



## Clinical Paper

# Higher achieved mean arterial pressure during therapeutic hypothermia is not associated with neurologically intact survival following cardiac arrest<sup>☆</sup>



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## ABSTRACT

**Introduction:** To determine if higher achieved mean arterial blood pressure (MAP) during treatment with therapeutic hypothermia (TH) is associated with neurologically intact survival following cardiac arrest.

**Methods:** Retrospective analysis of a prospectively collected cohort of 188 consecutive patients treated with TH in the cardiovascular intensive care unit of an academic tertiary care hospital.

**Results:** Neurologically intact survival was observed in 73/188 (38.8%) patients at hospital discharge and in 48/162 (29.6%) patients at a median follow up interval of 3 months. Patients in shock at the time of admission had lower baseline MAP at the initiation of TH (81 versus 87 mmHg;  $p = 0.002$ ), but had similar achieved MAP during TH (80.3 versus 83.7 mmHg;  $p = 0.11$ ). Shock on admission was associated with poor survival (18% versus 52%;  $p < 0.001$ ). Vasopressor use among all patients was common (84.6%) and was not associated with increased mortality. A multivariable analysis including age, initial rhythm, time to return of spontaneous circulation, baseline MAP and achieved MAP did not demonstrate a relationship between MAP achieved during TH and poor neurological outcome at hospital discharge (OR 1.28, 95% CI 0.40–4.06;  $p = 0.87$ ) or at outpatient follow up (OR 1.09, 95% CI 0.32–3.75;  $p = 0.976$ ).

**Conclusion:** We did not observe a relationship between higher achieved MAP during TH and neurologically intact survival. However, shock at the time of admission was clearly associated with poor outcomes in our study population. These data do not support the use of vasopressors to artificially increase MAP in the absence of shock. There is a need for prospective, randomized trials to further define the optimum blood pressure target during treatment with TH.

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## 1. Introduction

Cardiac arrest is a major public health issue, with an annual incidence approaching 400,000 in the United States.<sup>1</sup> Mild therapeutic hypothermia (TH) is now an established and recommended therapy to improve survival and neurological outcome following cardiac arrest.<sup>2–4</sup> Despite advances in post-resuscitation care, long-term outcomes following cardiac arrest remain dismal. Approximately

60% of patients suffering cardiac arrest will die in the field, and of those who survive to hospitalization, approximately 75% will not survive to discharge.<sup>5</sup> Given the high mortality seen in patients who are successfully resuscitated and survive to hospitalization, attention has turned to optimizing post-resuscitation management.

In-hospital mortality following cardiac arrest is often a result of the “post-cardiac arrest syndrome,” a complex condition characterized by multi-organ ischemic reperfusion injury, particularly in the brain and myocardium.<sup>6</sup> Profound reversible myocardial dysfunction and a robust pro-inflammatory response are pathophysiologic derangements seen in this syndrome that can result in hemodynamic instability.<sup>7–9</sup> Circulatory shock – a physiologic state of inadequate tissue perfusion and oxygenation related to systemic hypotension – is common in the post-resuscitation period and known to be associated with increased mortality.<sup>7,10,11</sup>

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Clinical guidelines for the hemodynamic management of patients undergoing TH are not clearly specified, largely due to the lack of robust clinical data. This has resulted in a wide range of hemodynamic targets in the published literature and subsequent inconsistency in clinical practice. Several TH studies do not define hemodynamic goals such as a target mean arterial blood pressure (MAP).<sup>3,12–15</sup> In studies with a defined target MAP, the range is remarkably variable, ranging from >60 mmHg<sup>16</sup> to 90–100 mmHg.<sup>4</sup>

Prior animal and human studies show that cerebral blood flow and autoregulation are abnormal following cardiac arrest.<sup>27,28</sup> Therefore, it has been suggested that MAP should be maintained at a higher level to secure cerebral blood flow.<sup>17</sup> In light of recent studies suggesting that the use of vasopressors following cardiac arrest may improve the likelihood of return of spontaneous circulation (ROSC) and short-term survival at the expense of worse long-term clinical outcomes, MAP goals following successful resuscitation need to be carefully considered.<sup>18–21</sup>

Given the high incidence of shock in the post-resuscitation time period, the harm associated with both systemic arterial hypotension and vasopressor use, and the paucity of clinical data that supports an ideal MAP target during TH, there is an urgent need for high quality clinical data to better define hemodynamic goals in this high risk patient population. We hypothesized that higher achieved MAP (specifically, a MAP  $\geq 80$  mmHg) during treatment with TH may be associated with improved neurological outcomes.

## 2. Methods

### 2.1. Study design

The study population included 188 consecutive patients following cardiac arrest that had successful ROSC and were treated with TH at Vanderbilt University Medical Center between May 2007 and March 2012. All patients were cooled externally using an active surface-cooling device to maintain a core body temperature of 32–34 degrees Celsius for a total of 24 h following ROSC, after which they were rewarmed actively at a rate of 0.25 degrees Celsius per hour. The standardized TH protocol at our institution recommends a MAP target of 80–90 mmHg and norepinephrine as the initial vasopressor of choice to treat hypotension.

Following approval from the institutional review board, data were collected prospectively on these patients, including initial rhythm, time to ROSC, receipt of bystander cardiopulmonary resuscitation, Cerebral Performance Category (CPC) score at hospital discharge, CPC score at outpatient follow up and time to follow up. In addition, we retrospectively collected all noninvasive (NIMAP) and invasive/arterial (AMAP) mean arterial blood pressure measurements as well as all vasopressor use and doses administered during treatment with TH. We defined shock on admission as a systolic blood pressure <90 mmHg or the need for any vasopressor or mechanical circulatory support at the time of admission. Medications considered vasopressors included norepinephrine, epinephrine, vasopressin, phenylephrine, dopamine, dobutamine and milrinone.

The cardiovascular portion of the Sequential Organ Failure Assessment (SOFA) score was used to reflect the achieved MAP for each patient. The SOFA score is a validated scoring system to quantify the number and severity of organ dysfunction over time in six organ systems (respiratory, hematologic, hepatic, cardiovascular, renal and neurological).<sup>22</sup> The SOFA score has been validated for both individual and aggregate organ dysfunction and provides clinicians with information on both the degree and progression of dysfunction. It has been studied and validated in critically ill patients including cardiovascular patients with acute myocardial infarction.<sup>23</sup> The cardiovascular portion of the SOFA score (CV

SOFA) accounts for both MAP and vasopressor requirement. Points are assigned for decreasing MAP and increasing vasopressor use, and therefore, the CV SOFA score is inversely associated with hemodynamic stability.

For the purpose of this study, the baseline MAP was defined as the mean of the first five consecutive MAPs recorded during TH. Achieved MAP was defined as the mean of all consecutive MAPs recorded during the longest period of time with the lowest CV SOFA score during TH over a minimum of five consecutive blood pressure measurements. Using this method, we were able to define the achieved MAP as the mean value of recordings during the period of time when the patient was the most hemodynamically stable.

Nurses in the cardiovascular intensive care unit of our institution routinely chart both NIMAP and AMAP measurements at regular time intervals, recording pressures hourly as a minimum requirement although more frequently as the clinical condition of the patient dictates. Because MAPs obtained by noninvasive means can be recorded quickly and do not require a procedure (i.e. arterial line placement), we anticipated that the NIMAP values would be a more complete dataset compared to AMAP, and therefore, pre-specified to use NIMAP in the primary analysis. AMAP values were subsequently used for the secondary analysis. To our knowledge, no data exists comparing the accuracy of NIMAP and AMAP values in this patient population.

The primary outcome for this study was CPC score at the time of follow up. The CPC score was developed as a measure of central nervous system function after cardiac arrest and is recommended and commonly used for this purpose.<sup>3,4,24</sup> A CPC score between 3 and 5 defines a poor neurological outcome in study patients and clinically represents a range of dysfunction from severe neurological disability to brain death.<sup>24</sup> Consistent with these recommendations, a CPC score between 3 and 5 was used to define a poor neurological outcome in this study. Secondary outcomes for this study included CPC score at hospital discharge, survival to hospital discharge and survival to follow up. We also evaluated outcomes based on vasopressor use and the presence of shock on admission.

### 2.2. Inclusion/exclusion criteria

All patients treated with TH at our institution who had at least five NIMAP measurements during hypothermia were included.

### 2.3. Statistical analysis

Descriptive statistics were calculated as the median with interquartile range (IQR) for continuous variables. For categorical variables, frequencies and percentages were presented. Clinical characteristics between patients with and without vasopressor use, and between patients with and without shock on admission, were compared using the Wilcoxon rank sum test or Pearson Chi-square test where appropriate. A logistic regression model was developed to assess the association between achieved MAP and the neurological outcome adjusting for baseline MAP, age, initial rhythm and time to ROSC. Achieved MAP, baseline MAP, age and time to ROSC were modeled as continuous variables with appropriate transformation using restricted cubic splines to account for non-linear relationships. All tests were two-tailed. All statistical analyses were performed using open source R statistical software<sup>25</sup> and RMS package.<sup>26</sup>

## 3. Results

Of 188 consecutive patients considered for inclusion, 174 had at least five consecutive NIMAPs recorded during TH and therefore, were included in the primary analysis. A total of 148 patients had at least five consecutive AMAPs recorded during TH and were

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