

# Induction of hypothermia in patients with various types of neurologic injury with use of large volumes of ice-cold intravenous fluid\*

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**Objective:** Mounting evidence suggests that mild to moderate hypothermia can mitigate neurologic and myocardial injury. The speed of induction appears to be a key factor in determining its efficacy. However, even when the fastest currently available cooling techniques are used, reaching target temperatures takes at least 2 hrs and usually longer. We hypothesized that infusion of refrigerated fluids could be a safe accessory method to increase cooling speed.

**Design:** Prospective intervention study.

**Setting:** University teaching hospital.

**Patients:** One hundred thirty-four patients with various types of neurologic injury (postanoxic encephalopathy, subarachnoid hemorrhage, or traumatic brain injury).

**Measurements and Main Results:** Hypothermia was induced in 134 patients with various types of neurologic injury, by means ice-water cooling blankets and infusion of refrigerated (4°C) saline (110 patients) or saline and colloids (24 patients). An average volume of  $2340 \pm 890$  mL of refrigerated fluids was infused in 50 mins. Core temperatures decreased from  $36.9 \pm 1.9^\circ\text{C}$  to  $34.6 \pm 1.5^\circ\text{C}$  at  $t = 30$  mins and to  $32.9 \pm 0.9^\circ\text{C}$  at  $t =$

60 mins (target temperature:  $32^\circ\text{C}$ – $33^\circ\text{C}$ ). Monitoring of blood pressure, heart rhythm, central venous pressure, blood gasses, electrolyte and glucose levels, and platelet and white blood cell count revealed no additional adverse effects. Mean arterial pressure increased by 15 mm Hg, with larger increases in blood pressure occurring in hemodynamically unstable patients. No patient developed pulmonary edema.

**Conclusions:** Induction of hypothermia by means of cold-fluid infusion combined with ice-water cooling blankets is safe, efficacious, and quick. Because the speed of cooling is important to increase its protective effects, we recommend that cold-fluid infusion be used in all patients treated with induced hypothermia. This should be combined with another method to safely and accurately maintain hypothermia once target temperatures have been reached. (*Crit Care Med* 2005; 33:2744–2751)

**KEY WORDS:** therapeutic hypothermia; neurologic injury; myocardial injury; cardiac arrest; cardiopulmonary resuscitation; traumatic brain injury; refrigerated fluids; intracranial pressure; side effects

Induced (therapeutic) hypothermia is being used with increasing frequency as a method to prevent or mitigate various types of neurologic injury. Potential indications include postanoxic coma following cardiac arrest, severe traumatic brain injury, different types of stroke, and prevention of fever in patients with neurologic injuries (1). Currently, its most widely accepted application is in patients who remain comatose after cardiac arrest. Three randomized controlled trials have been performed (2–4), two of which have demonstrated significant improvements in

neurologic outcome for patients with witnessed arrests and an initial rhythm of ventricular fibrillation or ventricular tachycardia in patients treated with hypothermia (2–3). A recently published meta-analysis concluded that the number-needed-to-treat to allow one additional patient to leave the hospital with favorable neurologic recovery was six, with a 95% confidence interval of 4–13 (5). Preliminary evidence suggests that there may be benefits regardless of the initial rhythm (6). The most recent guidelines from the International Liaison Committee on Resuscitation recommend using hypothermia following cardiac arrest if the initial rhythm was ventricular tachycardia or ventricular fibrillation and recommend considering its use for other rhythm disturbances (7).

Although hypothermia may have beneficial effects even when applied many hours after injury (3), it seems likely that the speed of cooling will be an important factor determining its potential benefits.

Animal studies suggest that there is a limited time window, beyond which the protective effects of hypothermia decrease significantly (8–10); the length of this window will depend on which destructive mechanisms are activated and the relative contribution of these mechanisms (neuroexcitotoxic cascade activation, reperfusion, inflammation, apoptosis, etc.) to the overall injury (1, 11).

Induced hypothermia has also been used in animal experiments and small clinical studies to reduce infarct size following myocardial infarction and reperfusion (1, 12–20). A pilot study of patients with acute myocardial infarction suggested that lowering body temperature to  $<35^\circ\text{C}$  before percutaneous coronary intervention was associated with a decrease in infarct size (20). These observations have led to the initiation of larger follow-up studies, one of which (the COOL-myocardial infarction study) was recently completed (21). An important problem encountered in all of these studies was

\*See also p. 2844.

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Table 1. Characteristics of the patients and effects of cold-fluid infusion

Characteristic	Mean $\pm$ SD (Range) or n
Number of patients	
Total	134
CPR	61
TBI	16
SAH	34
Other <sup>a</sup>	9
Age, yrs	49.6 $\pm$ 21.2 (17–80)
APACHE II score	21.2 $\pm$ 7.2 (12–42)
Without cardiac shock, cooled with surface cooling and saline only (n = 100)	
Total volume infused, mL	2340 $\pm$ 890
Core temperature, °C	
Before cooling	36.9 $\pm$ 1.9
At 30 mins	34.6 $\pm$ 1.5
At 60 mins	32.9 $\pm$ 0.9
Patients without cardiac shock, cooled with surface cooling and infusion of saline and geloplasma (n = 20)	
Total volume infused, mL	2390 $\pm$ 740
Sodium 0.9%	1680 $\pm$ 630
Geloplasma	710 $\pm$ 150
Core temperature, °C	
Before cooling	37.2 $\pm$ 1.9
At 30 mins	34.4 $\pm$ 1.3
At 60 mins	33.2 $\pm$ 0.8
Patients with cardiac shock, cooled with surface cooling and saline only (n = 10)	
Total volume infused, mL	1780 $\pm$ 440
Core temperature, °C	
Before cooling	36.8 $\pm$ 2.1
At 30 mins	35.2 $\pm$ 1.7
At 60 mins	34.2 $\pm$ 1.2
At 120 mins	33.1 $\pm$ 0.9

CPR, cardiopulmonary resuscitation; TBI, traumatic brain injury; SAH, subarachnoid hemorrhage; APACHE, Acute Physiology and Chronic Health Evaluation.

<sup>a</sup>Post-asphyxia without cardiac arrest (n = 6), hepatic coma with intracranial hypertension (n = 1), severe ischemic stroke with intracranial hypertension (n = 2), hypoxia due to severe and intractable acute respiratory distress syndrome (n = 1).

the difficulty of quickly lowering body temperature. Indeed, in the COOL-myocardial infarction study a large majority of patients failed to reach the target temperature of  $<35^{\circ}\text{C}$  before percutaneous coronary intervention. On subsequent analysis no differences in average infarct size were observed in the overall group, but infarct size was smaller in patients in whom a temperature  $\leq 35^{\circ}\text{C}$  had been achieved before the percutaneous coronary intervention procedure (21). Although these observations should be interpreted with some caution, they suggest that benefits could be obtained if body temperatures could be lowered more quickly.

All this implies that methods to lower body temperatures quickly, safely, and reliably and to subsequently maintain these temperatures at the desired level for prolonged periods of time are urgently required. Methods to induce hypothermia can be broadly divided into surface and

core cooling techniques. Cooling rates achieved in clinical studies have ranged from  $0.5^{\circ}\text{C}$  to  $2.0^{\circ}\text{C/hr}$  for surface cooling methods and from  $1.5^{\circ}\text{C}$  to  $2.5^{\circ}\text{C/hr}$  for cooling with specially designed endovascular catheters (22–23). Although improved surface cooling techniques and endovascular catheters have improved cooling rates, average periods of 2 to 3 hrs are usually still required to reach target values (usually  $32^{\circ}\text{C}$ – $34^{\circ}\text{C}$ ). Moreover, additional time is required for insertion of endovascular catheters, which also implies that they cannot be easily used outside the intensive care unit (ICU) or emergency department. In addition, most currently available devices for surface or endovascular cooling are relatively large and cumbersome, and using these devices in the very early stages after cardiac arrest (for example, in the ambulance) is currently not possible.

In theory, intravenous infusion of large volumes of cold fluids could be used to cool

the core compartment more quickly. This method requires few technical facilities and could easily be used outside the ICU setting. However, few data are available regarding the safety and effectiveness of this method. Only two small clinical studies, including 22 and 13 patients, respectively, have dealt with this issue; they involved the use of large volumes of Ringer's lactate to induce hypothermia in the prehospital setting (24–25). No detailed assessment of metabolic side effects was performed in these studies.

Use of refrigerated saline to induce hypothermia has been studied in only a small number of healthy volunteers (26–28); to our knowledge, no reports on clinical studies using refrigerated saline to cool patients in a clinical setting have been published. Therefore, we decided to perform a large study to assess the feasibility, speed, and complication rates of induction of hypothermia through infusion of large volumes of refrigerated saline, alone or together with geloplasma, in combination with surface cooling in a large group of patients admitted to our ICU.

## PATIENTS AND METHODS

The study was performed according to guidelines of the hospital ethics committee. One hundred thirty-four consecutive patients treated with hypothermia for various types of neurologic injury (mostly postanoxic encephalopathy following cardiopulmonary resuscitation, subarachnoid hemorrhage, and traumatic brain injury) were included in the study. Characteristics of the patients are provided in Table 1. Our protocol is depicted in Figure 1. Hypothermia was induced through infusion of refrigerated fluids ( $4^{\circ}\text{C}$ ) in combination with surface-cooling devices (Blanketrol II hyperhypothermia cooling blankets, Cincinnati SubZero, Cincinnati, OH, or Arctic Sun cooling blankets, Medivance, Boulder, CO). After target temperatures were reached, the surface-cooling systems were used to maintain target temperature.

Blood pressure and central venous pressure were continuously (invasively) monitored in all patients. All patients had urinary catheters, and diuresis was monitored continuously. Pulmonary artery catheters were used in 24 patients for reasons not directly related to the induction of hypothermia. In these patients mixed venous saturation was measured either continuously or at 1-hr intervals.

Levels of glucose and electrolytes such as magnesium, potassium, phosphate, calcium, sodium, and chloride were measured in all patients at 30-min intervals during induction

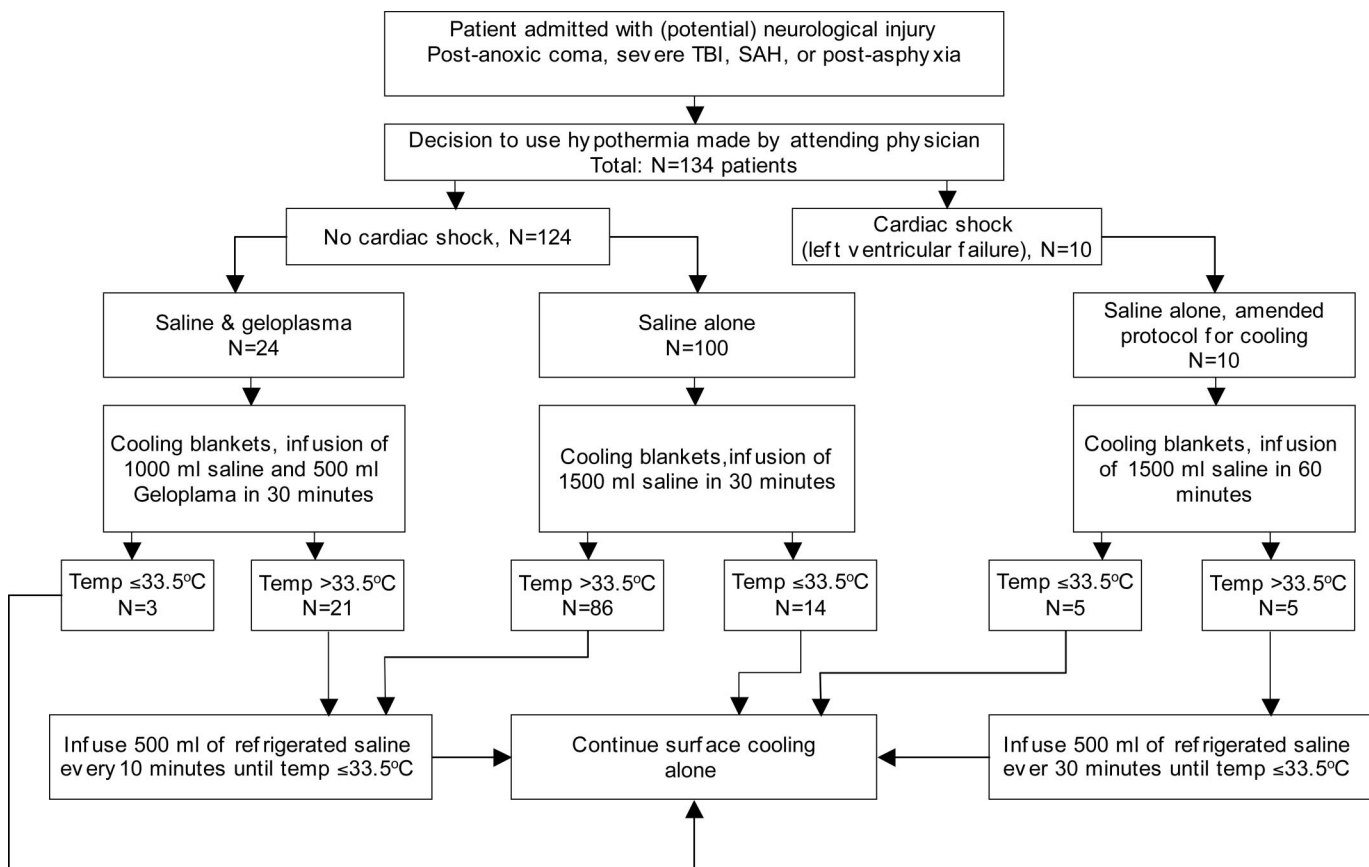


Figure 1. Study protocol flowchart. *TBI*, traumatic brain injury; *SAH*, subarachnoid hemorrhage.

of hypothermia and at 6-hr intervals thereafter, according to methods described previously (29). Platelet, red blood cell, and white blood cell counts, as well as levels of bicarbonate, lactate, and amylase and various other laboratory parameters, were measured before initiation of cooling and thereafter at 6-hr intervals. All patients were mechanically ventilated with low tidal volumes (average, 7.2 mL/kg). The  $\alpha$ -stat method was used for blood gas analysis to guide ventilator settings.

Vasoactive medication was used as clinically necessary to maintain adequate blood pressure (usually defined as mean arterial pressure  $\geq 60$  mm Hg in patients with cardiopulmonary resuscitation,  $\geq 80$  mm Hg in patients with traumatic brain injury, and  $\geq 90$  mm Hg in patients with subarachnoid hemorrhage). All patients received sedatives and analgesia according to a sedation protocol based on the Ramsey sedation score. The target score was 5 or 6 for all patients for as long as hypothermia was maintained. Fentanyl was used for analgesia, and propofol, midazolam, or a combination of both was used for sedation. These drugs were administered with continuous syringe pumps. Patients were not paralyzed; a single dose of a short-acting paralyzing agent (rocuronium, 50 mg) was administered to three patients to combat shiv-

ering. Most patients' shivering was treated with a bolus dose of fentanyl and/or by increasing the dosage of sedatives.

Temperatures were continuously monitored either intravascularly or with probes inserted in the rectum or bladder. Probes were connected to the cooling unit, and temperatures were maintained at the target value with use of a feedback system, as described previously (29).

Our protocol for fluid infusion is shown in Figure 1. In brief, all patients for whom the decision was made to induce hypothermia on clinical grounds were included. Patients with signs of cardiac shock were also included, but infusion rates were slightly modified for them (Fig. 1).

In patients without signs of cardiac shock, 1500 mL of refrigerated (4°C–6°C) fluids were infused over a 30-min period. If temperatures had decreased to  $\leq 33.5^\circ\text{C}$ , no additional refrigerated fluids were infused, and cooling was continued with surface cooling alone. If temperatures remained  $> 33.5^\circ\text{C}$ , an additional 500 mL of refrigerated fluid was infused over a period of 10 mins. This was repeated until temperatures had reached levels  $\leq 33.5^\circ\text{C}$ . The reason for stopping saline infusion at temperatures slightly above target temperature was to avoid "overshoot"; patients also underwent

surface cooling with 4°C cooling blankets, and lower temperatures of the skin and subcutaneously could lead to a further drop in temperature due to equilibration between core and peripheral compartments. In addition, a time lag between measurement of the temperature in the bladder or rectum vs. the actual core temperature (measured by pulmonary artery catheter, the "gold standard") could lead to overestimation of the actual temperature and to an "afterdrop" (30). Therefore, a margin of 1.5°C was used.

In patients with cardiac shock the initial 1500 mL of saline was infused over a period of 60 mins instead of 30 mins. For these patients our protocol called for temporary discontinuation of infusion if central venous pressure increased  $> 5$  mm Hg in 5 mins. After the initial 1500 mL, additional bags of refrigerated saline were infused over 30 mins rather than in 10-min periods. Geloplasma was not used in these patients unless the attending physician wished to administer colloids on clinical grounds.

Both refrigerated saline and geloplasma were used for induction of hypothermia in the first 24 patients included in our study; in the subsequently included patients, only refrigerated saline was used. Patients with cardiac shock were excluded from the colloid and sa-

Table 2. Physiological parameters and vasoactive drug administration

Variable	During Cooling				
	Before Cooling	At 30 Mins	<i>p</i> Value <sup>a</sup>	At 60 Mins	<i>p</i> Value <sup>a</sup>
MAP, mm Hg	73 ± 26	77 ± 24	NS	82 ± 29	.01
CVP (range), cm H <sub>2</sub> O	9 (2–15)	11 (4–16)	.01	12 (5–16)	.01
Average increase in CVP, cm H <sub>2</sub> O			2 (–1 to +6)		

	Before Cooling	During Cooling	<i>p</i> Value
Medications, mg/hr			
Dopamine, n = 54	17.4 ± 12.0	10.2 ± 9.2	<.01
Norepinephrine, n = 56	0.42 ± 0.24	0.22 ± 0.18	.01
Dobutamine, n = 24	34.1 ± 32.2	32.2 ± 41.3	NS
Enoximone, n = 22	3.2 ± 3.6	3.0 ± 3.0	.13

MAP, mean arterial pressure; NS, not significant; CVP, central venous pressure.

<sup>a</sup>All statistical comparisons for values compared with baseline. Values are mean ± sd.

line group, but administration of colloids was allowed if the attending physician deemed this necessary on clinical grounds. The maximum volume of colloids allowed was 500 mL in patients with cardiac shock due to left ventricular dysfunction and 1000 mL in all other patients, including patients with signs of right ventricular dysfunction.

To counter potential side effects (which occur especially during the induction phase of hypothermia (22), i.e., while the temperature is decreasing), large amounts of potassium, magnesium, and phosphate were administered to most patients during initiation of hypothermia to prevent hypothermia-induced electrolyte depletion, according to a protocol described previously (29). All patients treated with hypothermia received antibiotic prophylaxis with cephalosporins and selective decontamination of the digestive tract. Insulin infusion was started in all patients if glucose levels increased to ≥8.0 mmol/L, with a target of maintaining glucose levels between 3.8 and 6.5 mmol/L.

**Statistical Analysis.** Student's unpaired *t*-test was used for comparisons between groups and for comparisons of changes from baseline. All values are given as mean ± sd. Statistical significance was accepted for *p* < .05.

## RESULTS

The results are summarized in Tables 1 through 4.

Characteristics of patients, reasons for induction of hypothermia, and various physiologic parameters are shown in Table 1. In the group of 100 patients without signs of cardiac shock receiving refrigerated saline only, an average of 2340 ± 890 mL of refrigerated fluids was in-

fused within 60 mins. Core temperatures decreased from 36.9 ± 1.9°C to 34.6 ± 1.5°C at *t* = 30 mins and to 32.9 ± 0.9°C at *t* = 60 mins (final target temperature: 32°C–33°C). Similar results were obtained when both refrigerated saline and geloplasma were used for cooling. In these 24 patients, 1680 ± 630 mL of refrigerated saline and 710 ± 150 mL of refrigerated geloplasma was infused within 45 mins. Core temperatures decreased from 37.2 ± 1.9°C to 34.4 ± 1.3°C at *t* = 30 mins and to 33.2 ± 0.8°C at *t* = 60 mins (target temperature: 32°C–33°C).

Ten patients had signs of cardiac shock before initiation of cooling. In these patients the infusion rate of refrigerated fluids was decreased according to predefined criteria (Fig. 1). These patients' core temperatures decreased from 36.8°C to 35.2 ± 1.7°C at *t* = 30 mins and to 34.2 ± 1.2°C at *t* = 60 mins. At *t* = 120 mins, temperature had decreased to 33.1 ± 0.9°C (target temperature: 32°C–33°C).

Continuous monitoring of arterial blood pressure, heart rhythm, central venous pressure, arterial blood gasses, and serum levels of electrolytes, platelets, and white blood cells revealed no significant additional adverse effects. No severe arrhythmias occurred in our patients during infusion of refrigerated fluids. Twenty-one patients received amiodarone because of previous arrhythmias (mostly during or following cardiopulmonary resuscitation). Mean arterial blood pressure increased by 15 mm Hg, with the largest increases in blood pressure observed in

patients who had been hemodynamically unstable before initiation of cooling. Positive end-expiratory pressure (PEEP) levels were increased in eight patients in the 12-hr period during and following infusion of refrigerated fluids because pulmonary edema was suspected (on the basis of mild decreases in arterial oxygen levels, with improvements after increase of PEEP). The average increase in PEEP levels was 4 cm H<sub>2</sub>O (range, 2–9 cm H<sub>2</sub>O); the average increase in the whole group of patients was 0.3 cm H<sub>2</sub>O. Five of these patients had signs of cardiac shock before initiation of cooling. Seven other patients required increases in PEEP levels for other reasons, mostly aspiration pneumonia, indicated by the presence of one-sided pulmonary infiltrates rather than bilateral pulmonary edema. Increases in PEEP levels in these patients were presumed not to be linked to the infusion of refrigerated fluids. Four of these patients required proning to stabilize their pulmonary situation. Cooling was continued in all these patients.

Following its initial induction, hypothermia was maintained for varying periods of time, ranging from 24 hrs for cooling necessitated by postanoxic coma following cardiac arrest to several days for cooling used to control intracranial pressure in traumatic brain injury or subarachnoid hemorrhage. Patients cooled for postanoxic coma were rewarmed slowly over a period of 12 to 24 hrs. Rewarming in patients cooled for other indications was based on intracranial pressure measurements.

## DISCUSSION

The results of our study demonstrate that large volumes of refrigerated (4°C) fluids can be safely and effectively used as an accessory means to quickly induce hypothermia in various categories of patients. To our knowledge, the cooling rates reported here are the fastest reported to date for a clinical study in the ICU setting. Even patients with cardiac shock, in whom infusion rates of refrigerated fluids were decreased, had cooling rates that compare favorably to those reported following previous clinical trials. This is important because the speed of cooling is a key factor in realizing the protective effects of hypothermia (1, 8–11). In addition, the risk of some of the side effects associated with hypothermia may decrease significantly when cooling is achieved more quickly. These side ef-

Table 3. Fluid balance, in milliliters, from time of intensive care unit admission

Patients	1 hr	6 hrs	24 hrs	48 hrs	72 hrs
Without cardiac shock	+2220 ± 440	+1710 ± 1130	+780 ± 860	+480 ± 980	+520 ± 660
With signs of cardiac shock	+1420 ± 770	+1610 ± 680	+520 ± 720	+380 ± 650	340 ± 670

Table 4. Laboratory parameters and metabolism

Value	Mean ± SD and p Value						
	Before Cooling	T = 60 Mins	p Value	T = 6 hrs	p Value	T = 24 hrs	p Value
Na	131 ± 12	135 ± 14	<.05	138 ± 13	<.01	136 ± 15	<.05
K <sup>a</sup>	3.6 ± 1.9	3.7 ± 1.4	NS	4.3 ± 1.2	<.02	4.2 ± 1.5	<.05
Cl	96 ± 8	99 ± 9	NS	102 ± 7	<.05	104 ± 8	<.01
Mg <sup>a</sup>	0.86 ± 0.42	0.92 ± 0.32	NS	1.12 ± 0.20	<.05	1.20 ± 0.35	<.01
pH	7.32 ± 0.12	7.36 ± 0.12	NS	7.30 ± 0.11	NS	7.32 ± 0.14	NS
Lactate	2.8 ± 2.2	2.3 ± 2.0	<.05	2.9 ± 3.4 <sup>b</sup>		2.7 ± 2.6 <sup>b</sup>	NS
Glucose	7.3 ± 6.2	7.4 ± 5.2	NS	6.2 ± 4.2	<.05	5.2 ± 3.8	<.01
WBCs, ×10 <sup>9</sup> /L	8.2 ± 5.8	8.4 ± 5.2	NS	8.6 ± 6.1	NS	2.6 ± 4.2	<.01

WBC, white blood cell; NS, not significant.

<sup>a</sup>Most patients received supplementation of K and Mg; <sup>b</sup>induced hypothermia usually leads to a slight increase in lactate levels and mild extracellular acidosis, whereas intracellular pH levels usually increase; these changes are physiologic and are a normal consequence of hypothermia. All electrolyte values are mmol/L. All statistical comparisons are for values compared with baseline.

fects can be roughly divided into *immediate effects* that occur in the cooling phase (i.e., while temperature is decreasing) and *delayed effects*, which occur in later stages, after target temperatures have been reached. Particularly the immediate side effects (such as hypothermia-induced [cold] diuresis with risk of hypovolemia and hypotension, electrolyte loss, and shivering, which occur mainly in the temperature range from 35.5°C down to 34°C) can often be wholly or partly prevented through quicker induction of hypothermia (22, 23). Once the core temperature drops below ±34°C, patients tend to become more stable. Thus, for various reasons (maximizing protective effects, minimizing side effects) it makes sense to induce hypothermia as quickly as possible. The high cooling rates achieved are probably due to the simultaneous cooling of both the core and surface compartments and to the minimizing of the time period during which physiologic rewarming responses such as shivering occur.

On the basis of these considerations and the findings in this study, we recommend the use of cold-fluid infusion as an accessory tool when hypothermia is used as a clinical tool in the intensive care setting, with the possible exception of

patients who are not mechanically ventilated.

This cooling method offers many additional advantages. First, it can be easily combined with other methods, either surface cooling or core cooling. Second, because it does not require sophisticated devices or procedures, it can be initiated as soon as (peripheral or central) venous access has been established. This means that cooling can easily be started in the ambulance and/or emergency department; in these settings, cold-fluid infusion could be combined with surface cooling via ice packs.

Relatively high volumes of fluids were required to achieve the cooling rates realized in our study. Initial fears that such rapid infusion rates might cause pulmonary edema in many patients proved unfounded. Only eight patients required a moderate increase in PEEP levels; before initiation of fluid infusion, five of these patients had signs of left ventricular failure (defined by the occurrence of at least three of the following signs and symptoms: persistent hypotension, pulmonary edema, high central venous pressure, and impaired ventricular function evidenced by echocardiography). Thus, as expected, the risk of developing pulmonary edema was greater in the group of patients with

signs of cardiac shock before fluid infusion than in those who did not have such signs (25% vs. 3%, respectively); however, the problems related to pulmonary edema were easily managed in all patients with slight increases in PEEP levels. Moreover, it seems highly likely that some of the patients with signs of cardiac shock before fluid infusion would have developed a degree of pulmonary edema anyway. Seven of our patients did require significant (>5 cm H<sub>2</sub>O) increases in PEEP levels; however, this was presumed to be related to aspiration pneumonia, indicated by the presence of one-sided pulmonary infiltrates rather than bilateral pulmonary edema.

We do not recommend cold-fluid infusion as the sole means of inducing and maintaining hypothermia. Controlling and maintaining hypothermia within a narrow range would be too difficult with cold fluids alone; the associated risk of overshoot (too-deep cooling) or too early and/or rapid rewarming would be too great. The risk of side effects increases exponentially when temperatures decrease below 28°C to 30°C (22); avoiding this overshoot while still achieving temperatures ≤33°C would be too difficult with cold-fluid infusion alone. In addition, slow, controlled rewarming is an important feature of hypothermia therapy; uncontrolled, rapid rewarming is associated with increased neurologic injury and may negate part of the protective effects of hypothermia (1). Therefore, reliable methods to maintain temperature within the intended narrow therapeutic range are required. However, addition of cold-fluid infusion in the induction phase of cooling as an accessory method to achieve a more rapid rate of cooling can significantly increase the efficacy of other methods. As explained previously, another important benefit of quick cooling is that it decreases side effects (22). We therefore see the place of cold-fluid infusion in the induction phase, to facilitate rapid cooling. We feel that the subsequent maintenance of temperatures within a narrow range should be accomplished by other methods (23). The protocol used for our study could serve as a basis for clinical usage and can be adapted to local circumstances.

The currently available evidence suggests that different types of fluid can be used for cooling. Bernard et al. used intravenous infusion of 30 mL/kg of ice-cold Ringer's lactate, combined with surface cooling with ice packs, to induce

hypothermia in 22 patients following cardiac arrest; the average temperature decrease was 1.7°C, and the authors reported no significant side effects in their patients (24). Virkkunen et al. reported average temperature reductions of 1.8°C following rapid administration of 30 mL/kg Ringer's lactate to 13 cardiac arrest patients, also in a prehospital setting (25). Rajek et al. infused 40 mL/kg of refrigerated saline in nine healthy volunteers via a central venous line, leading to average temperature reductions of 2.5 ± 0.4°C (26). Baumgartner et al. used lower volumes (5 mL/kg) of refrigerated albumin 5% to lower temperature in neurosurgical patients who had already been cooled to 34°C by surface-cooling methods in the perioperative setting (31). They reported temperature reductions of 0.6 ± 0.1°C in their patients when rapid infusion rates were used. Although all of these studies have included only relatively small numbers of patients or volunteers, none revealed serious adverse events. Cooling rates in these studies have averaged between 0.8°C and 1.2°C per liter of fluid infused. At 2.3 ± 0.4°C in the first 30 mins and 4.0 ± 0.3°C after 60 mins, cooling rates in our study were slightly higher, probably because of the combination of cold-fluid infusion with surface cooling.

Our study, including a much larger number of patients, is the first to also systematically monitor for potential metabolic changes. No unfavorable effects such as induction of hyperchloremic acidosis were observed. Overall, our data strongly suggest that rapid infusion of large volumes of refrigerated fluids is a safe and effective method of inducing hypothermia.

We used refrigerated saline alone in most of our patients. We also used a combination of saline with geloplasma in some patients to determine whether addition of colloids would produce additional adverse effects. Although we did not find this to be the case, we recommend using either refrigerated saline or Ringer's lactate in most patients, adding colloids only if the decision is made to infuse colloids on clinical grounds not directly related to cooling. However, if colloids are given during the cooling phase, our results suggest that these should also be refrigerated, to maximize rates of cooling.

A potential limitation of our study is that all our patients were mechanically ventilated. This allowed us to infuse large

volumes of fluid over short periods of time, with the option of increasing PEEP in cases of pulmonary edema. In theory, the risk of developing pulmonary edema could be greater in patients without mechanical ventilation. Previously published clinical studies assessing the use of refrigerated fluids to induce hypothermia all involved mechanically ventilated patients (24–25, 31) or healthy volunteers (26–28). The results of our study suggest that cold-fluid infusion could probably be safely used also in nonventilated patients; the number of patients whose respiratory parameters deteriorated in the 12 hrs during and following saline infusion was small (eight patients, or 6%), and most of these patients had signs of cardiac shock before initiation of infusion. Only one patient who had no such signs had a deterioration in respiratory parameters requiring PEEP adjustment following rapid fluid infusion. This strongly suggests that the associated risk of inducing pulmonary edema in patients without signs of cardiac shock is very low. Nevertheless, we currently do not recommend using our cooling strategy in nonventilated patients; further studies will be required to address this issue. However, if a decision has been made to induce hypothermia in a nonventilated patient (for example, to limit myocardial injury following ischemia/reperfusion) and to administer fluids to this patient on clinical grounds, refrigerated fluids rather than fluids stored at room temperature should be used to speed up the cooling process.

Thus, although the safety of this cooling method in nonventilated patients remains to be determined, this will not be an issue when treating comatose patients in the intensive care setting, because all such patients are mechanically ventilated. For patients treated with hypothermia for traumatic brain injury or subarachnoid hemorrhage, administration of large volumes of fluid is usually part of the overall management strategy, to induce hypervolemia and prevent hypotension (32–33). Therefore, using refrigerated fluids in these patients is unlikely to add significantly to the overall fluid load, because fluids currently administered at room temperature to maintain euvolemia or induce hypervolemia could simply be replaced by refrigerated fluids.

A separate but related issue is the treatment of fever in patients with neurologic injury. Various studies have linked fever to the development of additional neurologic injury (1). Animal stud-

ies have shown that hyperthermia directly stimulates numerous destructive processes at the cellular level (1), and fever is an independent predictor of mortality and adverse neurologic outcome in various clinical studies (1, 34–36). Fever may also induce additional cardiac injury; Takino et al. reported worse outcome for adult patients who developed fever after cardiac arrest in a small retrospective study (37), and animal studies show that induction of fever by external warming leads to increased myocardial necrosis (14–15). Thus, there is increasing awareness that prevention of fever should be a goal of therapy for patients with neurologic and perhaps myocardial injury. However, maintaining normothermia in patients with neurologic injuries has proved difficult (38, 39, 40); we feel that the method described in our study could be used as an accessory method to maintain normothermia in this category of patients and that probably lower volumes of fluid would be required to achieve the target temperature. Further studies will be required to address this issue.

In our study, central venous catheters and (in some patients) pulmonary artery catheters were used for monitoring. If cold-fluid infusion is used outside the ICU setting, these monitoring tools will not be (immediately) available. However, our study shows that changes in treatment management based (solely) on these measurements were rarely needed. This is confirmed by the observations in two smaller clinical studies described previously, in which refrigerated fluids were used in the emergency room (24) or in the prehospital setting (25). Thus, we feel that the cold-fluid infusion strategy can be safely used without having central venous access, provided that the patient is intubated and mechanically ventilated. After infusion of 1500 mL of saline (combined with surface cooling), none of the patients in our study had a temperature decrease below 32°C. This implies that this volume of cold fluids can be safely given even without availability of (continuous) temperature monitoring (in the ambulance, for example).

No serious adverse events occurred during or immediately following cold-fluid infusion in our study. Specifically, no severe arrhythmias were observed. It should be noted that around 50% of the patients in our study had already received antiarrhythmic medication (mostly amiodarone) on clinical grounds, mostly post-cardiac arrest arrhythmias or ar-

**I**nduction of hypothermia by rapid infusion of large volumes of refrigerated fluids, combined with surface cooling, is a safe, efficacious, quick means of inducing hypothermia in patients with various types of neurologic injury.

rhythmias related to neurologic injury (in patients with subarachnoid hemorrhage). As expected, there was an improvement in hemodynamic parameters in our patients; physiologic effects of cooling include an increase in blood pressure (by 10–15 mm Hg at temperatures below 34°C) and a slight rise in central venous pressure (1). We also found no specific adverse metabolic consequences associated with cold-fluid infusion. It should be strongly emphasized, however, that induced hypothermia itself is associated with numerous potentially serious side effects that require careful monitoring and preemptive treatment. These include severe electrolyte disorders, hyperglycemia, and increased risk of infection (22). Common metabolic effects include a slight increase in lactate levels and mild extracellular acidosis (whereas intracellular pH levels usually increase) and a decrease in leukocyte function and white blood cell count (22), which was also seen in many patients in our study (Table 4). Successful use of hypothermia as a medical tool critically depends on the proper recognition and treatment of these side effects, and rigorous protocols are required for any unit that uses this therapy (22, 41).

Our protocol included administration of large amounts of electrolytes to counteract hypothermia-induced electrolyte depletion, caused by a combination of increased urinary excretion and intracellular shift (42). Infusion of large amounts of potassium carries a theoretical risk for hyperkalemia when a patient is rewarmed, because of back-shift of potassium from the intracellular to the extracellular space. However, this was not found to be a clinical problem in large

hypothermia trials when renal function was normal and rewarming was not too quick (22, 29).

In summary, the results of our study demonstrate that induction of hypothermia by rapid infusion of large volumes of refrigerated fluids combined with surface cooling is a safe, efficacious, quick method of inducing hypothermia in patients with various types of neurologic injury. Cold-fluid infusion will help to increase the rates of cooling, thereby enhancing efficacy and decreasing the risk of side effects of hypothermia. This method can be applied in the ICU setting but can also be used in the ambulance and emergency department as an accessory means to induce hypothermia in all endotracheally ventilated patients. Further studies will be needed to determine whether this method can also be safely used in nonventilated patients.

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