Clinical paper

The association between intra-arrest therapeutic hypothermia and return of spontaneous circulation among individuals experiencing out of hospital cardiac arrest

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ABSTRACT

Introduction: Therapeutic hypothermia has been shown to improve both mortality and neurologic outcomes following pulseless ventricular tachycardia and fibrillation. Animal data suggest intra-arrest induction of therapeutic hypothermia (IATH) improves frequency of return of spontaneous circulation (ROSC). Our objective was to evaluate the association between IATH and ROSC.

Methods: This was a retrospective analysis of individuals experiencing non-traumatic cardiac arrest in a large metropolitan area during a 12-month period. Six months into the study a prehospital IATH protocol was instituted whereby patients received 2000 ml of 4°C normal saline directly after obtaining IV/IO access. The main outcome variables were prehospital ROSC, survival to admission, and to discharge. A secondary analysis was conducted to assess the relationship between the quantity of cold saline infused and the likelihood of prehospital ROSC.

Results: 551 patients met inclusion criteria with all the elements available for data analysis. Rates of prehospital ROSC were 36.5% versus 26.9% (OR 1.83; 95% CI 1.19–2.81) in patients who received IATH versus normothermic resuscitation respectively. While the frequency of survival to hospital admission and discharge were increased among those receiving IATH, the differences did not reach statistical significance. The secondary analysis found a linear association between the amount of cold saline infused and the likelihood of prehospital ROSC.

Conclusion: The infusion of 4°C normal saline during the intra-arrest period may improve rate of ROSC even at low fluid volumes. Further study is required to determine if intra-arrest cooling has a beneficial effect on rates of ROSC, mortality, and neurologic function.

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1. Introduction

Therapeutic hypothermia improves mortality and functional neurologic outcomes in patients resuscitated from pulseless ventricular tachycardia and fibrillation (VT/VF).1,2 However, the optimal timing for inducing hypothermia remains uncertain. The post-resuscitation reperfusion injury evolves quickly and may be best attenuated by hypothermia induction immediately following return of spontaneous circulation (ROSC).3 Animal data suggest that intra-arrest induction of therapeutic hypothermia (IATH), or initiating cooling measures during resuscitation, improves rates of ROSC as well as neurologic outcome post-arrest.4-9

Early studies which demonstrated the efficacy of therapeutic hypothermia were associated with delays of 4–8 h from the time of ROSC to the initiation of cooling.1,2 More recent studies demonstrate that improved neurologic outcome is correlated with reduced time to goal temperature following ROSC.4,7,10 Thus, in an effort to reduce time to goal temperature, several studies have validated the safety of therapeutic hypothermia after successful prehospital ROSC by the rapid infusion of 21 of 4°C intravenous fluids.11,12 Patient temperature decreased an average of 1.2°C prior to hospital arrival when cooling was initiated following ROSC. The degree to which the patients were cooled was directly related to the amount of fluid infused prior to hospital arrival.

There may be another benefit to early therapeutic cooling. Animal data suggest that intra-arrest induction of therapeutic...
hypothermia (IATH) improves rates of ROSC from cardiac arrest.4–9 This is corroborated by a report describing an impressively high ROSC rate of 60.8% among patients receiving IATH.11 This was a higher frequency of ROSC than reported in similar patient groups.13 We are unaware of any clinical study that has evaluated the effect of IATH on ROSC. This study sought to investigate the association of IATH with the frequency of ROSC, survival to admission, and survival to discharge when compared to individuals who did not receive IATH. Based upon results from previous animal studies, it was hypothesized that IATH improves the rate of ROSC among individuals experiencing an out-of-hospital cardiac arrest.

2. Methods

This was a retrospective analysis of individuals experiencing an out-of-hospital cardiac arrest (OHCA) in a large metropolitan area from October 1st 2008 to September 30th 2009. This study was approved by the institutional review board of Carolinas Medical Center. The emergency medical service (EMS) system was a single-tier, all advanced life support service that incorporated a priority dispatch system and included basic life support first responders equipped with automatic external defibrillators. The call volume was approximately 90,000 during the study period. Patients were included in this study if they suffered a non-traumatic OHCA, and were ≥ 18 years of age. Patients were excluded from the study if they were pregnant, suffered arrest secondary to drowning, or if paramedics did not attempt resuscitation due to an active do not resuscitate order or obvious signs of death defined as lividity, rigor mortis, or any stage of decomposition.

During the study period cardiac arrest resuscitation followed the 2005 American Heart Association ACLS guidelines. On April 1, 2009, a prehospital therapeutic hypothermia protocol was initiated which stipulated that all patients experiencing non-traumatic OHCA were to receive 4°C normal saline immediately following intravenous or intraosseous (IV/IO) line placement for a maximum of 2000 ml. This protocol was developed and approved for implementation by the EMS agency’s Medical Control Board. Prehospital providers were trained in the protocol and refrigerators were mounted in each ambulance to maintain consistent temperatures for the IV fluids.

2.1. Variable description

The primary outcome variables were prehospital ROSC, survival to hospital admission, and survival to hospital discharge. Prehospital ROSC was obtained from EMS patient care reports and defined as a return of pulses during the resuscitation. Survival to hospital admission and discharge was determined by reviewing hospital medical records. Neurological status at the time of discharge was also collected and defined by the cerebral performance categories (CPC) score. CPC scores of 1 and 2 were considered a good outcome, while scores of 3, 4, and 5 were considered poor.14

The primary independent variable of interest was IATH. This was a dichotomous variable with patients classified as either receiving any IATH or no IATH. A secondary analysis also explored the quantity of chilled saline infused as a continuous variable. Other data collected included cardiac arrest characteristics including initial presenting rhythm classified as ventricular fibrillation or pulseless ventricular tachycardia (VF/VT) or non-VF/VT, whether or not the arrest was witnessed, and the occurrence of bystander CPR. Demographic information included race, gender, and age.

2.2. Data analysis

All data analyses were performed using Stata v 10.1 (College Station, TX) on an “as treated” basis since several patients did not receive IATH after protocol initiation. Cardiac arrest characteristics and demographic data were analyzed using counts, frequencies, means, and standard deviations. Where appropriate, tests for differences in population characteristics were performed using chi-squared analysis or t-tests. Primary data analysis focused on a two group comparison of receipt of IATH compared to the dichotomous outcome prehospital ROSC. Initially, univariate logistic regression was performed to estimate the measure of effect between the independent and outcome variables. The effect measure reported was the odds ratio (OR) and corresponding 95% confidence interval (CI). An adjusted OR was also calculated utilizing multivariable logistic regression in order to adjust for the potential cardiac arrest and demographic variables collected. Similar analyses were conducted for the outcome variables survival to hospital admission and discharge.

A secondary analysis was also conducted to assess the relationship between the amount of cold saline that was infused among individuals in the IATH group and the likelihood of obtaining prehospital ROSC. This analysis consisted of modeling a logistic regression model with a continuous independent variable indicating the amount of cold saline administered. Model output was then presented in a graph with model predicted ORs and 95% CI for each 50 ml interval of fluid from 0 to 1200 ml. A descriptive analysis of the plots of these data was conducted.

3. Results

During the study period 573 patients met inclusion criteria. Of those, 31 patients were excluded from analysis because of missing data. Of the remaining 542 (94.6%) patients, 208 (38.4%) patients received IATH while 334 (61.6%) did not.

Demographic and arrest characteristics of the study population are shown in Table 1. There were 119 (22.0%) patients who had an initial presenting rhythm of VF/VT and 290 (53.5%) patients had witnessed cardiac arrest by either a bystander or EMS personnel. There were no statistically significant differences between the two groups of patients related to demographic or arrest characteristics. Additionally, therapeutic hypothermia was utilized in hospital at a similar frequency regardless of the prehospital treatment (12.0% and 13.8%, p = 0.20). An average of 548 ml (SD = 428.8) of cold saline was administered to patients in the IATH group.

Overall, 166 (30.6%) patients had prehospital ROSC, 137 (25.3%) survived to hospital admission and 66 (12.2%) survived to hospital discharge, with 51 (9.4%) having a good neurological outcome. There were 76 (36.5%) patients who received IATH and had prehospital ROSC, compared to 90 (26.9%, p = 0.018) who did not receive IATH (Table 2). After controlling for potentially confounding arrest characteristics and demographic variables, patients who received IATH were 1.83 (95% CI 1.19–2.81) times more likely to experience prehospital ROSC than those who did not. While the frequency of survival to hospital admission and discharge was increased among those receiving IATH, the differences were not statistically significant.

A subgroup analysis of ROSC was conducted in order to compare a more homogenous population. The association between the outcome variables and treatment group stratified by initial cardiac rhythm is included in Table 3. This analysis indicated that in patients experiencing witnessed VF/VT and VF/VT arrest, the absolute difference between frequencies of ROSC between the two treatment groups was similar to the main analysis. However, we failed to have sufficient numbers to demonstrate statistical significance.
### Table 1
Study population demographics and arrest characteristics by receipt of cold fluids.

<table>
<thead>
<tr>
<th>Variable name</th>
<th>Total population</th>
<th>Normothermic</th>
<th>IATH&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, 95% confidence interval)</td>
<td>64.5 (63.0–66.0)</td>
<td>63.9 (62.0–65.7)</td>
<td>65.9 (63.6–68.2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>212 (39.1%)</td>
<td>127 (38.0%)</td>
<td>85 (40.9%)</td>
</tr>
<tr>
<td>Male</td>
<td>330 (60.9%)</td>
<td>207 (62.0%)</td>
<td>123 (59.1%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minority</td>
<td>264 (48.7%)</td>
<td>161 (48.2%)</td>
<td>103 (49.5%)</td>
</tr>
<tr>
<td>White</td>
<td>278 (51.3%)</td>
<td>173 (51.8%)</td>
<td>105 (50.5%)</td>
</tr>
<tr>
<td>Presenting rhythm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-VF/VT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>423 (78.0%)</td>
<td>259 (77.5%)</td>
<td>164 (78.8%)</td>
</tr>
<tr>
<td>VF/VT</td>
<td>119 (22.0%)</td>
<td>75 (22.5%)</td>
<td>44 (21.2%)</td>
</tr>
<tr>
<td>Witnessed arrest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>252 (46.5%)</td>
<td>148 (44.3%)</td>
<td>104 (50.0%)</td>
</tr>
<tr>
<td>Yes</td>
<td>290 (53.5%)</td>
<td>186 (55.7%)</td>
<td>104 (50.0%)</td>
</tr>
<tr>
<td>Bystander CPR&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>377 (69.6%)</td>
<td>232 (69.5%)</td>
<td>145 (69.7%)</td>
</tr>
<tr>
<td>Yes</td>
<td>165 (30.4%)</td>
<td>102 (30.5%)</td>
<td>63 (30.3%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> IATH = intra-arrest therapeutic hypothermia.
<sup>b</sup> VF/VT = ventricular fibrillation/ventricular tachycardia.
<sup>c</sup> CPR = cardio-pulmonary resuscitation.

### Table 3
Subgroup analysis of the frequency of ROSC by initial rhythm.

<table>
<thead>
<tr>
<th>IATH</th>
<th>Normothermic</th>
<th>Unadjusted OR&lt;sup&gt;a&lt;/sup&gt; (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witnessed VF/VT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>19 (63.3%)</td>
<td>34 (54.8%)</td>
</tr>
<tr>
<td>VF/VT</td>
<td>27 (61.4%)</td>
<td>40 (53.3%)</td>
</tr>
<tr>
<td>PEA/asystole</td>
<td>49 (29.9%)</td>
<td>50 (19.3%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> OR = odds ratio.
<sup>b</sup> VF/VT = ventricular fibrillation/ventricular.
<sup>c</sup> PEA = pulseless electrical activity.

### 3.1 Secondary analysis

A linear association was found between the amount of total chilled saline that was infused and the likelihood of obtaining prehospital ROSC (Fig. 1). This association may imply that any amount of chilled saline results in an increased likelihood of prehospital ROSC. While this is physiologically unlikely, further analysis of this association indicates that the likelihood of prehospital ROSC significantly changes twice along this curve. Fig. 1 demonstrates that 200 ml of chilled saline was the minimal quantity required for having a significantly increased likelihood of prehospital ROSC when compared to patients who received less than 50 ml of chilled saline. Furthermore, the likelihood of prehospital ROSC does not become statistically different from that seen at 200 ml until 700 ml of chilled saline had been infused.

![Fig. 1. Association between the amount of cold fluid infused and resultant increased likelihood of obtaining ROSC.](image)

### Table 2
Association between IATH and ROSC, survival to admission, and discharge.

<table>
<thead>
<tr>
<th>Prehospital ROSC&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yes</th>
<th>No</th>
<th>Unadjusted OR&lt;sup&gt;b&lt;/sup&gt; (95% confidence interval)</th>
<th>Adjusted&lt;sup&gt;d&lt;/sup&gt; OR (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normothermic</td>
<td>90 (26.9%)</td>
<td>244 (73.1%)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>IATH</td>
<td>76 (36.5%)</td>
<td>132 (63.5%)</td>
<td>1.56 (1.07–2.26)</td>
<td>1.83 (1.19–2.81)</td>
</tr>
<tr>
<td>Survival to admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normothermic</td>
<td>78 (23.4%)</td>
<td>256 (76.6%)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>IATH</td>
<td>59 (28.4%)</td>
<td>149 (71.6%)</td>
<td>1.30 (0.88–1.93)</td>
<td>1.50 (0.96–2.36)</td>
</tr>
<tr>
<td>Survival to discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normothermic</td>
<td>40 (12.0%)</td>
<td>294 (88.0%)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>IATH</td>
<td>26 (12.5%)</td>
<td>182 (87.5%)</td>
<td>1.05 (0.62–1.78)</td>
<td>1.03 (0.54–1.98)</td>
</tr>
</tbody>
</table>

<sup>a</sup> ROSC = return of spontaneous circulation.
<sup>b</sup> OR = odds ratio.
<sup>c</sup> OR adjusted for confounding variables age, gender, race, initial presenting rhythm, witnessed arrest, and bystander CPR.
<sup>d</sup> IATH = intra-arrest therapeutic hypothermia.

### 4. Discussion

This retrospective study demonstrated that routine initiation of 4°C normal saline during cardiac arrest was feasible in EMS practice and was associated with improved frequency of ROSC. We noted an increase in the frequency of ROSC following IATH regardless of initial rhythm. It is widely believed that the effectiveness of therapeutic hypothermia is secondary to the attenuation...
of the neuronal reperfusion/post-anoxic injury. However, cooling seems to have an independent effect upon the endocardium and myocardium. Although it is unlikely that 300 ml had a significant effect upon core body temperature, the likelihood of obtaining ROSC after 250–500 ml of 4 °C normal saline was 1.83 times higher compared to those who did not receive any cold fluid. One possible explanation for this phenomenon is that the potential beneficial effect is not related to core body temperature, but rather intra-cardiac temperature and subsequent effects on the endocardium and myocardium. Cold fluids returning directly to the heart may preferentially cool the myocardium, providing the beneficial effects even at very low infusion volumes. In essence, this small volume of cold saline primes the endocardium and myocardium, increasing the likelihood of successful ROSC. Obtaining ROSC quickly with the resulting decrease in time spent in a low flow circulation would have obvious downstream effects on both hospital mortality and neurologic function, independent of the effect of mild hypothermia in the post-arrest inflammatory state. Though we noted a trend towards these effects, we lacked sufficient power to demonstrate this difference. This represents a distinct shift in the manner in which therapeutic hypothermia is utilized in the patient suffering from cardiac arrest.

A further extrapolation of this line of reasoning would suggest that 4 °C normal saline may be used in a similar manner to our current intravenous ACLS medications. Current intra-arrest treatments do not obtain ROSC rates greater than those seen in our study with IATH. In 2009 Olasveengen et al. reported a 40% rate of ROSC in patients randomized to treatment with intravenous ACLS drugs versus 25% in those treated without intravenous drugs. The reported odds ratio for ROSC was 1.99 though no statistically significant difference was noted in rates of survival to discharge. In our study the odds ratio of ROSC with IATH, independent of the amount of fluid administered, was 1.83 (95% CI 1.19–2.81), however we saw an odds ratio of 2.4 (95% CI 1.41–4.24) in the subset of patients who received >700 ml of 4 °C normal saline.

It is unlikely that we significantly changed the patient’s core body temperature with the amount of fluid infused; however we did demonstrate a significant increase in pre-hospital ROSC following IATH. These results have been seen in animal models of cardiac arrest. Menegazzi et al. randomized pigs to either pre-treatment hypothermia, intra-arrest hypothermia, or normothermic resuscitation. VF was induced and the animals were left untreated for 8 min, after which mechanical cardiopulmonary resuscitation was begun. Rescue shocks were delivered after 13 min of VF. Mean temperature in the IATH group was 37.9 °C (±0.9) versus 37.8 °C (±0.9) in the normothermic group. ROSC rates were 86% versus 43% in the IATH and normothermic group respectively, leading to an odds ratio of approximately 2. Survival in the IATH group was 57% versus 36% in the normothermic group. Despite no difference in the core body temperature at the time of defibrillation, the IATH group demonstrated superior ROSC rates. Similar findings have been reported in other animal models. Several other methods of inducing therapeutic hypothermia have been described in animal models, some of which demonstrated a similar beneficial effect on ROSC.

Two measurement errors confounded our secondary analysis of fluid volumes. Our fluid volume measurements are based upon the volume infused as recorded in the electronic patient care report. These values tended to be estimates which were often rounded to the nearest easily reported number. The accuracy of these values is questionable. In addition, we do not know how much of the fluid was received prior to ROSC. We were only able to obtain the total amount of fluid infused prior to arrival at the Emergency Department. Thus it is possible a significant portion of the 4 °C normal saline was not given during the intra-arrest period.

Modeling of the dose response curve demonstrated a linear effect upon ROSC. For every 200 ml increase in 4 °C normal saline administered there was a resultant increase in the likelihood of ROSC of 1.20 (95% CI 1.07–1.33). We did not see a threshold effect, according to our regression analysis patients who received 10 ml of 4 °C normal saline were more likely to have pre-hospital ROSC than their cohorts. It is difficult to see how this could be plausible; we feel this is a result of the confounding measurement errors. The 95% confidence intervals of the regression analysis and those of the baseline rate of ROSC diverge around 200 ml. Due to the measurement error and large confidence intervals this effect plateaus and is not statistically different until 700 ml. This could represent thresholds of treatment, or, more specifically, starting doses of 4 °C normal saline for further study. Further prospective studies are required to determine the appropriate dose to improve ROSC.

There are several other limitations to this study. This was a retrospective study and was inherently subject to a number of biases which could influence our results. One potential factor biasing our results could be due to changing the protocol itself. By adding chilled saline to the protocol it is possible that the paramedics became more focused on the quality of care in the cardiac arrest patients. Similar to an observer bias, this could have resulted in improved CPR and ACLS with the resultant improvement in our outcomes. Surrogate measures of CPR and ACLS quality, duration of resuscitation efforts and the number of patients who qualified for termination of resuscitative efforts, were similar in the two groups. However, it remains possible that the quality of chest compressions improved, though this data was not captured in this analysis. Additionally, the previously mentioned measurement errors likely confound our study. It is plausible that our measurements were overestimates of the total fluid infused, an effect which would have tended to push our results towards the null.

Prehospital temperatures were also not recorded, so we assumed that the quantity of fluid infused caused a predictable decrease in core temperature. Prior studies have demonstrated the effectiveness of rapid infusion of 4 °C normal saline to decrease core body temperature. Studies performed by Bernard, and Kim et al have demonstrated an expected temperature decrease of 1.7–2.0 °C with infusion of 21 of fluid. Kim et al further demonstrated that in the pre-hospital setting patients receiving between 500 ml and 2000 ml of 4 °C normal saline have an average core body temperature decrease of 1.23 ± 1.09 °C. Core body temperature did not change significantly in those patients who received less than 500 ml of 4 °C normal saline. We did not record pre-hospital temperatures and so must assume that the quantity of fluid infused would cause a predictable decrease in core body temperature dependent upon the quantity of fluid infused. In our experience we were unable to infuse the total fluid bolus secondary to access failure, displacement of the intraosseous needle, slow drip rates through the IV/IO needle, and/or short transport times to the hospital. In this study the average amount of 4 °C normal saline infused was 548 ml in patients whom the protocol was initiated. Additionally we were unable to obtain data on the amount of fluid infused in the group who did not receive IATH, though paramedic protocols called for a normal saline bolus as part of the resuscitative effort. Though unlikely, it is possible that there was a difference in quantity of saline infused between the two groups. Further study is required to determine if these effects are real.

5. Conclusion

The infusion of 4 °C normal saline during the intra-arrest period may improve the frequency of return of spontaneous circulation even at fluid volumes unlikely to change core body temperature. Further study is required to determine if intra-arrest cooling has a
beneficial effect on rates of ROSC, as well as mortality and neurologic function.

Conflicts of interest statement

All authors report that they have no real or perceived conflicts of interest with individuals or organizations to disclose.

References