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Clinical paper

Haemodynamic management strategies are not explicitly defined in the majority of therapeutic hypothermia implementation studies☆

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ABSTRACT

Background: Therapeutic hypothermia (TH) has revolutionized the management of comatose post-cardiac arrest syndrome (PCAS) patients. The 2008 ILCOR/AHA Consensus Statement for the treatment of PCAS suggests that goal-directed therapy, targeting mean arterial pressure (MAP), central venous pressure (CVP), and central venous oxygen saturation ($ScvO_2$), should be employed to normalize oxygen delivery. However, the optimal PCAS haemodynamic management strategy has not been defined and few objective data exist to guide clinicians.
Objective: To describe the haemodynamic strategies used in TH implementation studies.
Methods: A Medline search (time period, 3/2002 to 3/2010) was performed using the terms cardiac arrest and hypothermia, induced, then limited post-search to implementation studies of TH in comatose adults. The identified studies were examined for explicit definitions of the following terms: MAP; systolic blood pressure (SBP), CVP, $ScvO_2$, pulmonary artery catheter (PAC), echocardiogram (ECHO), lactate, and volume status.
Results: Forty-four implementation studies were identified and 43% (19/44) of them mentioned haemodynamics in any fashion. At least one haemodynamic goal was specifically defined in 16/44 (36%). The median number defined was 4 (range 1–6); individual goals as follows: MAP, 13/44 (30%); SBP, 3/44 (7%); CVP, 5/44 (11%); $ScvO_2$, 4/44 (9%); PAC, 7/44 (16%); ECHO, 7/44 (16%); lactate, 5/44 (11%); and volume status, 8/44 (18%).
Conclusions: Specific haemodynamic goals are defined in a minority of published TH implementation studies. Given the volatile haemodynamics of the PCAS and lack of consensus on an optimal resuscitation strategy, explicit description of haemodynamic goals should be provided in future studies.

1. Introduction

Therapeutic hypothermia (TH) has revolutionized the management of comatose post-cardiac arrest patients. The results of two randomized trials published in the *New England Journal of Medicine* in 2002[1,2] led to numerous implementation studies from diverse institutions utilizing a wide variety of cooling techniques.[3–5] The 2010 American Heart Association (AHA) Guidelines give TH a Class I recommendation for comatose patients who have return of spontaneous circulation (ROSC) after out-of-hospital ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT) cardiac arrest (OHCA). Generalization of this therapy to in-hospital arrests and non-VF rhythms received a Class IIb recommendation.[6]

The post-cardiac arrest syndrome (PCAS) is a complex disease entity affecting all major organ systems.[7,8] The proximal phase of PCAS, soon after ROSC, can be complicated by haemodynamic instability. Immediately after ROSC, there are high levels of circulating catecholamines (both exogenous and endogenous), which can contribute to cardiovascular instability and dysfunction.[9] If the arrest is caused by an acute coronary occlusion, focal ischaemia and necrosis of myocardial tissue can produce regional wall motion

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abnormalities, compromising ejection fraction and stroke volume.[10] Even in the absence of an acute coronary syndrome, myocardial stunning from global ischaemia, reperfusion, and subsequent inflammation can have profound effects on cardiac output in the first hours to days after cardiac arrest.[11] In addition, since cerebral autoregulation is frequently deranged after a period of ischaemia and reperfusion, post-arrest cerebral perfusion is dependent upon maintenance of an adequate mean arterial pressure (MAP).[12] It follows logically that optimal post-arrest outcomes depend not only upon efficient delivery of TH but also on adequate haemodynamic resuscitation.

Despite this logical clinical concern, optimal post-arrest haemodynamic management has not been studied extensively. Of the two landmark hypothermia trials, the Bernard et al. trial[1] had cardiogenic shock (defined as a systolic blood pressure [SBP] < 90 mmHg despite adrenaline [epinephrine] infusion) as an exclusion criterion and utilized specific haemodynamic goals clearly defined in the published paper, whilst the Hypothermia After Cardiac Arrest (HACA) trial[2] does not mention specific haemodynamic goals, only mentioning ongoing hypotension (MAP < 60 mmHg 30 min after ROSC and before randomization) as an exclusion criterion. The Bernard group attempted the following haemodynamic strategy in the post-arrest period: MAP was maintained between 90 and 100 mmHg, using adrenaline or nitroglycerin infusions, as indicated; pulmonary artery catheter (PAC) placed upon intensive care unit (ICU) arrival to guide haemodynamics; and haemodynamic variables including MAP, cardiac index, and systemic vascular resistance were recorded at frequent intervals.[1]

Almost a decade has passed since the landmark studies were published in 2002, but there continues to be a paucity of data to inform resuscitation practice in PCAS patients. In 2005, the AHA published their guidelines for the management of PCAS suggesting, based on little evidence, the use of a resuscitation strategy similar to that recommended for patients with septic shock.[13] The authors incorporated evidence that the post-resuscitation period is a sepsis-like syndrome[14] to suggest that early goal-directed therapy (EGDT), targeting MAP, central venous pressure (CVP), and central venous oxygen saturation ($ScvO_2$), should be employed to normalize oxygen delivery.[15] However, the optimal PCAS haemodynamic management strategy has not been defined and few objective data exist to guide clinicians. Even in 2010, the AHA Guidelines for Post-Cardiac Arrest Care remain far from robust, recommending only: frequent blood pressure monitoring/a-line; MAP > 65 mmHg or SBP > 90 mmHg; fluid bolus if tolerated; and serial lactate to confirm adequate organ perfusion.[6] These recommendations fall far short of a systematic haemodynamic resuscitation strategy that can be objectively employed by clinicians at diverse institutions taking care of critically ill PCAS patients.

Although TH clearly saves lives and improves neurocognitive outcomes for comatose survivors of cardiac arrest, further improvements in patient outcome will likely require advances in our understanding of how best to resuscitate these OHCA patients post-ROSC. Recognizing the paucity of knowledge currently available, we sought to objectively describe the haemodynamic goals used in TH implementation studies to establish a baseline for future investigations of haemodynamic strategies for PCAS patients.

2. Methods

We performed a Medline search using the terms hypothermia, induced and cardiac arrest ("heart arrest") for the time period from 3/2002 to 3/2010, limited to human studies in English. We supplemented this search with a search strategy similar to that utilized in the 2010 AHA Worksheet on TH (http://circ.ahajournals.org/site/C2010/ALS-PA-044.pdf), performing a PubMed search, "heart arrest" OR "cardiopulmonary resuscitation" AND "hypothermia, induced", limited to human studies in English. The identified studies were reviewed for the following inclusion criteria: evidence of being an implementation study in comatose adult post-arrest patients and a specific description of a post-arrest TH protocol. Exclusion criteria included: post hoc analysis of randomized control trials published prior to the search period; individual case reports; implementation surveys; review articles; studies focused primarily on neuroprognostication and providing little or now information about the TH protocol or other aspects of PCAS care; and studies utilizing other therapies including emergency cardiopulmonary bypass and continuous veno-venous haemofiltration. In addition, the references of the reviewed papers were examined for relevant papers missed by the electronic search techniques. Explicit haemodynamic and oxygen delivery terms chosen a priori included: MAP, SBP, CVP, $ScvO_2$, PAC, echocardiogram (ECHO), lactate, and volume status, including intravenous fluid infusion, measurement of urine output, and other assessments of volume status. During the study review, adrenaline, noradrenaline [norepinephrine], dopamine, vasopressin, phenylephrine, nitroglycerin, dobutamine, and milrinone were considered vasoactive agents and mention of titration of a vasoactive agent to a target MAP or $ScvO_2$ was considered evidence of an explicit haemodynamic strategy. The methods, tables, and results of the identified studies were examined for explicit definitions of and goals for the haemodynamic variables. These variables were entered into an Excel (Excel 2003, Microsoft Corporation, Redmond, WA) database and analyzed using built-in software. Percentages were calculated and for continuous data means with ranges were calculated.

3. Results

The initial Medline search produced 441 results. Thirty-seven of these studies met inclusion criteria. The PubMed search produced 698 results and 7 of these studies met inclusion criteria and had not been identified by the Medline search. Thus, a total of forty-four implementation studies met inclusion criteria, three of which were database studies. Nineteen of the 44 (43%) studies made any mention of haemodynamic management. At least one haemodynamic variable was specifically defined in 16/44 (36%) studies.[3–5,10,16–27] The median number of haemodynamic variables mentioned in the studies was 3 (range 1–6). Individual variables were specifically defined in the studies as follows: MAP, 13 studies (30%) with 5 (11%) defining a goal range and 7 (16%) a lower limit only; the most common lower and upper limits specified were 80 mmHg (range 65–90 mmHg) and 100 mmHg (range 100–150 mmHg), respectively; SBP, 3 studies (7%); CVP, 5 studies (11%) defining specific CVP goals, with 3 (7%) providing a target range; the most common lower and upper limits specified were 8 mmHg (range 4–8 mmHg) and 12 mmHg (range 8–12 mmHg), respectively; $ScvO_2$, 4 studies (9%), with 3 (7%) specifying a target of >65%; PAC, 7 studies (15%) mention PAC use but give no guidance for its use or specific variables to obtain; ECHO, 7 studies (16%) mention ECHO use but give no guidance for its use or specific variables to obtain; lactate, 5 studies (11%), with 5 (11%) specifying serial lactates and 4 (9%) targeting lactate clearance; and volume status, 8 studies (18%), with none providing specific goals (see Table 1). Just over 50% (8/15) of the studies mentioned a specific vasoactive drug used in the haemodynamic treatment approach. The median number of vasopressors mentioned was 1 (range, 0–6). The most common vasopressor mentioned was noradrenaline, which was mentioned in 7 studies.