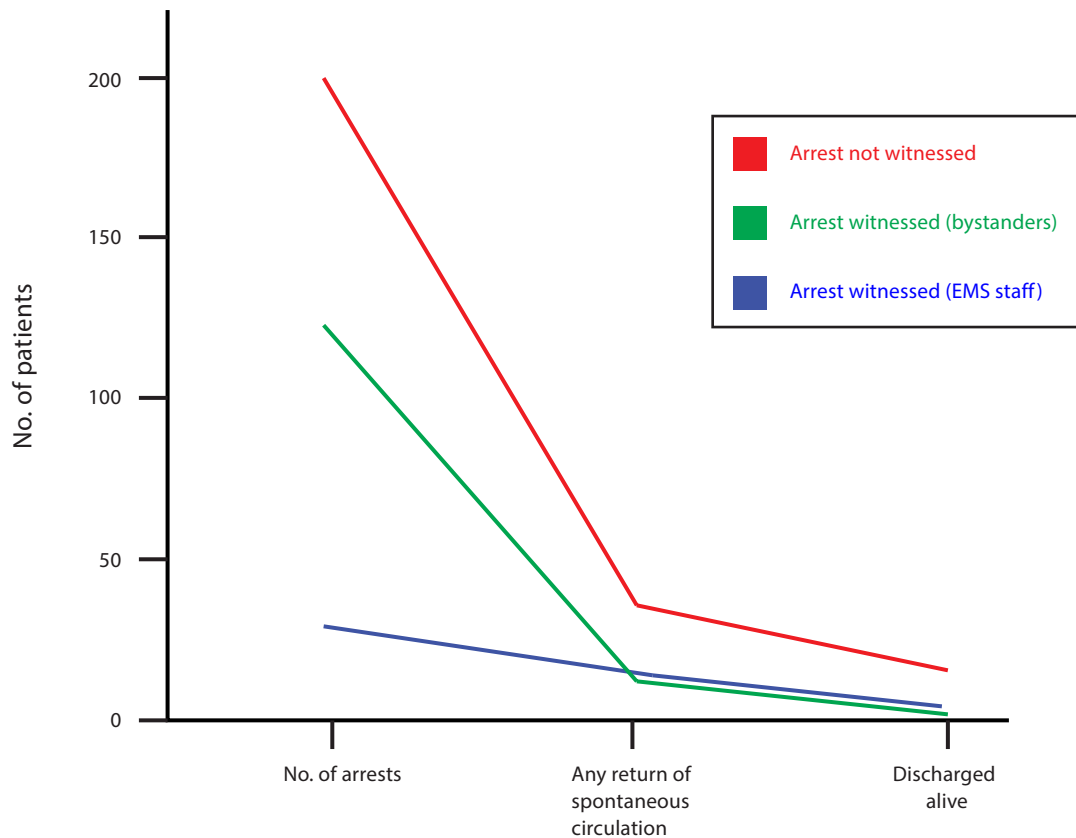


Fig. 5. Discharge survival following out-of-hospital cardiac arrest and return of spontaneous circulation in Singapore. Data from the Cardiac Arrest and Resuscitation Epidemiology in Singapore (CARE I) study<sup>44</sup>. Only one-third of patients who achieve return of spontaneous circulation left hospital alive.

An alternative explanation that might account for the apparent lack of benefit is that it took approximately 6–8 hours before the temperature curves in the 33°C and 36°C treatment groups achieved good separation. This might have masked differences that could have resulted if the goal temperatures were achieved earlier.

A third possible explanation for the negative result is that in the TTM study, the resuscitation statistics were very favourable: cardiac arrests were witnessed in 90% of cases, bystander CPR was administered in 70%, and the median time to CPR was just 1 minute. Therefore, it could be argued that the study inclusion criteria selected out cases where TH might have potentially altered outcome i.e. those with higher risk for cerebral hypoxia. In support of this, mortality in the 36°C arm of the TTM study (most closely corresponding to normothermia) was 48%, compared to 55% and 68% in the normothermia arms of the HACA and Bernard *et al.* studies. While it is not possible to directly compare these figures with certainty, the numerically lower mortality figure in the “control” arm of the TTM study raises the possibility a less sick group of patients may have been enrolled by the study.

Arguing against this explanation, the resuscitation statistics for the other studies are not clearly inferior to the TTM study; for example, in the HACA<sup>20</sup> study, >98% of arrests were witnessed (compared to 90% in TTM) and time to ROSC was about 21 to 22 minutes (compared to 25 minutes in TTM). Furthermore, with an overall mortality of 48% and a high incidence of neurological injury, it seems difficult to argue that the TTM patient cohort was at low risk of cerebral hypoxia.

As a final point, it is noteworthy that the TTM trial, unlike the Bernard *et al.*<sup>21</sup> and HACA<sup>20</sup> studies, included patients with both shockable and non-shockable rhythms. The percentage of non-shockable rhythms was relatively low (20%), and subgroup analysis did not show either group benefited from cooling to 33°C versus 36°C. Therefore, the difference in outcome between the TTM and prior studies cannot be accounted for by the inclusion of patients with non-shockable rhythms, who have intrinsically a poorer outcome.

For now, the TTM trial has not resulted in alteration in guideline recommendations. Practitioners of therapeutic hypothermia are currently divided

Box 1. Some unresolved questions in therapeutic hypothermia.

Assuming therapeutic hypothermia is effective, what is the mechanism by which it works? Is hypothermia itself the important component, or abatement of pyrexia?
Are there identifiable patient subgroups who benefit and those who do not? Do patients where the initial rhythm is not ventricular fibrillation or non-perfusing ventricular tachycardia benefit? Relatedly, is this treatment effective in other setting such as ST-segmented myocardial infarction, stroke and traumatic brain injury?
Is early or late induction of hypothermia better? What is the optimum target temperature? Relatedly, what is the optimum temperature of hypothermia?
Does the method used to achieve hypothermia matter (cold fluid infusion, surface cooling, endovascular cooling, regional cooling)?
Do any of the above variables differ by patient subgroup?
What is the effect of therapeutic hypothermia on prognostication following cardiac arrest?

between cooling to 33°C versus 36°C (rather than no cooling at all). On a practical level, in deciding between therapeutic hypothermia and what may be called “induced normothermia”, it is worth noting that there does not appear to be a significant safety difference between the two temperatures.

***Effect of Pre-hospital Induction of Mild Hypothermia on Survival and Neurological Status Among Adults with Cardiac Arrest: A Randomised Clinical Trial<sup>34</sup>***

The second large trial that garnered significant interest in 2013/2014 was of pre-hospital induction of hypothermia<sup>38</sup>. In total, 1364 patients who suffered out-of-hospital cardiac arrest were randomised; the treatment arm received up to 2 litres of 4°C normal saline as soon as possible following return of spontaneous circulation. Control patients received therapeutic hypothermia beginning with hospital arrival only. All initial rhythms were eligible. This study showed that use of pre-hospital cooling reduced core temperature by hospital arrival and reduced the time needed to reach a temperature of 34°C by one hour, but had no apparent impact on survival or neurological status, irrespective of initial rhythm.

This study was based on the premise that if induction of hypothermia following cardiac arrest is beneficial, earlier induction is likely to yield better outcomes. This hypothesis has some support from animal models; in Mongolian gerbils, delayed hypothermia beyond four hours substantially reduces hippocampal neuronal salvage and impairs behavioral measures in rescued animals<sup>33</sup>. However, prior clinical data is less clear — some studies report that delay in initiation of therapeutic hypothermia and reaching target temperature predicts poorer neurologic outcomes<sup>35</sup>, whereas others report

significantly higher mortality when therapeutic hypothermia is started within 2 hours of cardiac arrest compared to when it is started later<sup>41</sup>. Still others report that timing and speed of hypothermia has no discernable impact on outcome<sup>42</sup>.

The reason(s) why early induction of hypothermia failed to lead to improved outcomes are still unclear. It was observed that patients randomised to the intervention arm had lower first arterial blood gas pH and PaO<sub>2</sub>, both of which are predictors of poor outcomes. They were also more likely to experience rearrest and pulmonary oedema, potentially impacting survival. Arguing against this, early deaths did not differ by treatment status. Nevertheless, it is possible that rearrest worsened brain ischaemia in a manner that did not affect early mortality but manifested as increased risk of death later during the hospitalisation.

Another suggestion is that the mode of achieving early hypothermia may have been important. In a swine model of cardiac arrest, induction of hypothermia using intravenous volume loading was associated with significantly decreased coronary artery perfusion pressure compared with post-resuscitation surface cooling methods<sup>43</sup>. This is relevant as decreased coronary artery perfusion pressure is consistently associated with poorer survival in both animal and human studies. Thus, these associated adverse effects may have mitigated a potential benefit from pre-hospital cooling.

For now, although there is doubt about the effectiveness of induction of hypothermia in the field, the general consensus is that cooling should be started as soon as possible after return of spontaneous circulation in hospital.

## EXPERIENCE OF THERAPEUTIC HYPOTHERMIA IN SINGAPORE AND CONCLUDING REMARKS

In Singapore, the PAROS (Pan-Asian Resuscitation Outcomes Study) group recorded approximately 1666 sudden cardiac deaths for 2013 (unpublished data from one of the authors of this review). This corresponds to a crude annual incidence of 31 per 100,000. In terms of the local experience of therapeutic hypothermia, a pilot program for out-of-hospital cardiac arrest has been implemented in Singapore General Hospital, the largest tertiary hospital in the country<sup>44</sup>. This showed that therapeutic hypothermia was safely and easily implemented. Consistent with the experience elsewhere, it also showed a trend for improved neurological function and survival with therapeutic hypothermia. At the same time, the reported survival for such patients in the country as a whole remains disappointingly low, at 2.7%<sup>45</sup>. Particularly as the Cardiac Arrest and Resuscitation Epidemiology in Singapore (CARE 1) study<sup>40</sup> also showed that there is a large drop in survival following return-of-spontaneous circulation (Fig. 5), it is apparent that correct implementation of therapeutic hypothermia could have a significant impact on survival for out-of-hospital cardiac arrest in Singapore.

It is worth noting that both in Singapore<sup>45</sup> and overseas<sup>46</sup>, only 20–30% of out-of-hospital cardiac arrest patients have VT/VF as the initial recorded cardiac rhythm, and this percentage has decreased in recent years, most likely because of a combination of factors such as earlier detection and improved treatment of patients with coronary artery disease, and the advent of implantable cardioverter-defibrillators for the prevention and treatment of patients at risk of lethal arrhythmias<sup>47,48</sup>. Even for in-hospital cardiac arrest, the prevalence of VF/VT rhythms does not exceed 25–30%. Given these facts, it is clear that therapeutic hypothermia is only one component (albeit an important one) of a much larger effort that is needed to improve outcome for all survivors of out-of-hospital cardiac arrest.

To summarise, while it is clear that questions and controversies remain (Box 1), the experimental and clinical evidence supports therapeutic hypothermia for patients with witnessed cardiac arrest where the presenting rhythm is ventricular fibrillation or non-perfusing ventricular tachycardia. When incorporated as an integral part of post-resuscitation care, it consistently results in significantly better outcomes.

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