Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest

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A B S T R A C T

Background: Comatose survivors of out-of-hospital cardiac arrest (OHCA) have high in-hospital mortality due to a complex pathophysiology that includes cardiovascular dysfunction, inflammation, coagulopathy, brain injury and persistence of the precipitating pathology. Therapeutic hypothermia (TH) is the only intervention that has been shown to improve outcomes in this patient population. Due to the similarities between the post-cardiac arrest state and severe sepsis, it has been postulated that early goal-directed hemodynamic optimization (EGDHO) combined with TH would improve outcome of comatose cardiac arrest survivors.

Objective: We examined the feasibility of establishing an integrated post-cardiac arrest resuscitation (PCAR) algorithm combining TH and EGDHO within 6 h of emergency department (ED) presentation.

Methods: In May, 2005 we began prospectively identifying comatose (Glasgow Motor Score < 6) survivors of OHCA treated with our PCAR protocol. The PCAR patients were compared to matched historic controls from a cardiac arrest database maintained at our institution.

Results: Between May, 2005 and January, 2008, 18/20 (90%) eligible patients were enrolled in the PCAR protocol. They were compared to historic controls from 2001 to 2005, during which time 18 patients met inclusion criteria for the PCAR protocol. Mean time from initiation of TH to target temperature (33°C) was 2.8 h (range 0.8–23.2; SD = h); 78% (14/18) had interventions based upon EGDHO parameters; 72% (13/18) of patients achieved their EGDHO goals within 6 h of return of spontaneous circulation (ROSC). Mortality for historic controls who qualified for the PCAR protocol was 78% (14/18); mortality for those treated with the PCAR protocol was 50% (9/18) (p = 0.15).

Conclusions: In patients with ROSC after OHCA, EGDHO and TH can be implemented simultaneously.

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Introduction

There are more than 300 000 cardiac arrests per year in the United States.1,2 More than 250 000 of them die and many survivors have significant neurologic deficits. Therapeutic hypothermia currently represents the most efficacious treatment option to reduce neurologic injury and mortality in comatose patients who have ROSC after cardiac arrest.3,4 It is unknown whether adjunctive therapies used in concert with TH further improve outcomes.5

Clinical and laboratory investigations support the concept that the immediate post-arrest period exhibits a number of similarities to the sepsis syndrome, with elevated serologic markers of global inflammation, endothelial dysfunction and microcirculatory hypoperfusion.6 Some investigators have referred to this pathophysiologic state as the “post-resuscitation syndrome”.7 Using early goal-directed therapy (EGDT), an early goal-directed hemodynamic optimization (EGDHO) strategy applied at the most proximal phase of critical illness, Rivers and colleagues reduced in-hospital...
mortality from 46.5% to 30.5% in patients with severe sepsis and septic shock.\textsuperscript{8} This resuscitation strategy was endorsed by the Surviving Sepsis Campaign and incorporated into its sepsis care bundles.\textsuperscript{9} Subsequent publications describing the feasibility of implementing EGDT along with other aspects of a sepsis care bundle have demonstrated similar mortality reductions.\textsuperscript{10–13}

Given the similarities between the inflammatory responses associated with septic shock and the post-resuscitation syndrome, it is plausible that EGDHO may result in similar survival benefits in patients with ROSC after cardiac arrest. A post-resuscitation care bundle may benefit post-arrest patients in a similar fashion as sepsis care bundles have benefited patients with severe sepsis and septic shock.\textsuperscript{14} In fact, several recent publications have addressed other aspects of post-resuscitation care in addition to TH, including early percutaneous coronary intervention (PCI), intra-aortic balloon pumps for treatment of cardiogenic shock, EGDHO strategies, glucose and ventilator management strategies, and evaluation for relative adrenal insufficiency.\textsuperscript{15–21}

However, none of these implementation studies have examined a specifically defined hemodynamic optimization strategy implemented at the most proximal phase of the post-resuscitation syndrome. We sought to evaluate the feasibility of implementing a comprehensive EGDHO protocol during induction of TH in patients immediately after ROSC. Our protocol incorporates clearly defined resuscitation endpoints and mandates implementation of EGDHO simultaneous with induction of TH and continuation of hemodynamic monitoring throughout the period on therapeutic cooling. We hypothesized that hemodynamic optimization of key physiologic endpoints—mean arterial pressure (MAP), central venous pressure (CVP), and central venous oxygen saturation (ScvO\textsubscript{2})—could be achieved within 6 h of ROSC while implementing TH.

Methods

In this study, we performed an analysis of a prospectively collected database of cardiac arrest patients with ROSC treated with a combination of TH and EGDHO.

Establishment of hypothermia protocol

A PCAR protocol working group with members from Emergency Medicine, Pulmonary and Critical Care Medicine, and Cardiology was established in May, 2004 and regular meetings were held over the next year to develop consensus recommendations for the management of comatose patients with ROSC after OHCA. The PCAR protocol was implemented in May, 2005 at the Hospital of the University of Pennsylvania (HUP), an urban, tertiary care teaching hospital with 58,000 annual ED visits. Patients eligible for the PCAR protocol were admitted from the ED to either the Medical Intensive Care Unit (MICU) or the Cardiac Care Unit (CCU) and followed during their inpatient stays by trained research staff. We also included patients specifically transferred from outside hospitals to the CCU for implementation of the PCAR protocol.

Enrollment

We aimed to enroll patients without severe pre-arrest conditions who achieved rapid ROSC after OHCA (inclusion and exclusion criteria are detailed in Table 1). Determination of eligibility for and initiation of the PCAR protocol were done in the ED, but various steps of protocol implementation were completed in the ED, MICU or CCU, depending on bed availability. If the patient was eligible for emergent PCI, transfer to the catheterization laboratory was not delayed to accomplish any of the initial steps of the protocol.

In these instances, EGDHO and TH were initiated in the ED and continued in the catheterization laboratory during PCI.

All patients eligible for the PCAR protocol were identified through a combination of: real-time pager notification of study team by ED clinical staff; and a regularly performed internet search of the ED’s electronic medical record, designed to capture any eligible patients who were not prospectively enrolled.

Induction and maintenance of hypothermia

Therapeutic hypothermia was accomplished by three means used in concert: chilled saline infusion, surface cooling devices, and ice packs. Initial induction of TH was by 2 L bolus of 4°C normal saline solution (NSS) via peripheral intravenous catheter(s). Induction of hypothermia was completed and maintained using surface cooling with either a water blanket temperature transfer system (Meditherm III & Rapr.Round; Gaymar Industries, Orchard Park, NY), or a gel adhesive pad temperature transfer device (Artic Sun; Medivance Corporation, Louisville, CO). Ice packs, placed in the axillae and groin, were used if there was difficulty achieving the target temperature of $33\degree$C (range $32–34\degree$C). Active cooling was performed for 24 h from the onset of cooling; active rewarming was achieved by increasing the temperature set point by $0.5\degree$C/2 h, with a goal of rewarming over a minimum of 8 h.

Early goal-directed hemodynamic optimization

Coincident with induction of TH, an arterial catheter was placed for continuous blood pressure monitoring and a continuous oximetric triple lumen central venous catheter (PreSep; Edwards Lifesciences, Irvine, CA) was placed for CVP and ScvO\textsubscript{2} monitoring. End-points of EGDHO were addressed in an algorithmic fashion, beginning with MAP, then addressing CVP, and then ScvO\textsubscript{2} (see Figure 1).

Other components to the PCAR protocol

Several other changes in ICU management were incorporated in the PCAR protocol, including evaluation for relative adrenal insufficiency; protocolized management to keep serum glucose less than 150 mg/dL, and low tidal volume ($6–8$ cc/kg) ventilator management strategies where applicable.

Data collection

Data collection for our clinical treatment intervention was approved by the Institutional Review Board at the University of Pennsylvania. A database was constructed following the Utstein framework.
style, using standard database software (Access; Microsoft Corporation, Redmond, WA). For mortality comparisons, the patients eligible for and enrolled in the PCAR protocol were compared to historic controls, seen in the ED from January 2001 through April 2005, who, on chart review, would have been eligible for the PCAR protocol. The classification of historic controls was performed by two of the investigators (DFG and JH) with 95% agreement (K = .90).

Statistical analysis

Continuous variables were analyzed by means with standard deviations and ranges, compared using Student’s t-test, and expressed in unadjusted odds ratios with 95% confidence intervals as well as p values; time variables were recorded in 24 h time format; non-continuous variables were compared using Fisher’s exact test and also were expressed in unadjusted odds ratios with 95% confidence intervals as well as p values.

Results

Between May, 2005 and January, 2008, 208 patients with OHCA presented to our ED; 132/208 (64%) were of presumed cardiac etiology. Non-cardiac etiologies included hemorrhagic shock, intracranial hemorrhage, and environmental hypothermia. Of the presumed cardiac etiology subgroup, 38/132 (29%) had ROSC, and 34/132 (26%) survived to hospital admission. Of those admitted, 20/34 (59%) met inclusion criteria for the PCAR protocol; 18/20 (90%) of these patients were recognized prospectively by the...
clinical team managing patient care and were enrolled in the protocol; 2/20 (10%) were not recognized as candidates for the PCAR protocol and were treated neither with TH nor EGDHO. In the historic database, 230 OHCA patients presented to our ED; 156/230 (68%) of these were of cardiac etiology. Of these, 56/156 (36%) had ROSC, and 46/156 (30%) survived to hospital admission. Less than half (18/46, 39%) would have met inclusion criteria for the PCAR protocol and were treated as controls [see Table 2 for complete data and basic demographic information].

The mean age of patients treated with the PCAR protocol was 57 years (SD = 18 years); 12/18 (67%) were male; 8/18 (44%) were African-American; 8/18 (44%) were Caucasian; and 2/18 (11%) were Asian. In comparison, for historic controls the mean age was 67 years (SD = 13 years); 50% (9/18) were male; 11/18 (61%) were African-American and 7/18 (39%) were Caucasian.

Median time from ROSC to implementation of TH was 1.7 h (IQR 1.1–2.8 h); mean starting temperature was 35.8 °C (range 31.0–37.0 °C; SD = 1.4 °C); median time from initiation of TH to achievement of target temperature was 2.5 h (IQR 2.0–5.3 h); median time from ROSC to achievement of target temperature was 4.2 h (IQR 3.1–8.1 h); mean rate of cooling during induction of TH was 0.8 °C/h; mean length of time patients were cooled for was 19.3 h (range 17.0–29.0 h; SD = 8.3 h), excluding two patients who had care withdrawn by their families at hours 7 and 9, at which time cooling was terminated; mean time from start of rewarming to conclusion of TH was 14.7 h (range 6.0–17.0 h; SD = 7.1 h). Immediate PCI was performed in 17% (3/18) of patients in the PCAR protocol group versus 11% (2/18) of patients in the historic control group. Thirty-nine percent (7/18) of the patients in the PCAR group had PCI during their hospital stay versus 11% (2/18) of the historic controls.

Immediate echocardiogram (during the first 6 h after ROSC) was performed in 85% (15/18) of the PCAR patients (mean EF = 39%; median EF = 45%; IQR = 25–65%) versus 38% (7/18) of the historic controls (mean EF = 31%; median EF = 25%; IQR = 13–50%); follow up echocardiograms were performed in 58% (10/17) of the surviving EGDHO patients by 72 h post-ROSC (mean EF = 43%; median EF = 43%; IQR = 25–50%) versus 20% (2/10) of the historic control patients (mean EF = 63%).

For patients treated with the PCAR protocol, the mean initial CVP was 12.8 mmHg (range 5–26; SD = 5.8 mmHg); the mean initial MAP was 95.1 mmHg (range 67–147; SD = 21.1 mmHg); the mean initial ScvO2 was 79.1% (range 54–90; SD = 9.8%); 7/18 (39%) patients required vasopressor infusions for greater than 6 h; average intravenous fluid infusion volume over the first 12 h was 5761 mL (range 2250–14795 mL); 14/18 (78%) had interventions based upon EGDHO parameters; 13/18 (72%) of patients achieved their EGDHO goals within 6 h of implementation of TH and EGDHO. For historic controls, the mean initial MAP was 81 mmHg (range 41–106 mmHg); 22% (4/18) required vasopressors initially; average intravenous fluid infusion volume over the first 12 h was 1451 mL (range 658–4305 mL) [see Tables 3, 4 and 5A].

Pre-implementation mortality was 14/18 (78%) for historic control patients who qualified for the PCAR protocol; post-implementation mortality for patients who qualified for and were treated with the PCAR protocol was 10/20 (50%) and 9/18 (50%), respectively (p = 0.16); 4/18 (22%) historic controls and 9/18 (50%) patients treated with PCAR protocol survived to hospital discharge; two patients enrolled in TH protocol had care withdrawn by family at hours 7 and 9; mortality for patients who completed TH was 44% (7/16; p < 0.05); 4/4 (100%) of surviving historic controls and 8/9 (89%) of surviving patients treated with the PCAR protocol had good neurologic outcomes, defined as cerebral performance category (CPC) 1 or 2 [see Table 5B for details].

Discussion

Our study demonstrates successful implementation of TH and EGDHO in a hospital employing a multi-disciplinary post-cardiac arrest resuscitation protocol. We found that 78% of patients required interventions based upon our treatment algorithm and that 72% of patients were able to achieve EGDHO goals within 6 h of ROSC. We demonstrated a 28% absolute reduction in mortality when compared with historic controls, though the study was underpowered for the results to reach statistical significance.

Therapeutic hypothermia has been demonstrated to improve neurologic function and survival in a number of clinical trials. One of the benefits of hypothermia is a decrease in systemic and cerebral metabolic rates of oxygen consumption. This may be especially helpful when systemic oxygen delivery does not meet metabolic demands and may prevent recurring oxygen debt.

In the original early goal-directed therapy trial, by correcting CVP, MAP, and ScvO2 in a stepwise fashion within 6 h of presentation, Rivers et al.8 reduced in-hospital mortality from 46.5% to 30.5% in patients with severe sepsis and septic shock. Subsequent publications describing the feasibility of implementing EGDT along with other aspects of a sepsis care bundle have demonstrated similar mortality reductions.10–13 While the mechanisms for improved outcomes are not completely clear, Rivers et al. suggested that EGDT optimizes hemodynamics at the proximal phase of critical illness, which may prevent sudden cardiovascular collapse. In addition, in

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Table 2
Baseline demographics.

<table>
<thead>
<tr>
<th></th>
<th>Historic controls (N = 18)</th>
<th>PCAR protocol patients (N = 20)</th>
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<tr>
<td>Arrests</td>
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<tr>
<td>Cardiac etiology</td>
<td>156</td>
<td>132</td>
</tr>
<tr>
<td>ROSC (%)</td>
<td>56/156 (36%)</td>
<td>38/132 (29%)</td>
</tr>
<tr>
<td>Admitted (%)</td>
<td>46/156 (30%)</td>
<td>34/132 (26%)</td>
</tr>
<tr>
<td>Qualified PCAR (%)</td>
<td>18/46 (39%)</td>
<td>20/24 (50%)</td>
</tr>
<tr>
<td>Treated PCAR (%)</td>
<td>0/24 (0%)</td>
<td>18/20 (90%)</td>
</tr>
<tr>
<td>Age (years) (range)</td>
<td>67 (35–87)</td>
<td>57 (20–86)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>Male (%)</td>
<td>9/18 (50%)</td>
<td>12/18 (67%)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>9/18 (50%)</td>
<td>6/18 (33%)</td>
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<tr>
<td>Race</td>
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<td></td>
</tr>
<tr>
<td>Black (%)</td>
<td>11/18 (61%)</td>
<td>8/18 (44%)</td>
</tr>
<tr>
<td>White (%)</td>
<td>7/18 (39%)</td>
<td>8/18 (44%)</td>
</tr>
<tr>
<td>Asian (%)</td>
<td>0/18 (0%)</td>
<td>2/18 (11%)</td>
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<tr>
<td>Rhythm</td>
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<td></td>
</tr>
<tr>
<td>VT/VT (%)</td>
<td>8/18 (44%)</td>
<td>9/18 (50%)</td>
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<tr>
<td>PEA (%)</td>
<td>5/18 (28%)</td>
<td>6/18 (33%)</td>
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<tr>
<td>Asystole (%)</td>
<td>4/18 (22%)</td>
<td>3/18 (17%)</td>
</tr>
<tr>
<td>Unknown (%)</td>
<td>1/18 (6%)</td>
<td>0/18 (0%)</td>
</tr>
<tr>
<td>GCS (range)</td>
<td>5 (3–10)</td>
<td>4 (3–10)</td>
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</table>

Table 3
TH and EGDHO variables.

<table>
<thead>
<tr>
<th></th>
<th>Mean (range) Number (%)</th>
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<tr>
<td>TH variables</td>
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<tr>
<td>Starting T (°C)</td>
<td>35.8 (31.0–37.0)</td>
</tr>
<tr>
<td>Time from ROSC to goal T (°C)</td>
<td>4.5 (2.2–9.5)</td>
</tr>
<tr>
<td>Time, induction to goal T</td>
<td>2.8 (2.0–9.0)</td>
</tr>
<tr>
<td>Length of cooling</td>
<td>19.3 h (17–29)</td>
</tr>
<tr>
<td>Time of rewarming</td>
<td>10.1 h (6–17)</td>
</tr>
<tr>
<td>EGDHO variables</td>
<td></td>
</tr>
<tr>
<td>Initial CVP (mmHg)</td>
<td>12.8 (5–26)</td>
</tr>
<tr>
<td>Initial MAP (mmHg)</td>
<td>95.1 (67–147)</td>
</tr>
<tr>
<td>Initial ScvO2 (%)</td>
<td>79.2 (54–90)</td>
</tr>
<tr>
<td>Vasopressors &gt; 6h</td>
<td>7/18 (39%)</td>
</tr>
<tr>
<td>Achieved EGDHO endpoints in &lt;6h</td>
<td>13/18 (72%)</td>
</tr>
<tr>
<td>Interventions based on EGDHO variables</td>
<td>14/18 (78%)</td>
</tr>
<tr>
<td>Intravenous fluid (mL), 1st 12h</td>
<td>5761 (2250–14795)</td>
</tr>
</tbody>
</table>
and microcirculatory hypoperfusion. Serologic markers of global inflammation, endothelial dysfunction similar to that of patients with septic shock, characterized by elevated profile of patients who have ROSC after cardiac arrest is very similar to that of those of a standard therapy group.34 Our study demonstrated that when compared to historic controls, patients treated with the PCAR protocol were given larger volumes of intravenous fluids, a similar amount of vasopressors, more inotropes and more vasodilators. These differences appear to reflect more attention to maintenance of optimal hemodynamic parameters in patients treated with the PCAR protocol. It is possible that the addition of hemodynamic optimization to TH during the immediate post-resuscitation phase helps to modulate the inflammatory response, decrease apoptosis, and minimize reperfusion injury. Further, by improving systemic oxygen delivery, EGDHO improves cerebral oxygen delivery, which may be central to improving outcomes post-arrest.35 In a subset of patients, EGDHO may be vasopressor-sparing, improving microvascular flow, and possibly contributing to improved survival.36

On the other hand, it is also possible that EGDHO had no positive impact on outcomes. In contrast to the “resuscitation opportunities” identified by Rivers’ group, which were corrected by EGDT (i.e. marked deficits in preload, afterload, and contractility...
leading to a deficit in global O₂ delivery), we observed less marked initial deviation from normal values for the measured hemodynamic parameters (CVP; MAP) and infrequent evidence of global tissue hypoxia (ScvO₂) requiring correction through transfusion or administration of an inotrope. Ongoing efforts at maintaining hemodynamic optimization continued throughout the period of induced TH, however. Indeed, at 24 h post-ROSC, 29% (5/17) of the patients remained on vasopressors, 38% (6/17) on inotropes, and 18% (3/17) on vasodilators. This suggests that the period of hemodynamic optimization opportunities extends beyond the initial 6 h of algorithmic resuscitation.

Limitations

This study was performed at a single, academic medical center with a dedicated research and clinical staff to assist in the identification, enrollment, and management of patients eligible for TH and post-arrest EGDHO and, therefore, these results may not be generalizable to other institutions with different infrastructures and available resources. In addition, while 18/20 (90.0%) of the patients who qualified for the protocol were enrolled, this still may have served as a selection bias; furthermore, since the patients who were not enrolled by the clinical staff at the time of their arrest were identified by retrospective chart review, patients may have been missed. Similar concerns apply to the historic control group. Further, historic charts had more missing data on vasopressors, fluid infusion, urine output, and other variables and only 8/18 (44.4%) had complete records in this regard. The small number of patients enrolled in the protocol—a reflection of the large number of hospitals in the Philadelphia area and the policy of Philadelphia Fire Rescue to transport cardiac arrest patients to the nearest hospital—does not power the study sufficiently for outcome results to reach statistical significance. Because of the before—after design employed in this study, other care issues changed in the same time period (including low tidal volume ventilator strategies; steroid therapy for relative adrenal insufficiency; and tight glucose control) and these may have contributed to our results. Along with these clinical changes, attitudes about survivability of these patients may have changed, impacting on outcomes by increasing the level of aggressiveness in care. Including more expeditious PCI, more attention to minute to minute clinical details, neurologic assessment, and 1:1 nursing. Further, the contribution of TH cannot be separated from that of EGDHO—it may be that EGDHO does not add to the mortality reduction and neurologic benefit achieved by TH alone. Finally, the 2005 AHA Guidelines changed several aspects of resuscitation technique, which may have had an impact on mortality outcome related to better quality CPR, not to improved post-resuscitation care.

Conclusions

Our study demonstrated that performance of EGDHO optimization combined with TH is feasible in comatose cardiac arrest survivors. Using an algorithmic protocol, both hemodynamic and temperature goals can be achieved in the majority of patients within 6 h of ED presentation. Future clinical trials are needed to determine if EGDHO combined with TH improves outcome compared to therapeutic hypothermia alone in comatose cardiac arrest survivors.

Conflict of Interest

Data collection and research assistants involved in the protocol were supported by an unrestricted research grant from Gaymar Industries (Orchard Park, New York). Study sponsors did not participate in subject recruitment, data collection, analysis, or preparation of this manuscript and did not review the manuscript prior to its submission. Dr. Gaieski has received consulting fees and honoraria from Gaymar Industries; Dr. Goyal has received consulting fees from Gaymar Industries and honoraria from Edwards Lifesciences; Dr. Abella has received honoraria from Gaymar Industries, Alsius Corp. and Medivance Corp. No author declares intellectual property or equity ownership conflicts of interest.

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