

## Pilot Study of Rapid Infusion of 2 L of 4°C Normal Saline for Induction of Mild Hypothermia in Hospitalized, Comatose Survivors of Out-of-Hospital Cardiac Arrest

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**Background**—Recent clinical studies have demonstrated that mild hypothermia (32°C to 34°C) induced by surface cooling improves neurological outcome after resuscitation from out-of-hospital cardiac arrest. Results from animal models suggest that the effectiveness of mild hypothermia could be improved if initiated as soon as possible after return of spontaneous circulation. Infusion of cold, intravenous fluid has been proposed as a safe, effective, and inexpensive technique to induce mild hypothermia after cardiac arrest.

**Methods and Results**—In 17 hospitalized survivors of out-of-hospital cardiac arrest, we determined the effect on temperature and hemodynamics of infusing 2 L of 4°C cold, normal saline during 20 to 30 minutes into a peripheral vein with a high-pressure bag. Data on vital signs, electrolytes, arterial blood gases, and coagulation were collected before and after fluid infusion. Cardiac function was assessed by transthoracic echocardiography before fluid administration and 1 hour after infusion. Passive (fans, leaving patient uncovered) or active (cooling blankets, neuromuscular blockade) cooling measures were used to maintain mild hypothermia for 24 hours. Infusion of 2 L of 4°C cold, normal saline resulted in a mean temperature drop of 1.4°C 30 minutes after the initiation of infusion. Rapid infusion of fluid was not associated with clinically important changes in vital signs, electrolytes, arterial blood gases, or coagulation parameters. The initial mean ejection fraction was 34%, and fluid infusion did not affect ejection fraction or increase central venous pressure, pulmonary pressures, or left atrial filling pressures as assessed by echocardiography. Passive measures were ineffective in maintaining hypothermia compared with active measures.

**Conclusions**—Infusion of 2 L of 4°C cold, normal saline is safe and effective in rapidly lowering body temperature in survivors of out-of-hospital cardiac arrest. (*Circulation*. 2005;112:715-719.)

**Key Words:** cardiopulmonary resuscitation ■ hypothermia ■ heart arrest ■ echocardiography

After cardiac arrest, brain injury is a major source of morbidity and mortality. The majority of patients who are resuscitated from cardiac arrest never awaken.<sup>1-4</sup> Despite delays in its initiation of 4 to 8 hours, mild (32°C to 34°C) hypothermia in hospitalized survivors of ventricular fibrillation has been shown to improve neurological recovery and survival.<sup>5,6</sup> Mild hypothermia was achieved in those studies with the use of special cooling blankets, neuromuscular blockade, and sedation for a period of up to 24 hours. On the basis of these studies, the International Liaison Committee on Resuscitation currently recommends that all hospitalized survivors of ventricular fibrillation be cooled to 32°C to 34°C for 12 to 24 hours; however, no cooling method was specified.<sup>7,8</sup> Cooling for other rhythms in out-of-hospital cardiac arrest was considered to be possibly beneficial by the International Liaison Committee on Resuscitation.

Results from animal models suggest that the effectiveness of mild hypothermia could be improved if initiated as soon as possible after return of spontaneous circulation.<sup>9,10</sup> Bernard<sup>11</sup> and Bernard et al<sup>12</sup> have hypothesized that early initiation of rapid cooling, preferably in the field soon after return of spontaneous circulation, will have the maximum benefit in both neurological outcome and survival. Several methods have been proposed to induce rapid hypothermia, including the use of cooling blankets, placement of intravascular heat exchange catheters, and cooling helmets.<sup>13-15</sup> Each has limitations, especially for use outside the hospital setting.

Infusion of 4°C cold, normal saline is an attractive option because it would be easy to initiate in the field after the return of spontaneous circulation. In healthy volunteers who underwent general anesthesia and neuromuscular blockade with vecuronium, a 30-minute infusion of 4°C fluid reduced core

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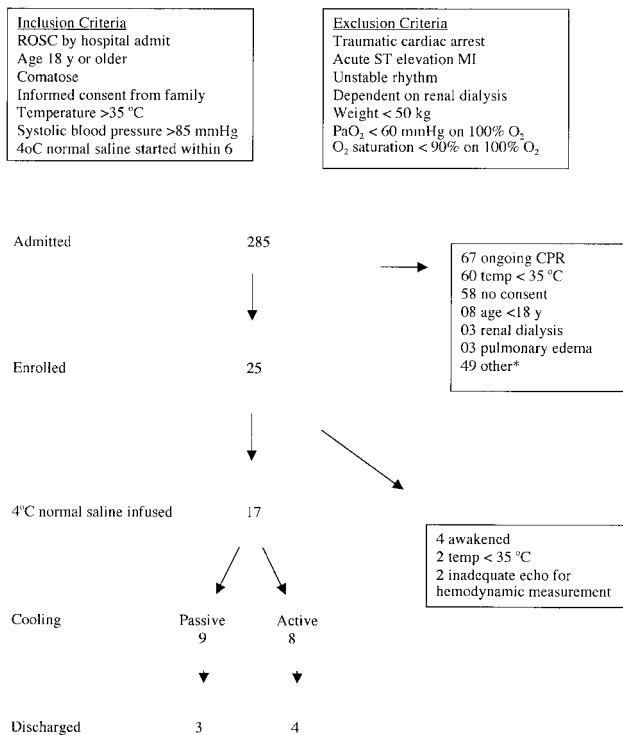
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**Figure 1.** Flow diagram describing number of patients screened, enrolled, receiving 4°C normal saline, receiving passive or active cooling, and discharged. ROSC indicates return of spontaneous circulation; MI, myocardial infarction; and CPR, cardiopulmonary resuscitation. \*Time >6 hours, study team not notified, family not approached.

temperature by 2.5°C within an hour after the infusion was started.<sup>16</sup> In a pilot study of ice-cold lactated Ringer's solution, 22 resuscitated cardiac arrest patients were cooled by 1.7°C.<sup>12</sup> These patients all received neuromuscular blockade before infusion of cold fluid. Before beginning a trial in the field, we conducted a pilot study of survivors hospitalized after out-of-hospital cardiac arrest, with the intent of establishing whether induction of mild hypothermia by rapid infusion of 4°C normal saline is simple, effective, and safe enough to justify further study of its use by paramedics.

## Methods

The University of Washington Human Subjects Committee reviewed and approved this pilot study, and consent for participation was always obtained from a legal next of kin. Patients were eligible if they were 18 years and older; resuscitated by paramedics from out-of-hospital cardiac arrest and transported to Harborview Medical Center; and still unconscious at the time the infusion was initiated. A full listing of inclusion and exclusion criteria is provided in Figure 1. Except for trauma, all causes of cardiac arrest, such as ventricular fibrillation, asystole, and pulseless electrical activity, were included. Patients meeting all of the eligibility criteria listed in Figure 1 underwent rapid infusion of 2 L of 4°C cold, normal saline. One-liter bags of normal saline were stored in a 4°C refrigerator before use. Each liter was rapidly infused into an 18-gauge peripheral intravenous line placed in the arm. Two liters of 4°C normal saline were infused during a period of 20 to 30 minutes with an intravenous pressure bag inflated to 300 mm Hg. We did not adjust the amount of 4°C normal saline to body weight but did exclude patients whose weight was <50 kg. All patients received intravenous midazolam (1

to 2 mg/h) for sedation before initiation of cold fluid and during the course of the study.

Baseline vital signs, including temperature measured by esophageal probes, were obtained before the infusion. Temperature was measured every 15 minutes for the first hour and then hourly for a total of 12 hours. Blood pressure and heart rate were measured hourly for a total of 12 hours. Baseline laboratory tests included sodium, potassium, chloride, blood urea nitrogen, creatinine, glucose, hematocrit, white blood cell count, platelet count, and international normalized ratio and were repeated 1 hour after infusion of 4°C normal saline.

Cardiac hemodynamic information was obtained by transthoracic echocardiography, which was completed before fluid administration and 1 hour after completion of the 4°C normal saline infusion. From a standard apical, 4-chamber view, the mitral E and A wave velocities and tissue Doppler E' velocity were measured. Using these values, we estimated left atrial filling pressures. When the ratio of E to E' was <8, left atrial pressure was considered normal, and when the E/E' ratio was >15, left atrial pressure was considered high (>12 mm Hg).<sup>17,18</sup> Central venous pressures were estimated from evaluation of inferior vena cava size, and pulmonary artery pressures were estimated from the velocity of tricuspid regurgitation and central venous pressure estimates. Left ventricular systolic function was assessed in standard views, and an ejection fraction (EF) was traced and measured with the apical biplane method of disks.

After infusion of 4°C normal saline, the first 9 patients received passive cooling, which included use of fans, leaving the patients uncovered, and lowering the ambient room temperature. Passive cooling measures were the recommended procedure in hospitalized cardiac arrest patients at Harborview Medical Center since November 2001. Because it became apparent that passive measures were ineffective in maintaining mild hypothermia, the original study protocol was modified after approval by the University of Washington Human Subjects Committee. Modifications included the use of active cooling by neuromuscular blockade with intravenous vecuronium (loading dose of 0.1 mg/kg followed by an infusion of 1 to 4 mg/h) before the start of the 4°C normal saline infusion and the application of cooling blankets, which was started at the end of the 4°C fluid infusion. The modified active cooling measures were used on the final 8 patients. Passive or active means were used for 24 hours after the cardiac arrest event, after which the patients were allowed to rewarm passively. Hospital discharge records were analyzed to determine whether the patient died or was discharged from the hospital.

Differences were analyzed by the Wilcoxon rank test with use of the SPSS statistical software package (version 11). Two-tailed, paired tests were performed, and the significance level was set at 0.05. All values presented are mean±SD.

## Results

A total of 285 survivors of out-of-hospital cardiac arrest were brought to the Emergency Department at Harborview Medical Center between December 2001 and April 2004. Recruitment was challenging for several reasons, as summarized in Figure 1, and only 25 were enrolled in the study, with 17 completing the infusion of 4°C normal saline. The cooling protocol was started within 6 hours after admission to the hospital. The average age of the enrolled patients was 54.4±10.6 years, and the average weight was 81.5±21.7 kg (range, 51 to 131). Baseline characteristics of the 17 patients who completed the infusion of 4°C normal saline are presented in Table 1.

## Temperature Data

Temperature data were collected for both the passive and active cooling groups for the first 12 hours; the average starting temperature was 36.2±0.9°C in the passive group

**TABLE 1. Characteristics of Patients Who Received 4°C Normal Saline (n=17)**

Average age, y	53.1±10.8
Sex (male), %	71
Weight, kg	82.4±24
Presenting rhythm (number discharged alive)	
Ventricular fibrillation	13 (7)
Asystole	2 (0)
Pulseless electrical activity	2 (0)

Values are mean±SD, percentage, or n (%).

and 35.4±0.7°C in the active group. The mean temperature difference between the starting temperature (time=0) and temperature at different time points was calculated for both groups, and these data are shown in Figure 2A. Midazolam with or without vecuronium was given before time 0 as indicated in the figure, and fluid was given during the first 20 to 30 minutes. Passive cooling measures or cooling blankets were placed at the end of fluid administration.

Temperature data for the first 8 hours after intravenous cooling are shown in Figure 2B. The active cooling group experienced a decline in temperature of -1.7°C, and the passive cooling group experienced a decline of -1.1°C within the first 30 minutes. The passive cooling group, however, exhibited rewarming despite the passive cooling measures and within 60 to 90 minutes after the initiation of 4°C normal saline achieved a mean temperature of >35°C. Only 1 of 9 patients who received passive measures was able

maintain temperatures of <34°C for the 12-hour period. On the other hand, 7 of the 8 in the active cooling group maintained a mean temperature <34°C during the entire 12-hour period.

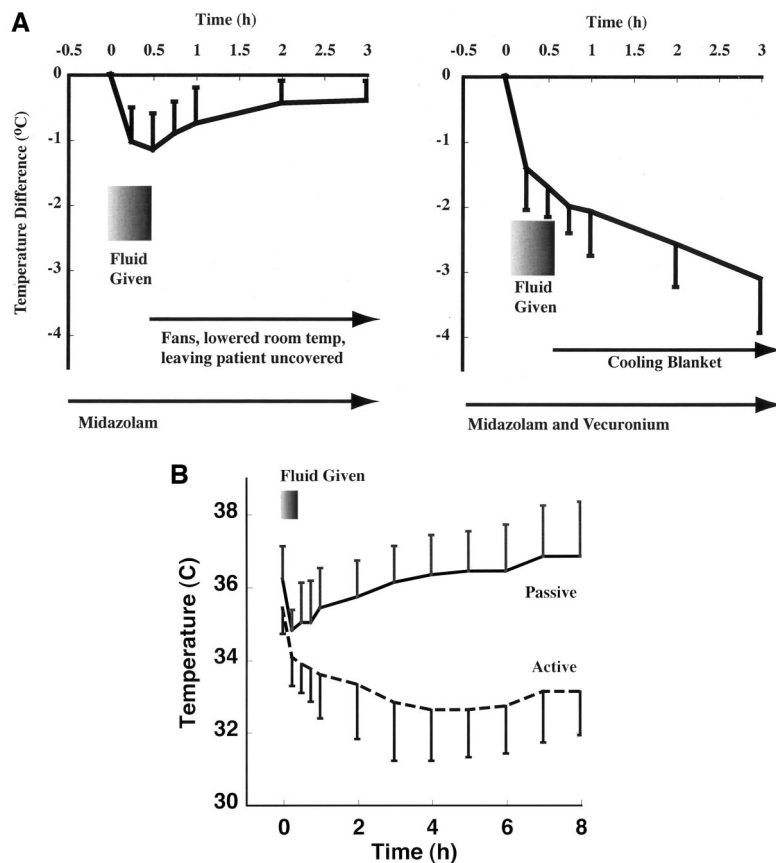
In Figure 3, the mean systolic and diastolic blood pressures and heart rates are plotted; these show no significant changes for the 12 hours after infusion of 4°C normal saline. None of the patients required pressors to maintain blood pressure.

### Laboratory Data

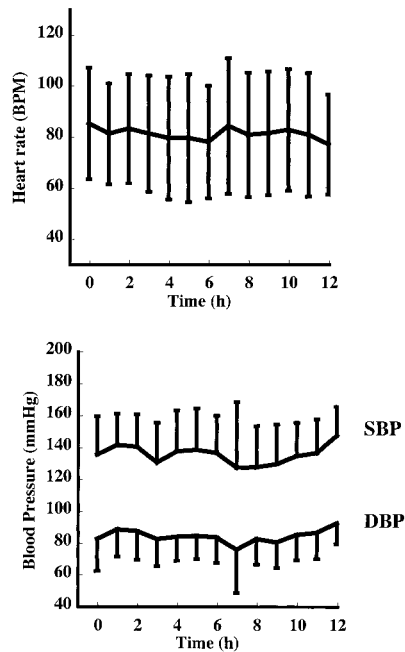
A total of 15 laboratory values were compared at baseline and at 1 hour after infusion of 4°C normal saline (Table 2). Several statistically significant differences were noted, but none of the laboratory changes was judged clinically important. Serum creatinine levels improved after 4°C normal saline. The significant decrease in PaO<sub>2</sub> levels reflects a decrease in inspired O<sub>2</sub> levels in these mechanically ventilated patients, and PaO<sub>2</sub> levels were well above normal. Significant changes in hematologic or coagulation tests were lacking.

### Echocardiogram Data

A total of 21 patients underwent a baseline study, and 17 patients underwent both the baseline and a follow-up study. Echocardiographic data are presented in Table 3 and Figure 4. The mean baseline EF was moderately reduced, at 34±18.6%, and the mean follow-up EF was 39.6±20.6%, a difference that was not significant. One patient had a calculated EF of 9%, and the infusion of 4°C normal saline did not result in changes in oxygenation or significant changes in



**Figure 2.** Temperature curves in response to infusion of 4°C normal saline in patients resuscitated from out-of-hospital cardiac arrest and admitted to hospital. A, Mean temperature differences between starting temperature and temperature at different time points were calculated (error bars represent SD). Patients received midazolam and/or vecuronium before start of cold intravenous fluid. Time=0 represents time when cold intravenous fluid was started. B, Temperature curves of patients after infusion of 2 L of 4°C normal saline, which was infused at time=0. Each point represents mean temperature, and error bars represent SD.



**Figure 3.** Mean heart rate and blood pressure after infusion of 2 L of 4°C normal saline. A, Mean heart rate ( $\pm$ SD) of 17 patients receiving 4°C normal saline. B, Mean systolic (SBP) and diastolic (DBP) blood pressure ( $\pm$ SD). Cold, normal saline was infused at time=0 and was completed within first 30 minutes.

pulmonary artery pressure estimates. The baseline mean E/E' ratio was 9.1, and after infusion, the ratio was 7.4, indicating that average left atrial pressure improved after 4°C normal saline, a difference that was not significant. The pulmonary artery pressure and central venous pressure showed mild elevations at baseline without significant change 1 hour after 4°C normal saline.

Of the 17 patients who received 4°C normal saline, 7 (41%) survived until discharge from the hospital. All of the survivors had ventricular fibrillation as their initial rhythm.

**TABLE 2. Laboratory Values**

Measure	Baseline	1 Hour After Infusion	<i>P</i> , Baseline vs
			1 Hour After Infusion
Sodium, mmol/L	137 $\pm$ 4.2	138 $\pm$ 4.1	0.35
Potassium, mmol/L	3.97 $\pm$ 1	3.56 $\pm$ 0.62	0.013
Chloride, mmol/L	98 $\pm$ 5.3	105.5 $\pm$ 4.4	<0.0001
CO <sub>2</sub> , mmol/L	20.8 $\pm$ 4.1	20.7 $\pm$ 3.2	0.90
Glucose, mmol/L	14.2 $\pm$ 4.5	10.9 $\pm$ 3.3	0.035
Urea nitrogen, mmol/L	9.0 $\pm$ 8.2	8.8 $\pm$ 7.8	0.30
Creatinine, $\mu$ mol/L	150.3 $\pm$ 61.9	114.9 $\pm$ 61.9	<0.0001
White blood cells, $\times 10^3/\text{mm}^3$	12.4 $\pm$ 4.6	14.8 $\pm$ 3.6	0.15
Hematocrit, %	39.1 $\pm$ 6.1	38.2 $\pm$ 6.9	0.06
Platelet count per microliter	255 $\pm$ 94.3	224 $\pm$ 88.0	0.020
Prothrombin time, s	15.3 $\pm$ 3.2	15.5 $\pm$ 2.6	0.012
International normalized ratio	1.18 $\pm$ 0.3	1.21 $\pm$ 0.3	0.08
pH	7.28 $\pm$ 0.16	7.37 $\pm$ 0.06	0.042
PaO <sub>2</sub> , mm Hg	323 $\pm$ 159	185 $\pm$ 96	<0.0001
PacO <sub>2</sub> , mm Hg	41.9 $\pm$ 16.6	32.9 $\pm$ 8.2	0.10

**TABLE 3. Echocardiographic Measurements**

	Baseline	1 Hour After Infusion	<i>P</i>
EF, %	34.1 $\pm$ 18.6	39.6 $\pm$ 20.6	0.09
E/E'	9.1 $\pm$ 6	7.4 $\pm$ 3.4	0.11
Pulmonary artery pressure, mm Hg	36.2 $\pm$ 15	34.0 $\pm$ 14	0.74
Central venous pressure, mm Hg	8.9 $\pm$ 5.9	8.4 $\pm$ 5.4	0.7

## Discussion

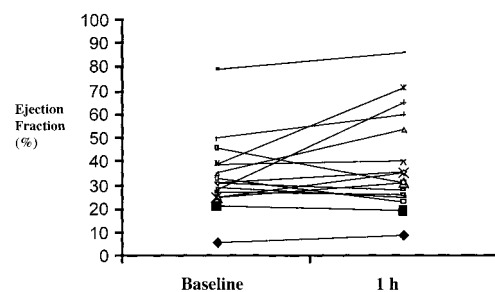
In this study, we have demonstrated that rapid delivery of 2 L of 4°C normal saline in resuscitated cardiac arrest patients was not associated with adverse hemodynamic parameters as measured by standard echocardiography.

## Echocardiographic Observations

A major concern at the beginning of this study was the effect of infusing a large volume of fluid in a resuscitated cardiac arrest patient and the possibility of pulmonary edema. Information on left ventricular systolic function during the first several hours after resuscitation is limited; however, it was suspected that overall left ventricular function might be reduced. In this study, an echocardiographic examination showed that the mean EF of hospitalized cardiac arrest patients was moderately reduced and did not change significantly after fluid administration. Estimates of left atrial, pulmonary artery, and central venous pressures did not significantly change after fluid administration. None of the 17 patients developed echocardiographic changes suggestive of fluid overload or required doses of diuretics. In these 17 patients, the mean EF before infusion was reduced; however, infusion of 2 L of cold fluid did not worsen cardiac hemodynamics.

## Use of Cold, Normal Saline Is Effective

The advantage of using an infusion of cold fluid is the rapidity in which temperature declines. Both the active and passive treatment groups demonstrated a temperature drop in response to 4°C normal saline:  $-1.7^\circ\text{C}$  for the active group and  $-1.1^\circ\text{C}$  for the passive group at 30 minutes. The difference in mean temperature drop between the 2 groups is likely a result of the use of vecuronium. The active group received vecuronium and midazolam before 4°C normal saline, whereas the passive group received midazolam only. The cooling blanket probably did not have a significant effect



**Figure 4.** Plot of EF as measured by 2D echocardiography for 17 patients at baseline and at 1 hour after infusion of 2 L 4°C normal saline.

on the temperature drop because the blankets were started after the infusion. This finding suggests that neuromuscular blockade augments the effect of 4°C normal saline and is probably required in a cooling protocol. Our long-range goals include using 4°C intravenous cooling by paramedics in the field; however, one potential limitation of this method is that neuromuscular blockade is often unavailable to paramedics.

The drop in temperature as a result of infusion of cold, normal saline is similar to previously published reports. Rajek et al<sup>16</sup> studied the effects of infusion of 40 mL/kg normal 4°C saline solution administered during 30 minutes in 9 anesthetized volunteers who received vecuronium and demonstrated a mean temperature decrease of 2.5°C. Similar results have been demonstrated in elective surgical patients; however, results in healthy, volunteer surgical patients or young volunteers may not be applicable to those with out-of-hospital cardiac arrest. Bernard et al,<sup>12</sup> in a study of 22 resuscitated cardiac arrest patients, observed a 1.7°C decrease after infusion of cold, lactated Ringer's solution (30 mL/kg) administered during 30 minutes. In all of these studies, neuromuscular blockade was used to augment the effects of infusing cold fluid.

We chose to use 2 L as a standard dose instead of a weight-based regimen because we are currently interested in developing an easily managed protocol for treatment of out-of-hospital cardiac arrest patients in the field. The use of cooling fluids appears to offer the advantage of a quick decrease in temperature with minimal risk to the patient. Yet to be determined is whether such early initiation of cooling fluids will enhance survival and the neurological benefit that have been demonstrated with the use of cooling blankets in hospitalized patients who experienced out-of-hospital cardiac arrest.

Finally, although mild hypothermia has been shown to improve neurological outcome and survival, this practice has not gained widespread use in the hospital.<sup>19</sup> One reason cited is that cooling methods were technically too difficult or too slow. The results of our pilot study demonstrate that intravenous cooling may be a quick, effective, and safe means of cooling hospitalized cardiac arrest patients.

### Limitations

This study has a number of limitations. There was no control group with which to compare changes in temperature, serum electrolytes, or echocardiographic parameters. However, in previous studies, temperatures of patients who were not actively cooled did not decrease spontaneously.<sup>5,6</sup> Improvement or changes in serum electrolytes may have occurred despite the induction of mild hypothermia with cold, normal saline. Nevertheless, the results from this pilot study are important because they demonstrate no significant harm in using cold, normal saline for induction of mild hypothermia. To our knowledge, no published series exist describing echocardiographic studies of hospitalized, out-of-hospital cardiac arrest patients. Again, hemodynamic parameters may have changed despite the administration of fluid; however, the important finding from this study is that no adverse hemodynamic effects were detected.

We conclude that infusion of 4°C normal saline appears to be safe and effective for induction of mild hypothermia in

hospitalized, out-of-hospital cardiac arrest survivors. Administration of cold fluid was not associated with adverse effects on blood pressure, heart rate, or cardiac hemodynamics, as assessed by limited transthoracic echocardiography.

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