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Original Article

Technical Refinements and Drawbacks of a Surface Cooling Technique for the Treatment of Severe Acute Ischemic Stroke

Alex Abou-Chebl,[1] Michael A. DeGeorgia,[1] John C. Andrefsky,[1] and Derk W. Krieger[1]*

[1]Section of Stroke and Neurological Critical Care, Department of Neurology, The Cleveland Clinic Foundation, Cleveland, OH

Purpose: To describe a technique for the induction of hypothermia and its complications for the treatment of acute ischemic stroke.

Methods: Adults with acute (< 8 hours), severe (National Institutes of Health Stroke Scale > 14) ischemic stroke of the anterior circulation were enrolled. Patients were intubated, sedated, and paralyzed. Surface cooling to 32° ± 1°C was performed with a cooling blanket and an alcohol/ice bath. Hypothermia was maintained for 12–72 hours. Physiological parameters were measured continuously. A computed tomography scan of the brain was obtained at 24 hours. Rewarming was initiated 12 hours after middle cerebral artery recanalization at a rate of 0.25°C/hour. All complications and adverse outcomes were documented from initiation of hypothermia until hospital discharge.

Results: Eighteen patients with a mean National Institutes of Health Stroke Scale = 21.4 ± 5.6 were treated. The goal temperature was reached within 3.2 ± 1.5 hours. Cooling time was proportional to body weight ($p = 0.009$) and decreased with immediate paralysis to prevent shivering ($p = 0.033$). Maintenance and rewarming were characterized by fluctuations in core temperature. All patients developed a decrease in blood pressure, heart rate, and potassium values that were proportional to temperature ($p < 0.05$). Complications were generally mild, but pneumonia and myocardial infarction or both occurred in five patients. There were trends for increased risk of complications with longer duration of hypothermia ($p = 0.08$) and increasing age ($p = 0.0504$). Rewarming was well-tolerated with rebound cerebral edema occurring in only one patient.

*Correspondence and reprint requests to: Alex Abou-Chebl, MD, Section of Stroke and Neurological Critical Care, Department of Neurology, S91, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195. E-mail: achebla@ccf.org.

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Conclusion: Surface cooling for the treatment of acute ischemic stroke can be performed rapidly with early neuromuscular paralysis. Advanced age and prolonged hypothermia may be associated with an increased risk of complications.

Key Words: Stroke; hypothermia; adverse effects; neuroprotection; surface cooling.

Introduction

There exists a pressing need for effective neuroprotectant therapy for acute ischemic stroke. The only US Food and Drug Administration (FDA)-approved treatment for acute ischemic stroke, intravenous -tPA, must be given within 3 hours of stroke onset. An effective neuroprotectant may limit the extent of injury, even in the absence of recanalization, by increasing the "time window" during which r-tPA may be given safely, thereby increasing the number of patients treated. Hypothermia may fulfill this need *(1)*. Several studies have shown that hypothermia can limit the degree of ischemic damage, decrease infarct volume, extend the time required for damage to occur ("time window"), and improve outcomes *(1,2)*. Hypothermia may also limit reperfusion injury *(3,4)*.

Preliminary studies, including our series of 10 patients, have shown that rapid induction of moderate hypothermia to 32°C with a surface cooling technique is feasible in the treatment of acute ischemic stroke *(5–8)*. Although some academic centers have experience with the induction and maintenance of hypothermia via surface cooling for traumatic head injury *(9,10)* and cardiac arrest *(11,12)*, there is little experience in the setting of acute ischemic stroke *(5–8)*. Patients with ischemic stroke differ from those with traumatic brain injury, which mainly occurs in young men, and from patients with diffuse anoxia, which typically results from cardiac arrest. The potential complications and physiological responses to treatment of ischemic stroke in the elderly with hypothermia are likely to differ from those in the young patient with trauma or the patient with cardiac arrest. Furthermore, a variety of cooling techniques have been used and detailed information on the various methods and complications are not available.

Since our initial report of surface cooling for acute ischemic stroke, more experience has been gained and the methods have been refined *(8)*. This article reviews the details of these refinements and the physiological changes and complications experienced by this unique patient population. Our study could serve as a guide for others performing hypothermia with surface cooling in the setting of acute ischemic stroke.

Materials and Methods

The entry and selection criteria have been published previously *(8)*. Briefly, adults with acute (< 8 hours) middle cerebral artery (MCA) territory ischemic stroke with an initial National Institutes of Health Stroke Scale (NIHSS) score > 14 were enrolled. Patients with sepsis, coagulopathy, thrombocytopenia, hemodynamically significant cardiac arrhythmias or a QTc interval > 450 ms were excluded.

Patients were admitted to the neurological intensive care unit, and arterial, central venous, nasogastric tubes, and indwelling urinary bladder catheters with thermistor probes (Mon-A-Therm, Mallinckrodt Medical, St. Louis, MO) were inserted. Studies of complete blood cell count, electrolytes, blood urea nitrogen, creatinine, glucose, albumin, creatine phosphokinase with myocardial band (CPK-MB) fractionation, liver function tests, amylase, lipase, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, arterial blood gases, urinalysis, blood and urine cultures, chest X-ray, and electrocardiogram (ECG) were obtained in all patients at baseline and then daily, except for blood, urine, sputum cultures, which were repeated if infection was suspected. Patients were placed on a cooling blanket (Aquamatic K-Thermia EC600, American Medical Services, Bellville, OH), with the controller at the maxi-

mum setting of 4°C. The hoses to the blanket were clamped to prevent circulation of the coolant until the induction of anesthesia. This overcame the significant lag time that it took the machine to effectively cool while preventing patient discomfort and shivering. The patients were then electively intubated.

To prevent shivering, all patients were paralyzed with atracurium (0.4 mg/kg bolus followed by an infusion of 5 µg/kg/minute). The dose was titrated to achieve visible suppression of shivering. For the first five patients, atracurium was initiated with the onset of shivering. Thereafter, atracurium was given before cooling. All patients were sedated with propofol (5 µg/kg/minute) after intubation. The infusion rate was increased by 5–10 µg/kg/minute every 10–20 minutes until adequate sedation was achieved. For the first five patients, this was defined as a comfortable appearance associated with a heart rate (HR) < 100 bpm and a blood pressure (BP) <185/110 mmHg. For the remainder, who were immediately paralyzed, the vital signs were used to guide sedation. Sedation was continued until the discontinuation of paralytics and hypothermia. Patients were ventilated using the assist control ventilation mode, with a minute volume of 8–12 L/minute. The fraction of inspired oxygen was adjusted to maintain the arterial partial pressure of oxygen (pO_2) > 100 mmHg (13.3 kPa). "Alpha stat" pH management was used, because this method is commonly used in several clinical settings where hypothermia is used, including cardiac bypass.

Immediately after sedation and paralysis, the cooling blanket hoses were unclamped. Patients were undraped, and ice packs were placed in the axillae and beneath the neck. The patients' eyes were taped closed and covered. The first two patients were intermittently sandwiched between two cooling blankets or rubbed down with a 50/50 mixture of ice and isopropyl alcohol. Thereafter, patients were kept on top of one cooling blanket, while continuous whole body ice/alcohol rubs were performed using washcloths. During the bath, excessive dripping of liquid onto the patients' skin was avoided to allow for maximum evaporative heat removal. The head was covered in a ice/alcohol-soaked cloth that was changed every 2–3 minutes. For the first four patients, refrigerated intravenous fluids were infused and gastric lavage with ice water was performed. The ventilator air-humidifier and warmer were turned off during cooling. When the core temperature (T_c) reached 34°C, the ice/alcohol rubs were discontinued. The patients were then sandwiched between two cooling blankets, and the apparatus temperature (T_A) was maintained at 32–36°C, depending on the rate of the T_c decrease.

The T_c was continuously monitored and maintained at the goal of 32°C ± 1°C by continuously adjusting the T_A Whenever the T_c began to change in either direction, the T_A was immediately changed in an *opposite* direction to the T_c change. When after such a change in T_A, the T_c change was reversed, the cycle was repeated (e.g., after a decrease in T_c to below 32°C was stopped or reversed by a warmer setting on the apparatus, the T_A was adjusted back to a cooler setting to *oppose* the T_c change). The maintenance period was 12 hours in patients who had recanalization of the MCA before induction of hypothermia. In those not successfully recanalized, transcranial Doppler ultrasound (TCD) was obtained at 12- to 24-hour intervals and rewarming was initiated 12 hours after TCD confirmation of recanalization *(5)*. The maximum duration of hypothermia was 72 hours, regardless of MCA patency. Bladder temperature, HR, BP, and the ECG were continuously monitored. Clinical monitoring also consisted of once-daily neurological examinations without paralytics and with minimal sedation. All patients underwent a computed tomography (CT) scan at 24 hours.

Hypokalemia was not corrected during hypothermia, unless it was < 2.6 mmol/L or the patient had ECG changes. Antiplatelet agents, but not anticoagulants, were permitted during hypothermia. Intravenous normal saline was titrated to maintain euvolemia. All patients received prophylactic therapy with parenteral famotidine and lower extremity compression stockings. Patients were not fed during hypothermia.

Table 1
Patient Characteristics

Patient	*Age (years)*	*Sex*	*HTN*	*DM*	*Hyperlipidemia*	*CAD*	*AF*	*Early CT changes*	*Initial NIHSS*	*Cooling time (hours)*	*Maintenance duration (hours)*	*Rewarming duration (hours)*
1	76	M	N	N	Y	N	N	None	18	5.9	12	24
2	64	F	N	N	Y	N	Y	<1/3 MCA	23	2.5	12	25
3	55	M	Y	N	N	N	N	>1/3 MCA	18	3.5	36	22
4	83	M	Y	N	N	N	Y	None	16	6.5	12	24
5	43	F	N	N	N	N	N	<1/3 MCA	16	3.5	12	11
6	61	M	Y	Y	N	N	N	>1/3 MCA	22	2.5	48	19
7	64	F	Y	Y	N	N	N	<1/3 MCA	20	2.3	12	27
8	48	M	Y	Y	N	N	N	>1/3 MCA	27	1.8	48	
9	73	M	N	N	N	Y	Y	>1/3 MCA	25	3.5	72	
10	82	M	Y	N	N	N	N	<1/3 MCA	17	2.5	48	23
11	86	F	Y	N	N	N	N	None	23	2.3	24	39
12	85	F	Y	Y	Y	Y	Y	<1/3 MCA	22	3.0	12	22
13	91	F	Y	N	N	N	Y	None	24	2.5	12	31
14	71	M	N	N	Y	N	N	1/3 MCA	20	2.3	12	20
15	67	F	N	N	N	N	N	>1/3 MCA	30	2.8	12	20
16	69	M	Y	Y	Y	N	N	<1/3 MCA	20	2.2	12	22
17	48	M	Y	Y	N	N	Y	None	15	6.2	12	18
18	86	F	Y	N	Y	Y	N	<1/3 MCA	30	1.8	12	15
Mean	69.6								21.4	3.2	22.7	22.8
Std. Dev.	14.6								4.6	1.5	18.3	6.6
Median	70.0								21.0	2.5	12.0	22.0

M, male; F, female; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; AF, atrial fibrillation; NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; MCA, middle cerebral artery.

Controlled rewarming was performed at a rate of 0.25–0.5°C/hour by setting the T_A to 34–35°C. If T_c increased >0.5°C/hour, then the T_A was set to cool until the T_c stabilized, at which time the apparatus was turned off. Rewarming was an active process requiring close monitoring of temperature changes. Paralytics were discontinued at 36°C. When normothermia (the initial T_c) was reached, the propofol was adjusted to maintain comfort until extubation.

The Cleveland Clinic Foundation Institutional Review Board (IRB) approved the study. Informed consent was obtained from all patients or their legal surrogate. Ten of the patients included in this report were also included in an earlier report *(8)*. Three additional patients who fell outside of the time window were enrolled on a compassionate use basis. Informed consent and IRB approval were obtained in each of these cases. All data, including complications, were recorded into a database program (Access, Microsoft Corporation, Seattle, WA) and analyzed with SAS (version 8.0, SAS Institute Inc., Carry, NC) and SPSS (version 9.0, SPSS Inc, Chicago, IL) statistical packages. One-tailed Spearman correlation coefficients were used to measure the association between temperature and laboratory and physiological variables. The mean rates of change of physiological variables were determined using linear regression techniques. Differences between means of continuous variables were assessed with the *t*-test.

Results

Eighteen patients were treated. Patient characteristics are listed in Table 1. The mean age was 69.6 ± 14.6 years (range 43–91), and 8 of the 18 were women. The mean initial NIHSS score was 21.4 ± 5.6. Thirteen (72%) of the 18 patients had early infarct signs on initial CT scan. Medical comorbidities were common. Five patients (27.8%) had recent (< 2 days) surgery: two had open-heart surgery, two had a hemicraniectomy for the incident stroke, and one had a styloidectomy. In addition, one patient was receiving chemotherapy treatment for tongue carcinoma. Five patients received intraarterial and two received intravenous thrombolysis, whereas the remainder were not treated with fibrinolysis for several reasons, including postoperative stroke, outside the time window, or patent MCA on angiography. Enrollment in this study did not preclude or interfere with recanalization therapy.

The average cooling time was 3.2 ± 1.5 hours (range 1.75–6.5), with an average cooling rate of 1.72°C/hour (95% confidence intervals [CI], 1.39–2.04). All patients reached goal temperature. Cooling required a team of two nurses, a respiratory therapist, and at least one physician. Ice water gastric lavages, refrigerated saline infusions, and sandwiching patients between two cooling blankets were not used after the first four patients. The protocol was changed to include pharmacological paralysis before cooling and continuous rubbing with the alcohol/ice mixture. This resulted in more rapid cooling. Comparing the first five patients with the last five patients, the mean cooling time decreased from 4.4 hours to 2.3 hours ($p = 0.033$). There was a lag time of 41.7 minutes ± 19.8 minutes (range 15–75 minutes) in drop in T_c from the onset of cooling that was proportional to patient weight ($p = 0.046$). Cooling time was also proportional to weight ($p = 0.009$). When corrected for patient weight, the cooling time decreased, with increased experience and changes in technique from 0.049 hour/kg to 0.034 hour/kg ($p = 0.029$). Shivering caused increases in T_c, prolonging cooling times. During cooling there was an overshoot of T_c in 14/18 (78%) patients to a mean low temperature of 30°C ± 0.8°C (range 28.4–30.9°C). The more rapid the drop in T_c, the more likely the patient was to continue to drop and overshoot 32°C. Continued cooling with the ice/alcohol rub until the temperature reached 32°C always resulted in excessive cooling and was not needed to reach goal T_c.

The mean duration of the maintenance phase was 24.6 hours ± 17.7 hours. Maintenance T_c fluctuated; half of the patients had T_c that fell outside of the 32°C ± 1°C range. The mean proportion of time spent outside of the desired range was 26% ± 11.7% (range 6–45%). Most out-of-

Table 2
Complications

Complication[a]	*N*
Bradycardia	13
Hypotension	8
Fever	5
Myocardial infarction	5
Pneumonia	5
Atrial fibrillation	3
Ventricular ectopy	3
Acidosis[b]	2
Congestive heart failure	2
Death[b]	2
Transtentorial herniation[b]	2
Coagulopathy[b]	1
Intracranial hemorrhage[b]	1
Pancreatitis	1

[a] *See* text for definitions and details.

[b] All occurred in two patients, *see* text for details.

range temperatures were low rather than high (mean T = 30.3°C, range 29.5–30.9°C). Hour-to-hour fluctuations in T_c averaged 0.42°C (range 0.18–0.8°C). The daily neurological examinations without paralytics and sedatives did not cause shivering or fluctuations in T_c.

Rewarming was initiated after 12 hours in 11 patients, 24 hours in 3 patients, 48 hours in 2 patients, and 72 hours in 1 patient. The family of one patient for whom hypothermia was induced on a compassionate use basis after the failure of hemicraniectomy, decided to withdraw care after 48 hours without rewarming. Rewarming required frequent adjustments of T_A to prevent a rapid rise in T_c, prolonging the rewarming period to 22.8 hours ± 6.6 hours (range 11–39 hours). The average rate of rewarming was 0.21°C/hour (95% CI, 0.16–0.26°C/hour). One patient with complete MCA and posterior cerebral artery infarcts and a Type 1 aortic dissection developed signs of herniation when the T_c reached 33.3°C, which reversed with recooling. Rewarming was reattempted after giving mannitol and hyperventilation, but signs of herniation recurred. He developed lactic acidosis and hypotension. Care was withdrawn after 99 hours, without further attempts at rewarming. Nine of the 16 patients (56%) who were successfully rewarmed developed hyperthermia, with a mean temperature of 37.9°C ± 0.4°C (range 37.5–38.5°C). In five of the nine patients, no source of fever was found.

The most frequent and serious complications are listed in Table 2. There was a trend for increased risk of complications with increasing duration of hypothermia ($r^2 = 0.19$, $p = 0.08$) and increasing patient age ($r^2 = 0.23$, $p = 0.0504$) (Fig. 1). Other factors (stroke severity, weight, sex, medical comorbidities, cooling rate, or temperature overshoot) did not increase the risk of complications. Most patients had an initial diuresis during cooling. All patients developed a decrease in HR (mean decrement of 9.2 bpm/hour [95% CI, 4.1–14.3]) during the cooling phase. Thirteen (72.2%) developed bradycardia (HR <55 bpm). The mean T_c at the onset of bradycardia was 32.2°C ± 1.3°C (range 30.1–34°C). Two patients developed critical bradycardia: one required temporary transvenous pacing, the other developed brief hypotension that responded to fluids. Neither patient had permanent sequelae.

Of four patients with underlying atrial fibrillation (AF), three developed rapid ventricular rates during the cooling and maintenance phases. One became hypotensive but responded to rate control. AF developed in one patient during hypothermia and two others after rewarming. Two of these three had a history of AF. Ventricular ectopy occurred in only three patients and was not significant.

On average, arterial BP declined 5.9 mmHg/hour (95% CI, 0.1–11.7) during the cooling phase and then stabilized. Eight patients developed hypotension (BP < 90/50) mainly at low temperatures (mean 33.2°C ± 3°C), although one became hypotensive during induction (T_c = 36.7°C) and another after rewarming (T_c =

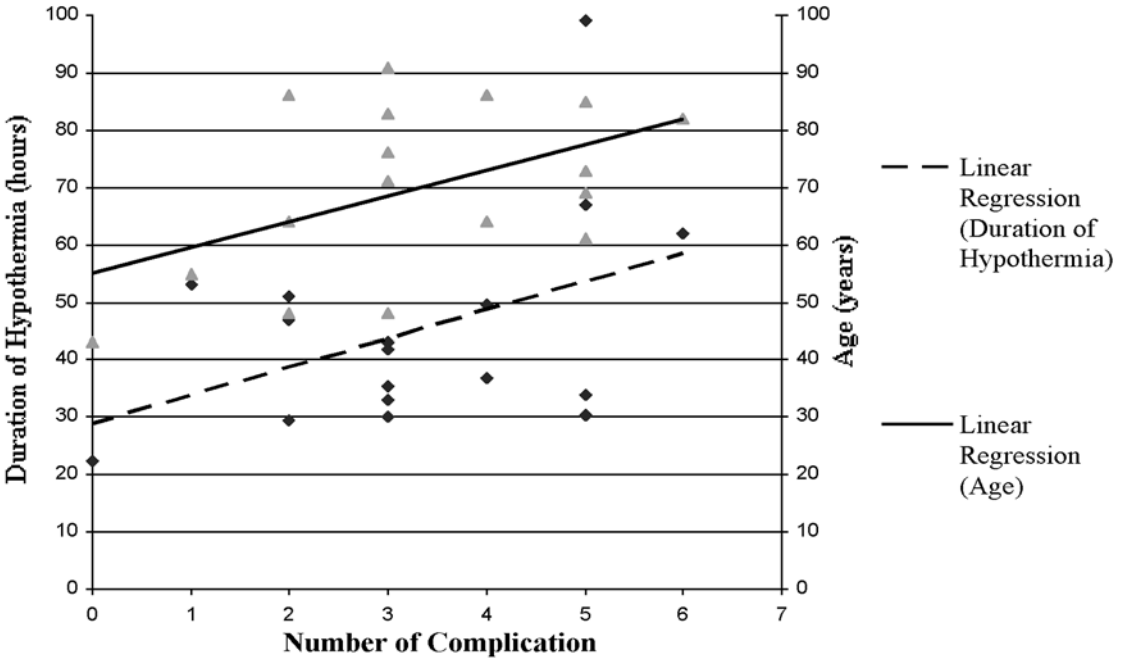

Fig. 1. Although the correlations were not statistically significant, there was a trend for a positive correlation between increasing age ($r^2 = 0.23$, $p = 0.0504$) and duration of hypothermia ($r^2 = 0.19$, $p = 0.08$) and the number of complications.

37.5°C). Five patients required vasopressor support. Five patients developed elevations of CPK-MB enzymes. One patient who had AF before cooling had elevations of CPK-MB on prehypothermia laboratory studies that only became available after the patient reached a T_c of 32°C. There were no ECG or myocardial function changes in this patient. Three patients developed elevations of CPK-MB while they were hypothermic and receiving vasopressors (phenylephrine in one and dopamine and phenylephrine in two). Vasopressors were used in two of these patients for the induction of hypertension to maintain cerebral perfusion in the setting of a large vessel occlusion. Neither one had troponin elevation or ECG or myocardial function changes. The third, an 85-year-old woman with a history of coronary artery disease receiving vasopressors for hypotension, did have ECG changes and a small area of myocardial akinesis by echocardiography. The last patient, an 88-year-old woman, developed CPK-MB elevation and ischemic ECG changes after rewarming but before extubation. She developed a bundle branch block, a decline in ejection fraction, and mild congestive heart failure (CHF).

Pulmonary complications occurred in eight patients. Aspiration pneumonia was treated successfully in three. Two others without radiographic evidence of pulmonary infiltrates were treated for suspected pneumonia because of fever and increased airway secretions. Two patients developed mild CHF requiring diuresis, one during hypothermia and the other after hypothermia (*see* previous paragraph). One patient developed atelectasis and a small pleural effusion that resolved with diuresis. Fourteen of the 18 (77.8%) patients were extubated on average 30.9 ± 42.7 hours after the completion of rewarming (range 0–144 hours, median 16 hours). The remaining four patients died after withdrawal of care. Two of these were not rewarmed as mentioned. The other two were

successfully rewarmed, but care was withdrawn because of stroke severity. Three of the four were intubated before enrollment into the study for airway protection (mean NIHSS = 25).

Seven patients developed infections, including the three confirmed and two possible cases of pneumonia mentioned in the previous paragraph. One of these had undergone thoracotomy 2 days before hypothermia. Another, with presumed pneumonia, had just completed a course of chemotherapy. One patient who was intubated the day before hypothermia developed sinusitis. One patient who had open-heart surgery developed *Pseudomonas bacteremia* 5 days after rewarming. All infectious complications were successfully treated, and there were no cases of sepsis. None of the patients with recent surgery experienced wound infections.

One patient who had received chemotherapy developed transient pancytopenia, consistent with his previous responses to chemotherapy. A large intracranial hematoma and disseminated intravascular coagulation (DIC) developed in a man treated with intravenous r-tPA. He then developed hypotension and lactic acidosis. Care was withdrawn after he developed herniation, despite attempted surgical evacuation of the hematoma.

Seventeen patients developed hypokalemia (mean $K^+ = 2.95 \pm 0.32$ mmol/L, range 2.2–3.4 mmol/L). None was symptomatic, and all potassium values returned to normal on rewarming. Serum potassium values were highly correlated with T_c (*see* Table 3). Decrements of serum bicarbonate and pH (Spearman correlation 0.41 and 0.53, respectively) were the only other laboratory changes that were significantly associated with hypothermia ($p = 0.011$ and < 0.001, respectively) (*see* Table 3). Serum lactate values were measured only in the last 10 patients, 7 (70%) of whom had elevations. Metabolic acidosis and elevated lactate values were seen in four patients, and this was clinically significant only in the two patients previously discussed. Respiratory alkalosis developed in six patients and a mixed metabolic acidosis and respiratory alkalosis developed in six others. Other adverse events included transient, mild, asymptomatic elevations of amylase and lipase in one patient without sequelae.

Table 3
Correlations between Temperature and Physiological and Laboratory Variables

Variable	*Spearman correlation*	*P-value*
Systolic BP	0.18	<0.001
Diastolic BP	0.017	0.64
MAP	0.11	0.003
Heart rate	0.37	<0.001
Glucose	–0.28	0.08
HCO3	0.41	0.011
Potassium	0.79	<0.0001
Sodium	0.25	0.12
pH	0.53	<0.001
Amylase	0.18	0.35
Lipase	0.09	0.65
WBC	–0.09	0.6
Platelet count	0.03	0.86
INR	–0.1	0.55
PTT	–0.19	0.26
Fibrinogen	–0.1	0.72

BP, blood pressure; MAP, mean arterial pressure; WBC, white blood cell count; INR, international normalized ratio; PTT, activated partial thromboplastin time.

Discussion

Hypothermia protects neural tissues from ischemic injury through several mechanisms, including attenuation of polymorphonuclear leukocyte (PMN)-mediated inflammatory response and decreasing adherence of leukocytes to endothelium, a reduction of cerebral metabolism, decreased release of excitatory amino acids, decreased generation of free radicals, reduction in lipid peroxidation and DNA degradation, and preservation of the blood-brain barrier *(1,3,4)*. These mechanisms increase the brain's ability to withstand critical levels of

low perfusion and may prolong the treatment window for thrombolytic therapy. Our initial experience shows that hypothermia may be induced by surface cooling in patients with acute ischemic stroke in combination with recanalization therapy. This can be accomplished relatively safely, although physiological changes should be expected and complications can occur.

Surface cooling is effective because the skin serves as a large surface area for heat exchange with the core and viscera *(13)*. Blood flowing through the skin and subcutaneous tissues brings with it heat from the body core, which is then lost at the skin surface via conduction and convection. Surface cooling results in reduction of the core body temperature. Brain cooling occurs as cool blood from the core flows to the brain. In areas where there is no perfusion (vessel occlusion), brain tissue is cooled through conductive heat loss to the surrounding, cooler, perfused regions of brain.

Prolonged hypothermia is associated with an increased infection risk and hematological complications, among others *(13)*. To minimize complications and provide optimal benefit, recanalization of the MCA was chosen as the criterion for initiating rewarming. In this way, hypothermia was maintained only during the period of ongoing ischemia (MCA occlusion) and the period of reperfusion injury (MCA recanalization). Because not all patients had recanalization, hypothermia was limited to 72 hours. Although cerebral edema can develop more than 72 hours after stroke onset, it peaks at 72 hours and continuation of the same level of hypothermia beyond that point may not be justified *(14)*.

The induction of hypothermia rapidly after ischemia onset requires a shorter duration of hypothermia and a less profound decrease in core temperature to produce a neuroprotectant effect, as compared with delayed hypothermia *(2)*. Therefore, a rapid technique for inducing hypothermia is more desirable. The major predictors of cooling rate in our study were body mass, shivering, and technique. Rubbing on the alcohol-ice mixture combines the benefits of cooling via conduction (the cold liquid contacting the skin) and convection (the evaporation of alcohol) with the vasodilatory effect of rubbing, which increases cutaneous blood flow and cutaneous heat delivery *(13)* . With this approach, hypothermia to 32°C was induced rapidly (mean 3.2 hours). This duration was shortened to as little as 2.3 hours, with experience and early induced paralysis to prevent shivering. Shivering greatly reduces the efficacy of surface cooling by increasing heat production 250–1000 kcal/hour *(13)*. This is evidenced by our early experience when paralysis was delayed until shivering began. In previously published large series of induced hypothermia with surface cooling, the cooling time ranged from 3.5 to 6.8 hours *(7,10)*. Schwab and colleagues used cooling blankets without performing alcohol/ice baths, and Clifton et al. "applied" ice along with cold gastric lavage and room temperature air in the ventilator circuit *(7,10)*. Initially, the authors also gave cooled intravenous fluids and gastric lavage. They found that this did not increase the rate of cooling because of the large heat capacity of the human body. Large volumes of liquid must be infused by this method to cool effectively. Also, gastric lavage can cause gastric distension and predispose to aspiration if large volumes (>200–300 mL) are given *(13)*. Although the weight of the patients was not specified in these series, it is likely that the differences in cooling rates resulted from the authors' cooling technique. Others have used a forced-air apparatus to induce hypothermia, but cooling times were as long as 8 hours *(11)*. Naritomi and colleagues induced hypothermia to 33°C in four patients within 2 hours using a cooling method similar to ours, but they did not ventilate with air at room temperature *(5)*. Although the large surface area of the lungs is a potential large source for heat loss, it did not facilitate cooling in our study. The vigorous application of the ice-alcohol rub over the entire body with early paralysis is a highly effective and rapid means for inducing hypothermia.

Deeper states of hypothermia are associated with more complications, especially bradycardia, hypotension, and cardiac arrhythmias *(13,15)*. In experimental models, 32°C offers the best balance between providing cerebral protection while minimizing complications *(1,2)*. It was difficult to maintain patients' temperatures within the desired range with surface cooling, especially during the initial cooling phase. There were continuous temperature fluctuations that required frequent adjustments of the cooling apparatus to prevent T_c overshoot/undershoot and that prolonged the hypothermia by prolonging the rewarming phase. This results from the delay in transfer of heat from the periphery to the core and vice versa *(16)*. Another possible explanation is that we used bladder temperature to measure T_c, and this can often lag behind tympanic and esophageal temperatures, which more accurately and rapidly reflect true T_c *(13)*. With experience, the nursing staff learned to anticipate the magnitude of apparatus adjustment needed for any particular situation, but this was not precise. In addition to fluctuations in T_c, the authors' method of inducing hypothermia was quite laborious and added greatly to the complexity of nursing care for these patients. Alternatives to surface cooling, such as body cavity irrigation, extracorporeal cooling with cardiopulmonary bypass, or venous-venous cooling, are potentially more rapid and precise methods of cooling but are invasive, technically challenging, and not as readily available *(13)*. Newly developed intravenously placed heat exchange catheters may be a more accurate and rapid means of cooling, but they are not available outside of clinical trials.

The best approach to pH management in patients with hypothermia and acute stroke is not clear. With hypothermia, carbon dioxide (CO_2) becomes more soluble but the $PaCO_2$ decreases, maintaining CO_2 content constant. This causes pH to increase by 0.015°C, which is similar to the rate of pH change of pure water (0.017°C). This close relationship between pH and temperature is maintained through buffering by the alpha-imidazole moiety of protein-bound histidine. With decreases in [H+], the fraction of (OH-) on alpha-imidazole groups decreases simultaneously so that the normal 16/1 ratio of OH-/H+ remains constant *(17)*. Thus, despite appearing more alkalotic with decreased $PaCO_2$ and increased pH, the actual acid-base balance is the same during hypothermia. A strategy that allows for hypocarbia and alkalosis is called "*alpha-stat*." A strategy that corrects the hypocarbia and maintains a normal pH is called "*pH-stat*." The authors used alpha-stat management for all their patients. Arterial blood gas changes were variable. As expected, the most commonly observed pattern was an initial respiratory alkalosis. In most patients, this was followed by metabolic acidosis, perhaps from decreased peripheral tissue perfusion, shivering, or lactate production. Previous hypothermia studies have varied in their approaches *(7,10,18)*. Experimental models suggest that *pH-stat* is disadvantageous because of decreased cardiac output and increased lactic acidosis and ventricular arrhythmias *(19)*. In acute ischemia, *alpha-stat*-induced hypocarbia is theoretically disadvantageous because of cerebral vasoconstriction and shunting of blood away from ischemic regions. Although there is controversy about the optimal method of pH management, currently there are no clinical data in acute ischemic stroke to justify the use of one technique preferentially.

The main physiological changes that we observed are similar to those previously reported *(1,7,10)*. Bradycardia, hypotension, hypokalemia, and an initial diuresis occurred in almost all of the patients. These changes were temperature-dependent. We also found a trend for more complications in those patients who were cooled longer and who were older. The most common complication was hypotension. Hemodynamic support was needed in only five of eight patients with hypotension, most without sequelae. Myocardial infarcts occurred in two patients, only one was hypothermic at the time. Both patients were older and more likely to have underlying coronary artery disease. Multiple factors, including hypotension, vaso-

pressor use for induced hypertension, hypothermia-associated microcirculatory changes (e.g., increased blood viscosity) and cold-stress-induced increased cardiac O_2 consumption, may have contributed to the risk of coronary ischemia *(13)*. The isolated elevation of CPK-MB levels in two patients is of unclear origin and significance, because neither patient had electrographic or clinical evidence of ischemia. Myocardial irritability is well described with hypothermia, and AF is common at temperatures < 32°C *(13,15,20)*. Only one of our patients (who had a history of AF) developed AF while hypothermic.

Pneumonia was the next most common complication and occurred in 28% of patients. In several large studies of stroke patients of all severities, pneumonia developed in 5–9% of patients *(21–23)*. A combination of factors, including stroke severity (mean NIHSS = 21.4) and intubation, likely contributed to the 28% rate of pneumonia in the patients. In previous hypothermia studies, pneumonia was noted in up to 40% of patients, and it is unclear if hypothermia may predispose patients to pneumonia *(7)*. Previously reported complications, such as pancreatitis, thrombocytopenia, and coagulopathy, were rare or did not occur in our patients *(7,9,13,24)*. Platelet counts and fibrinogen levels were unaffected by temperature. PT and aPTT values measured by our laboratory at 37°C may not have reflected the true state of the coagulation system at hypothermic temperatures *(13)*. However, clinically there was no evidence of coagulopathy, except in the one patient who developed intracerebral hemorrhage (ICH) and DIC after intravenous r-tPA. Serious medical complications occur in 20–24% of all patients admitted with acute stroke, including a 3% incidence of myocardial infarction *(22,23)*. Most of the complications that occurred in the patients were mild, and nearly all of the critical complications occurred in only two patients. Because nearly 30% of the patients had surgery and one patient was receiving chemotherapy, the number of medical complications, especially pneumonia, experienced by our patients was acceptable.

Rewarming was uneventful, except for rebound edema and herniation in one patient. This patient had the largest stroke of all of the patients treated in the series. He was cooled the longest, 72 hours, but he still developed malignant intracranial hypertension on rewarming. Although hypothermia was reported to control intracranial pressure (ICP) by Schwab and colleagues, 44% of their patients died of elevated ICP, half while hypothermic and half during rewarming *(7)*. Prolonged hypothermia is effective in reducing elevated ICP (the authors effectively treated two patients for intracranial hypertension with hypothermia) but is probably not adequate to prevent malignant swelling on rewarming in all patients, although slower rates of rewarming have been associated with a decreased risk of rebound elevation of ICP *(25)*. Prevention of ischemic injury rather than intracranial hypertension may be the more effective application of hypothermia.

As discussed, the surface cooling method is imprecise and temperature fluctuations are common. This is a major drawback to surface cooling and may have contributed to a higher number of complications, particularly with low temperatures. Another limitation of surface cooling is the need to induce paralysis and sedation to prevent shivering. Although there are other potential methods for shivering suppression, they are most effective with the concomitant use of a warming blanket to block the skin-hypothalamic shivering circuit, a technique that obviously can not be used with surface cooling *(26,27)*. Another limitation of this study is the small number of patients and heterogeneous population treated. Because this was not an efficacy trial but rather a feasibility and safety study, the large number of physiological and laboratory data points collected allowed for statistically valid analyses to be performed. An additional limitation is that our cooling technique was not uniform. We adjusted the technique to maximize cooling efficiency, but because we did not perform a controlled trial comparing particular cooling methods individually (e.g., gastric lavage), it is possible that we

erroneously disregarded an effective method. The improvements in their cooling efficiency may have resulted from more experience with the technique. However, it was our intent to modify the technique to improve efficiency, and, using their protocol, they achieved rapid cooling rates *(7,10)*.

Conclusions

This report has shown that hypothermia can be administered quickly and with a relative degree of safety to patients with acute ischemic stroke. Preventing shivering and vigorous, whole body rubs with ice and alcohol are essential for rapid cooling. Older patients and those cooled for long time periods may be at increased risk for complications. Our experience with postoperative patients shows that hypothermia may be applied to a variety of patients with stroke, not just selected cases that fit an idealized trial design. Further studies are needed to determine the efficacy of this approach.

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