Original Research Article

Induction of Therapeutic Hypothermia During Out-of-Hospital Cardiac Arrest Using a Rapid Infusion of Cold Saline

The RINSE Trial (Rapid Infusion of Cold Normal Saline)

BACKGROUND: Patients successfully resuscitated by paramedics from out-of-hospital cardiac arrest often have severe neurologic injury. Laboratory and observational clinical reports have suggested that induction of therapeutic hypothermia during cardiopulmonary resuscitation (CPR) may improve neurologic outcomes. One technique for induction of mild therapeutic hypothermia during CPR is a rapid infusion of large-volume cold crystalloid fluid.

METHODS: In this multicenter, randomized, controlled trial we assigned adults with out-of-hospital cardiac arrest undergoing CPR to either a rapid intravenous infusion of up to 2 L of cold saline or standard care. The primary outcome measure was survival at hospital discharge; secondary end points included return of a spontaneous circulation. The trial was closed early (at 48% recruitment target) due to changes in temperature management at major receiving hospitals.

RESULTS: A total of 1198 patients were assigned to either therapeutic hypothermia during CPR (618 patients) or standard prehospital care (580 patients). Patients allocated to therapeutic hypothermia received a mean (SD) of 1193 (647) mL cold saline. For patients with an initial shockable cardiac rhythm, there was a decrease in the rate of return of a spontaneous circulation in patients who received cold saline compared with standard care (41.2% compared with 50.6%, \(P=0.03\)). Overall 10.2% of patients allocated to therapeutic hypothermia during CPR were alive at hospital discharge compared with 11.4% who received standard care (\(P=0.71\)).

CONCLUSIONS: In adults with out-of-hospital cardiac arrest, induction of mild therapeutic hypothermia using a rapid infusion of large-volume, intravenous cold saline during CPR may decrease the rate of return of a spontaneous circulation in patients with an initial shockable rhythm and produced no trend toward improved outcomes at hospital discharge.

Sudden out-of-hospital cardiac arrest (OHCA) is a common public health problem that affects approximately 360,000 patients per year in the United States. Although approximately half of patients receive an attempted resuscitation, only one-third of these achieve a return of spontaneous circulation (ROSC) and survival with good neurologic recovery is poor (≈6%). A major contributing cause of death or prolonged disability is hypoxic-ischemic neurologic injury.

One treatment for the neurologic injury in OHCA patients is therapeutic hypothermia. This is based on the findings of 2 clinical trials in which a temperature of 32°C to 34°C induced after hospital admission and maintained for 12 to 24 hours was compared with no temperature control. More recently, a study comparing induction of therapeutic hypothermia (33°C) with temperature controlled at 36°C for the first 24 hours after intensive care unit (ICU) admission found no difference in outcomes. Other studies examining the efficacy of earlier induction of therapeutic hypothermia using bolus, large volume, cold saline during transport to hospital also did not show improved outcomes.

However, laboratory and preliminary clinical studies have suggested that therapeutic hypothermia may be most effective when induced during cardiopulmonary resuscitation (CPR) rather than delayed until after ROSC. Intra-arrest induction of therapeutic hypothermia by paramedics is feasible using a rapid infusion of large-volume intravenous cold saline during cardiopulmonary resuscitation may cause harm in the subset of out-of-hospital cardiac arrest patients who present with shockable rhythm.

All patients had routine initial resuscitation treatment, including defibrillation for shockable rhythm, intravenous cannulation, administration of an initial dose of epinephrine and ventilation with 100% oxygen. If the patient remained in cardiac arrest after these procedures were
undertaken, an opaque envelope containing computer-generated random treatment allocation was opened. Patients then received either a rapid infusion of 30mL/kg cold saline (maximum 2 L) via a peripheral intravenous cannula, or continued standard care. The cold saline infusion was ceased if the tympanic temperature reached 33°C or if pulmonary edema was suspected (as indicated by the appearance of froth in the endotracheal tube or laryngeal mask airway).

Patients without shockable rhythm at any time who were in asystole after 30 minutes of resuscitation had cessation of resuscitation attempts and were not transported to the hospital. In some patients with refractory ventricular fibrillation or pulseless electric activity, transport to the hospital with CPR in progress was undertaken.

Patients with ROSC were transported to the nearest hospital with an emergency department and an ICU. At the time of commencement of the study, the standard care at most receiving hospitals for post cardiac arrest patients included thrombolysis or cardiac catheterization for ST-elevation myocardial infarction and a targeted temperature of 33°C in the ICU for the first 24 hours.

Outcomes
The primary outcome measure was survival at hospital discharge. Secondary outcome measures were the proportion of patients in shockable and nonshockable rhythms with ROSC, tympanic temperature in patients who arrived with ROSC at hospital, and discharge direction from hospital (directly to home, to a rehabilitation facility, to a nursing care facility, or deceased at hospital discharge).

Statistical Analysis
The target sample size was calculated using data from the Victorian Ambulance Cardiac Arrest Registry (VACAR). This Registry has data showing that patients who are in shockable rhythm on arrival of paramedics have a 40% rate of ROSC, and of these, 50% survive to hospital discharge, giving an overall survival rate of 20%. It was proposed that a rapid infusion of large-volume, cold IV saline would increase the rate of ROSC from 40% to 45%, and that very early therapeutic hypothermia would decrease neurologic injury and increase survival post ROSC from 50% to 60%, giving an overall survival rate of 27%.

Figure 1. Randomization, exclusions, and total patients who underwent evaluation in the study.
ADL indicates activity of daily living; EMS, emergency medical services; IV, intravenous; POM, primary outcome measure; and ROSC; return of spontaneous circulation.
With 80% power and a type 1 error of 0.05, the study required a sample size of 603 patients with an initial shockable rhythm in each arm (1206 in total).

Data from the VACAR also suggested that patients with an initial nonshockable rhythm represent 50% of patients with OHCA in whom resuscitation is commenced. These patients have a ROSC rate of 20% and, of these, 10% survive to hospital discharge, giving an overall survival rate of 2%. To demonstrate improved outcomes to 5% (an absolute difference of 3%) required 653 per group, a total of 1306 patients. Overall, the sample size of this study was planned to be 2512 patients. Data analysis was performed independently by a statistician who was blinded to the treatment allocation. Analysis of the primary outcome of survival to hospital discharge was performed using the χ² test. Additional binomial variables were expressed as proportions and 95% confidence intervals and groups compared by χ² tests or Fisher exact test. Variables that approximate a normal distribution were summarized as mean±standard deviation, and groups compared using t tests. Other continuous or ordinaly scaled variables were summarized as median±interquartile range, and groups compared using Mann-Whitney rank-sum tests. In a post hoc analysis of patients with a shockable rhythm, the impact of total fluid volume was examined using logistic regression. A standard score was calculated as the difference between the observed fluid volume and the mean fluid volume received divided by the standard deviation such that a 1 U increase corresponded to an increase in fluid volume of 1 standard deviation. All reported P values were 2-sided. The statistical software used was STATA (version 13.0, Stata Corporation, College Station, TX). The study analysis followed intention-to-treat methodology.

The study was stopped prior to the first planned interim analysis by the RINSE study (Rapid Infusion of Cold Normal Saline) Management Committee because a number of the receiving hospitals were changing their temperature management target in post cardiac arrest patients from 33°C to 36°C after publication of the Targeted Temperature Management trial.8

Ethics
The study was approved in each city by a Human Research Ethics Committee that provides oversight of the EMS and included waiver of informed consent. This approach is consistent with Australian National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007; see https://www.nhmrc.gov.au/guidelines-publications/e72). Information concerning the study was provided to surviving patients or next-of-kin by mail about 3 months after enrollment. Surviving patients or their next-of-kin could request that the patient’s data not be included in the study.

RESULTS
Patients and Interventions
The study was conducted between December 2010 and December 2014. The overall numbers of patients in cardiac arrest and who had resuscitation commenced by the 3 EMS during the study period are shown in Figure 1. There were 22775 patients in cardiac arrest on arrival of EMS of whom 11476 had resuscitation commenced. Of these, 1324 patients were randomized with 122 subsequently excluded from analysis due to meeting exclusion criteria. An additional 4 patients or their families requested patients data not be included in the study, leaving 1198 patients who underwent analysis for the primary

Table 1. Baseline Characteristics of the Patients*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intra-Arrest Cooling (n=618)</th>
<th>Standard Care (n=580)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y*</td>
<td>65.3±15.5</td>
<td>64.3±15.6</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>462 (74.8)</td>
<td>428 (73.8)</td>
</tr>
<tr>
<td>Characteristics of the cardiac arrest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bystander witnessed arrest, no. (%)</td>
<td>391 (63.3)</td>
<td>336 (57.9)</td>
</tr>
<tr>
<td>Bystander cardiopulmonary resuscitation performed, no. (%)</td>
<td>409 (66.2)</td>
<td>388 (66.9)</td>
</tr>
<tr>
<td>Location of arrest, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private residence</td>
<td>466 (75.4)</td>
<td>431 (74.3)</td>
</tr>
<tr>
<td>Public place</td>
<td>152 (24.6)</td>
<td>149 (25.7)</td>
</tr>
<tr>
<td>Presumed cause of arrest, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>599 (96.9)</td>
<td>557 (96.0)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>9 (1.5)</td>
<td>10 (1.7)</td>
</tr>
<tr>
<td>Drug overdose</td>
<td>10 (1.6)</td>
<td>13 (2.2)</td>
</tr>
<tr>
<td>Time from call to first paramedic arrival at patient, min</td>
<td>9.2±4.2</td>
<td>8.8±3.7</td>
</tr>
<tr>
<td>First monitored rhythm, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation/tachycardia</td>
<td>291 (47.1)</td>
<td>267 (46.0)</td>
</tr>
<tr>
<td>Asystole</td>
<td>203 (32.9)</td>
<td>190 (32.8)</td>
</tr>
<tr>
<td>Pulseless electric activity</td>
<td>120 (19.4)</td>
<td>119 (20.5)</td>
</tr>
<tr>
<td>Unknown rhythm (AED no shock advised)</td>
<td>4 (0.7)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Initial temperature, °C</td>
<td>35.9±0.9</td>
<td>35.8±0.9</td>
</tr>
<tr>
<td>Enrollment per site, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melbourne</td>
<td>316 (51.1)</td>
<td>312 (53.8)</td>
</tr>
<tr>
<td>Adelaide</td>
<td>164 (26.5)</td>
<td>154 (26.6)</td>
</tr>
<tr>
<td>Perth</td>
<td>138 (22.3)</td>
<td>114 (19.6)</td>
</tr>
</tbody>
</table>

*Means±SD.
AED indicates automatic external defibrillator.
end point with 618 allocated to intra-arrest therapeutic hypothermia and 580 allocated to standard prehospital resuscitation care.

The baseline characteristics of the eligible patients are shown in Table 1. This shows that the characteristics that are known to be associated with outcome such as EMS response time, performance of bystander CPR, age, sex, and initial cardiac rhythm were similar between the groups with \( P > 0.05 \) for all comparisons.

The treatments of the patients after allocation are shown in Table 2. Very few patients allocated to standard care received cold saline outside trial protocol. Patients allocated to intra-arrest cooling received larger total volumes of intravenous fluid, this also was seen when stratified by first monitored rhythm (nonshockable: 1213 mL±746 versus 918 mL±760, \( P < 0.001 \); shockable: 1568 mL±760 versus 1143 mL±725, \( P < 0.001 \)). Patients allocated to intra-arrest cooling also required a longer duration of CPR and additional epinephrine.

As seen in Table 3, there was a significant decrease in the numbers of patients with an initial shockable rhythm allocated to intra-arrest cold fluid who had ROSC at the scene (41.2% compared with 50.6%, \( P = 0.031 \)). We conducted a post hoc investigation of this latter finding, particularly to understand whether it could be explained by the treatment-induced disparity in fluid infusion volume. The unadjusted odds ratio (OR) of transport with ROSC for intra-arrest cooling versus standard care was 0.69 (95% CI, 0.49–0.96, \( P = 0.03 \)), and the corresponding OR for dying at the scene was 1.54 (95% CI, 1.09–2.17, \( P = 0.01 \)). Increasing total fluid volume received was associated with more frequent transport with ROSC (OR 1.46 per SD [773 mL]; 95% CI, 1.22–1.75, \( P < 0.001 \)). Adjustment for total fluid volume did not change the associations of intra-arrest cooling with transport with ROSC (OR 0.55; 95% CI, 0.38–0.79, \( P = 0.001 \)) or death at the scene substantially (OR 1.43; 95% CI, 1.00–2.04, \( P = 0.05 \)).

For patients with ROSC, the temperature was lower in the intra-arrest cooled group compared with the standard care group on arrival at hospital (34.7°C compared
with 35.4°C, \( P < 0.001 \). The patients allocated to intra-arrest cold fluid also had a higher rate of suspected pulmonary edema before or at arrival at hospital (10.0% compared with 4.5%, \( P < 0.001 \)).

**Patient Outcomes**

The outcomes at hospital discharge are shown in Table 4. Overall, there was no difference in outcomes between the groups. Of note, very few (3 out of 1198) patients were discharged to a nursing care facility. Figure 2 shows the outcomes in prespecified subgroups, and there were no significant differences in outcomes in any of these groups. In particular, despite the significant decrease in the rate of ROSC in patients with an initial shockable rhythm allocated to intra-arrest therapeutic hypothermia, there was no difference in overall outcomes in this subgroup at hospital discharge.

**DISCUSSION**

This large, multicenter study found that induction of mild therapeutic hypothermia using bolus large-volume, cold saline during CPR in patients with OHCA does not improve survival at hospital discharge when compared with standard prehospital care. Analysis of prespecified subgroups did not reveal any patient cohort that might benefit from intra-arrest cooling. An unexpected finding was a reduction in the rate of ROSC for patients with an initial shockable rhythm. An explanation for this may be that a rapid fluid administration leads to an increase in right atrial pressure that might decrease coronary artery perfusion pressure, and thus...
decrease myocardial perfusion. The fluid volume also may cause pulmonary edema that may not be apparent during CPR, but was seen in more patients allocated to intra-arrest cooling on arrival at hospital. It also is possible that ventricular fibrillation becomes less responsive to countershocks at a lower myocardial temperature; however, this is in contrast to a laboratory study that suggested that a lower myocardial temperature increased rather than decreased the rate of successful defibrillation.18 Our post hoc analysis of patients with an initial shockable rhythm that adjusted for total fluid volume suggests that the decrease in the rate of ROSC was due to peri-arrest cooling rather than the volume of fluid infused. However, given that this analysis was not prespecified, this data should be interpreted with caution. Another possible explanation for the decrease in ROSC rate in patients allocated to cold-saline infusion was that this intervention delayed other treatment, including subsequent defibrillation. This may be reflected in the longer time to ROSC in the intra-arrest cooling group.

Our finding that a bolus of cold saline is associated with a decrease in the rate of ROSC in patients with shockable rhythm is in contrast to a study by Garrett et al,15 in which 208 OHCA patients received 2 L of cold saline during CPR as soon as possible after obtaining IV or intraosseous access. In that before and after study, there was an increased rate of ROSC in the intra-arrest cooled patients compared with 334 patients during the previous 6 months who did not receive intra-arrest cold saline (36.5% versus 26.9%; OR 1.83; 95% CI, 1.19–2.81); however, outcomes at hospital discharge in that study were similar. A more recent study by Debaty et al14 prospectively allocated 245 OHCA patients to either an infusion of large-volume cold saline plus surface cooling during CPR or standard care. The primary outcome measure in their study was serum neuron-specific enolase concentration at 24 hours. The rate of patients admitted alive to hospital was similar between the intra-arrest cooled patients (33%) compared with hospital cooled patients (30%). In the intra-arrest cooled group, the time to reach a temperature ≤ 34°C was decreased by 75 minutes (95% CI, 4; 269), but there was no difference between the groups in the levels of neuron-specific enolase, or in survival at one month post resuscitation.

Our study did find that a rapid infusion of cold saline decreased tympanic temperature in patients with ROSC; however, this decrease was modest (mean 0.7°C) and it is uncertain whether such a small decrease in tempera-

### Table 4. Outcomes at Hospital Discharge

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intra-Arrest Cooling (n=618)</th>
<th>Standard Care (n=580)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome measure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival at hospital discharge, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>63 (10.2)</td>
<td>66 (11.4)</td>
<td>0.51</td>
</tr>
<tr>
<td>Non-shockable rhythm</td>
<td>8/327 (2.4)</td>
<td>4/313 (1.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>Shockable rhythm</td>
<td>55/291 (18.9)</td>
<td>62/267 (23.2)</td>
<td>0.21</td>
</tr>
<tr>
<td>Secondary outcome measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge destination, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>54 (8.7)</td>
<td>49 (8.4)</td>
<td>0.125</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>9 (1.5)</td>
<td>14 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Nursing care facility</td>
<td>0 (0.0)</td>
<td>3 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Survival to discharge in patients admitted to hospital,* no. (%)</td>
<td>63/304 (20.7)</td>
<td>66/317 (20.8)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

*Excludes patients who died at the scene.

![Figure 2. Subgroup analyses of the primary outcome measure.](http://circ.ahajournals.org/)

CPR indicates cardiopulmonary resuscitation.
ture would improve neurologic outcomes. Our study also found that bolus, large-volume cold saline increased the rate of pulmonary edema which also was seen in the study of post-ROSC cold fluid by Kim et al. In contrast to that study, we did not see an increase in the rate of rearrest prior to hospital arrival.

Our study was stopped early as many receiving hospitals advised that they were changing the target temperature in OHCA patients from 33°C to 36°C based on the findings from the Targeted Temperature Management trial. Given that there is laboratory evidence that rapid rewarming from therapeutic hypothermic levels may have an adverse effect on outcome, it was considered that such a major change in hospital practice during our study would make interpretation of the results in our study uncertain had it continued to enroll to the target number. Although it is possible that continuation of the trial to the target number might have shown a difference in outcomes at hospital discharge between the groups, it is highly unlikely that intra-arrest cooling using a rapid IV infusion of large-volume, cold saline would have been found to be beneficial with larger patient numbers given the significant decrease in the rate of ROSC that we observed in patients with an initial shockable rhythm.

Nevertheless, given the laboratory data supporting the efficacy of intra-arrest therapeutic hypothermia in the prevention of hypoxic-ischemic brain injury, clinical trials of other techniques of cooling in the prehospital setting should be considered including intranasal cooling using chilled gas, insertion of a cooled laryngeal mask airway, and surface cooling.

This trial has a number of limitations. First, paramedics and hospital staff were not blinded to the treatment allocation, and this could have resulted in bias in the making of treatment decisions.

Because our study did not collect data on interventions after hospital arrival, it is possible that patients in each group received different treatments during their inpatient stay. Second, tympanic temperature measurement may not reflect core temperature accurately; however, other more accurate techniques for core temperature measurement such as esophageal temperature generally are not available in road based EMS in Australia. Third, this trial enrolled only approximately 10% of all OHCA patients undergoing CPR. It was not feasible in this study to collect data on the reasons that patients in cardiac arrest were not eligible for enrollment or why those who may have been eligible for the study were not enrolled. Finally, the primary outcome measure of this trial was survival to hospital discharge and longer term functional outcomes may be a more robust measure of any treatment effect.

This trial has several strengths. It was a randomized, multicenter trial with allocation concealment, involving a substantial numbers of patients. Most patients allocated to cold-saline infusion received that treatment and very few patients allocated to standard care received cold saline. Patients were well matched at baseline and all enrolled patients were followed to the primary end point.

In summary, the results of this trial do not support the hypothesis that outcomes at hospital discharge of patients with OHCA can be improved by induction of mild therapeutic hypothermia during CPR using an intravenous bolus of large-volume, cold saline. Furthermore, our results suggest that this treatment decreases the rate of ROSC in patients with an initial shockable cardiac rhythm, although overall survival in that group was similar at hospital discharge. Given the compelling laboratory evidence that induction of mild therapeutic hypothermia during CPR is neuroprotective, additional studies of intra-arrest cooling will need to investigate alternate techniques other than bolus cold saline for induction of therapeutic hypothermia during CPR.

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DISCLOSURES

None.

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FOOTNOTES

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