



Therapeutic Hypothermia after Cardiac Arrest: Performance Characteristics and Safety of Surface Cooling with or without Endovascular Cooling

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Published online: 1 September 2007
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Abstract

Introduction Various methods are available to induce and maintain therapeutic hypothermia after cardiac arrest, but little data is available comparing device-mediated cooling to simple surface methods in this setting.

Methods To assess the performance characteristics of simple surface cooling with or without an endovascular cooling catheter system, we retrospectively reviewed all cases of hypothermia for comatose survivors of cardiac arrest treated at a single academically affiliated urban hospital. Forty two comatose survivors of cardiac arrest were treated over a 3.5-year period. Hypothermia was induced and maintained by simple surface methods (ice packs, cooling blankets) with or without placement of an endovascular cooling catheter system with automated temperature feedback regulation.

Results Overall, the rate of active cooling was not different between patients treated with endovascular catheter-assisted hypothermia and patients treated with surface cooling alone. However, use of a larger (14 F) catheter was associated with faster cooling rates. Maintenance of goal temperature (33°C) was far better controlled with the use of a cooling catheter. Use of surface cooling alone was associated with significant temperature overshoot. Patients treated with surface cooling alone spent more time bradycardic.

Conclusion Use of an endovascular cooling catheter as part of a treatment protocol for hypothermia after cardiac arrest provides better control during maintenance of hypothermia, preventing temperature overshoot. Active cooling rates may be enhanced by the use of a larger cooling catheter.

Keywords Cardiac arrest · Cardiopulmonary resuscitation · Anoxic brain injury · Therapeutic hypothermia

Introduction

More than 40 years have passed since the initial reports of induced hypothermia for cardiac arrest survivors [1–3]. Randomized clinical trials have now demonstrated that induction of mild hypothermia (~33°C) in patients who are comatose immediately after resuscitation from cardiac arrest improves both survival and neurological outcome [4–6].

Based on these clinical trial data, recently revised international and U.S. resuscitation guidelines [7–9], as well as other sources [10–13], now recommend that mild hypothermia should be standard of care for comatose survivors of out-of-hospital cardiac arrest in which the initial rhythm is ventricular fibrillation or ventricular tachycardia. Despite these recommendations, implementation of post-arrest hypothermia remains low [14, 15]. The reasons why post-arrest hypothermia has not been widely adopted are complex, but the lack of a universally accepted protocol and established best method for inducing and maintaining mild hypothermia may be one factor [14].

Here we report the experience to date with post-arrest therapeutic hypothermia at a single institution

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(San Francisco General Hospital (SFGH), San Francisco, California). Starting in early 2003, comatose survivors of cardiac arrest treated at SFGH were either cooled by surface methods alone (ice packs and manually regulated cooling blankets) or by surface cooling augmented by placement of an endovascular cooling catheter with an automated feedback system for temperature regulation (Innercool Celsius Control system, Innercool Therapies, San Diego, CA). In order to test the hypothesis that placement of a cooling catheter is a safe and effective adjunct for the induction and maintenance of hypothermia after cardiac arrest, we retrospectively compared the temperature performance characteristics and safety of these two approaches.

Materials and Methods

In order to assess the temperature performance characteristics and safety of surface cooling compared to catheter-assisted hypothermia for survivors of cardiac arrest, we performed a retrospective review of all cases of post-arrest resuscitative hypothermia at San Francisco General Hospital (SFGH, San Francisco, California). Cases were captured for retrospective analysis from the commencement of the SFGH Post-Arrest Hypothermia Protocol in February, 2003 until August, 2006, a 3.5-year period. The institutional protocol at SFGH for post-arrest hypothermia requires that all patients who are successfully resuscitated from cardiac arrest (either out-of-hospital or in-hospital) be screened by the Neurology Consult Service at SFGH and the Neurocritical Care Fellow or Attending. We therefore captured potential cases by querying our departmental database with a list of ICD-9 codes encompassing various forms of cardiac arrest and anoxic brain injury (427.5, 427.41, 427.42, 427.4, 427.1, 348.1, 997.1). Discharge dictation summaries and the electronic medical record were screened for all patients identified in this fashion.

For all patients identified as survivors of cardiac arrest treated with therapeutic hypothermia, we reviewed in detail all discharge dictation summaries, the electronic medical record, and the paper chart, including records from Emergency Medical Services (EMS) and the Emergency Department (ED). Vital signs data, including measurements of patient temperature, were obtained from a stored central database captured from the intensive care unit (ICU) monitoring system as well as from the EMS and ED paper records.

For the purposes of comparing surface to catheter-assisted cooling methods, we used a conservative approach and defined all cases in which a cooling catheter was placed, regardless of the timing of placement, as “catheter-assisted.” The assignment to surface-only or catheter-assisted hypothermia was made by the treating physicians.

We reviewed the physicians’ notes in the paper medical record of each patient to assess reasons provided for not using the cooling catheter. As allowed for in the SFGH therapeutic hypothermia protocol, surface methods could be continued along with catheter-induced hypothermia until the target temperature was reached. Surface cooling was performed by the application of ice packs to the patient’s core and non-adherent cooling blankets (Blanketrol 2, Cincinnati Sub-Zero Products, Inc.). The application and removal of ice packs and the application and temperature regulation of the cooling blanket were performed manually by the ICU bedside nurse. Endovascular cooling catheters, when placed, were either 10.7 F or 14 F (Innercool Celsius Control system, Innercool Therapies, San Diego, CA), with size choice made by the treating physicians. The endovascular cooling system became available to use at SFGH 9 months after the start of the cooling protocol, and both catheter sizes were available to use from this time forward.

All patient temperatures were measured by a rectal temperature probe. The target temperature in the SFGH therapeutic hypothermia protocol (see Table 1) is 33°C, so we used a target range of 32.5–33.5°C in calculations related to reaching and maintaining the mild hypothermia target. The following definitions related to hypothermia treatment were used for this study. The “time to target temperature” was defined as the time of return of spontaneous circulation (ROSC) to the first time at which a temperature of 33.5°C or less was recorded. The rate of cooling was calculated in two ways. First, the “overall rate of cooling” was determined from the maximum pre-cooling temperature to the target temperature (33.5°C), divided by the time to target temperature as defined above. Second, the “active rate of cooling” was determined from the last temperature recorded prior to active cooling to the target temperature (33.5°C), divided by the times at which these temperatures were recorded. Since the exact times of surface cooling initiation and endovascular cooling initiation were not systematically documented, the active cooling phase was defined as the period of downward deflection in temperature associated with therapeutic hypothermia, until the target of 33.5°C was reached. The maintenance phase extended from the time at which the target of 33.5°C was reached to the time at which rewarming began and the temperature was recorded above 33.5°C. Patients who were already hypothermic post-arrest at 34.5°C or below and did not undergo rewarming to 34.5°C or above prior to initiation of hypothermia were not used in our calculations of the time to target temperature or cooling rates, but these patients were used in calculations related to the maintenance phase.

Mild hypothermia (32–34°C), moderate hypothermia (28–32°C), and severe hypothermia (less than 28°C) were defined according to accepted criteria [16]. Overshoot and

Table 1 SFGH hypothermia after cardiac arrest protocol*Inclusion criteria:*

- (1) Age \geq 18 years.
- (2) Women \geq 50 or negative pregnancy test.
- (3) Cardiac arrest with return of normal rhythm.
- (4) No eye opening to noxious stimulation after resuscitation (no “waiting period”).
- (5) Blood pressure \geq 90 mm Hg systolic (spontaneously or with fluids/pressors).
- (6) Known time of arrest (may consider excluding “found down” of unknown duration).
- (7) All patients meeting inclusion and exclusion criteria for hypothermia following cardiac arrest are candidates for endovascular cooling (use of the intravascular cooling catheter).

Exclusion criteria:

- (1) Another reason to be comatose (e.g. convulsive status epilepticus).
- (2) Pregnancy.
- (3) Known terminal illness preceding the arrest.
- (4) Known severe coagulopathy or active bleeding (relative exclusion, particularly for patients on warfarin anticoagulation at time of cardiac arrest).
- (5) No limit on duration of resuscitation effort; however, <1 h most desirable.
- (6) Any condition that precludes placement of a large-bore catheter (up to 14 F) into the inferior vena cava via a femoral vein is an exclusion for use of the intravascular cooling catheter. History of an indwelling IVC filter is an exclusion for this reason.

Hypothermia Protocol (Goal temperature 33°C to be achieved as soon as possible):

- (1) Patients should be enrolled as quickly as possible. For out-of-hospital arrests, ED attending will make decision to implement protocol. For in-hospital arrests, CCU resident in charge of completed code will make decision.
- (2) Page on-call Neurology Consult Resident for immediate initial neurological assessment prior to pharmacologic paralysis. *Do not delay initiation of hypothermia pending this assessment.*
- (3) Cooling methods: All patients should have surface cooling begun immediately.
 - (a) Place ice packs under the armpits, next to the neck, on the torso and the limbs.
 - (b) Two cooling blankets should be used, one under and one over the patient.
- (4) Endovascular cooling catheter may be placed at discretion of Neurocritical Care Fellow or Attending.
- (5) Temperature-sensing Foley catheter should be placed if available, otherwise rectal or tympanic temperatures should be used (in that order).
- (6) Page the ICU Resident to manage the ventilator and sedation in consultation with the Neurocritical Care fellow.
- (7) The ventilator humidifier should be turned off and a Heat Moisture Exchanger (HME) should be used.
- (8) The room thermostat should be turned off.
- (9) Administer midazolam 2–6 mg/h IV and fentanyl 25–75 mcg/h IV. Propofol 10–50 mcg/kg/min IV can be considered as an alternative if patient is hemodynamically stable.
- (10) Once sedation started, give vecuronium 0.1 mg/kg bolus IV, then vecuronium 1 mg/h IV. Titrate the drip 0–5 mg/h to keep 1/4 twitches. Consider cisatracurium if renal failure present.
- (11) If seizures suspected, place patient on continuous EEG monitoring.
- (12) Patients should be on insulin drip if glucose >140 mg/dl, daily aspirin, on pressors and/or nitrates to maintain blood pressure, and any anti-arrhythmics necessary.
- (13) Patients may receive other cardiac interventions including systemic thrombolysis, anticoagulation, and urgent cardiac catheterization as needed. *Important: hypothermia should proceed concurrently with these interventions.*
- (14) Once the patient reaches 33°C (bladder, rectal, or tympanic), keep patient at 33°C using cooling catheter (if in place) or by removing ice packs and top cooling blanket if necessary.
- (15) Begin rewarming 24 h after the beginning of cooling (not 24 h after target temperature is reached). Patient should be slowly rewarmed to 37.0°C over 18–24 h:
 - (i) If cooling catheter is in place, then use console to control rewarming. Otherwise allow slow passive rewarming.
 - (ii) Turn room thermostat up to normal, turn on ventilator heater, turn off cooling blanket.
 - (iii) May use regular blankets, but *not* warming blankets.
- (16) Paralysis, then sedation, may be discontinued during or after rewarming, based on shivering and other critical care issues.

undershoot of the target temperature during the maintenance phase were assessed in several ways. The percentage of time spent within the target temperature range

(32.5–33.5°C) was calculated for surface cooling and catheter-assisted groups. The mean temperature error was defined as the mean absolute value of the difference

between the target temperature (33.0°C) and the temperature recorded each hour during the maintenance phase. The temperature error burden (in °C/h) was defined as the sum of the absolute values of the difference between the target temperature (33.0°C) and the temperature recorded each hour during the maintenance phase. The temperature error burden was further divided into the overshoot burden (lower than 33.0°C) and the undershoot burden (higher than 33.0°C) to determine if either cooling technique led to excessive overshoot, undershoot, or both. Overshoot was further characterized by the percentage of patients that experienced overshoot into at least the moderate hypothermia range (<32°C).

Retrospective chart and electronic medical record review was approved by the local institutional review board (UCSF Committee on Human Research).

Statistical analysis was performed using InStat version 3 (GraphPad Software, <http://www.graphpad.com/>) and Stata SE version 9 (StataCorp LP, <http://www.stata.com/>). Categorical data were compared using Fisher's exact test. Continuous data were assessed for normality by the Kolmogorov-Smirnov test. Normally distributed continuous data were compared by Student's *t*-test. Non-normally distributed continuous data were compared by the non-parametric Mann-Whitney test. Continuous data in more than two groups were analyzed by the Kruskal-Wallis test (nonparametric ANOVA), with post-hoc individual pair comparisons by Dunn's multiple comparisons method.

Results

During the 3.5-year study period, 42 patients were treated with therapeutic hypothermia after cardiac arrest at SFGH according to a hospital protocol (Table 1). The mean age was 55.8 ± 13.1 years (range 22–80). Of the 42 treated patients, 11 (26.2%) were female. In 38/42 patients (90.5%), the cardiac arrest occurred out of hospital. The initial documented code rhythm was ventricular fibrillation (VF) in 21/42 (50%), asystole in 11/42 (26.2%), pulseless electric activity (PEA) in 9/42 (21.4%), and ventricular tachycardia (VT) in 1/42 (2.4%). The first recorded temperature was 34.9 ± 2.2°C overall. However, spontaneous rewarming prior to initiation of the active cooling protocol occurred in 20/42 patients (47.6%). Among the 20 patients that experienced spontaneous rewarming prior to cooling, the mean maximum temperature reached was 36.0 ± 1.0°C, a mean rise in temperature of 1.4 ± 1.1°C (range 0.2–4.8°C).

An endovascular cooling catheter (Innercool Celsius Control) was used to assist therapeutic hypothermia in 19/42 patients (45.2%). The reasons for catheter nonuse were as follows: 8 patients were treated prior to the availability

of the cooling catheter at SFGH, 3 patients were coagulopathic, 3 patients were already at or beyond goal temperature at the start of the hypothermia protocol, 2 patients had unsuccessful attempts at catheter placement, 1 patient received intravenous thrombolysis for massive pulmonary embolus, and 1 patient had an acute abdominal process. In 5 patients, the reasons for catheter nonuse were not documented. In 6/19 patients (31.6%) in whom a catheter was placed, the catheter was a 14 F size and in 12/19 (63.2%) the catheter was a 10.7 F size.

Premorbid medical conditions in the treated population included hypertension in 22/42 (56.4%), hypercholesterolemia in 10/42 (25.6%), coronary artery disease in 10/42 (25.6%), illicit drug use in 8/42 (20.5%), end-stage renal disease in 8/42 (20.5%), diabetes mellitus in 7/42 (17.9%), atrial fibrillation in 7/42 (17.9%), alcoholism in 6/42 (15.4%), congestive heart failure in 5/42 (12.8%), and cardiomyopathy in 5/42 (12.8%). These and other baseline patient characteristics are stratified according to catheter use or nonuse in Table 2; no significant differences in baseline patient characteristics were detected between the catheter use and nonuse groups.

As described above, rates of cooling were assessed in two ways—the overall rate of cooling and the active rate of cooling (see Methods). Excluding 8 patients (5 surface, 3 catheter) who were already <34.5°C and did not spontaneously rewarm prior to initiation of active cooling, there was no difference in overall rates of cooling (from ROSC to goal temperature) according to cooling method. The overall cooling rate was 0.50 ± 0.32°C/h in the surface group and 0.56 ± 0.20°C/h in the catheter group (*P* = 0.13, Mann-Whitney test). The overall cooling rate for both groups was 0.52 ± 0.27°C/h. The time from ROSC to 33.5°C was also not different between the two groups: 421.9 ± 163.4 min in the surface group and 393.7 ± 141.3 min in the catheter group (*P* = 0.63, Student's *t*-test). Comparison of the three groups did not reveal a difference in the ROSC to 33.5°C time (*P* = 0.45, ANOVA). The overall time from ROSC to 33.5°C in our series was 408 ± 152 min, range 182–742 min.

The active rate of cooling was also not different between the two groups: 1.21 ± 0.65°C/h in the surface group and 0.96 ± 0.68°C/h in the catheter group (*P* = 0.16, Mann-Whitney test). We therefore tested the hypothesis that the two different catheter sizes used may have produced different cooling rates. The active rates of cooling in the 14 F catheter group (1.84 ± 0.72°C/h), 10.7 F catheter group (0.89 ± 0.29°C/h), and surface group (1.21 ± 0.65°C/h) were indeed different (*P* = 0.02, Kruskal-Wallis test), with a more rapid rate of cooling in the 14 F catheter group, when compared to either the 10.7 F catheter group or the surface group (*P* < 0.05, Dunn's multiple comparisons test).

Table 2 Baseline patient characteristics

	Surface (n = 23)	Catheter (n = 19)	Total (n = 42)	P
Mean Age in years ± SD	54.7 ± 12.2	57.2 ± 14.3	55.8 ± 13.1	0.55
Female sex	39.1% (9/23)	10.5% (2/19)	26.2% (11/42)	0.08
Hypertension	57.1% (12/21)	55.6% (10/18)	56.4% (22/39)	0.59
Diabetes mellitus	9.5% (2/21)	27.8% (5/18)	17.9% (7/39)	0.22
Hypercholesterolemia	19% (4/21)	33.3% (6/18)	25.6% (10/39)	0.47
Atrial fibrillation	23.8% (5/21)	11.1% (2/18)	17.9% (7/39)	0.42
Congestive heart failure	9.5% (2/21)	16.7% (3/18)	12.8% (5/39)	0.65
Cardiomyopathy	19% (4/21)	5.6% (1/18)	12.8% (5/39)	0.35
Coronary artery disease	33.3% (7/21)	16.7% (3/18)	25.6% (10/39)	0.29
Pacemaker	4.5% (1/22)	0% (0/18)	2.5% (1/40)	1.0
Valvular heart disease	4.8% (1/21)	11.1% (2/18)	7.7% (3/39)	0.59
Peripheral vascular disease	9.5% (2/21)	11.1% (2/18)	10.3% (4/39)	1.0
End-stage renal disease	14.3% (3/21)	27.8% (5/18)	20.5% (8/39)	0.43
Illicit drug use	23.8% (5/21)	16.7% (3/18)	20.5% (8/39)	0.70
Alcoholism	14.3% (3/21)	16.7% (3/18)	15.4% (6/39)	1.0
Psychiatric disease	0% (0/21)	16.7% (3/18)	7.7% (3/39)	0.09
Initial code rhythm = VF/VT	56.5% (13/23)	42.1% (8/19)	50% (21/42)	0.54
Out of hospital arrest	91.3% (21/23)	89.5% (17/19)	90.5% (38/42)	1.0
Time to EMS arrival (min) ^a	4.9 + 2.4	6.1 + 2.4	5.4 + 2.4	0.16
Time to ED arrival (min) ^a	40.0 + 11.5	40.6 + 11.3	40.3 + 11.2	0.89
Time to ROSC (min)	33.2 + 14.9	33.4 + 15.5	33.3 + 15.0	0.98

Data are presented either as percent of group (number in group/total in group) or as mean ± standard deviation. *P* values are for Fisher's exact test comparing surface and catheter groups for categorical data and for *t*-test comparison between surface and catheter groups for continuous data (age). VF = ventricular fibrillation. VT = ventricular tachycardia. Time to EMS Arrival = time from EMS activation to EMS arrival. Time to ED Arrival = time from EMS activation to ED arrival. Time to ROSC = time from EMS activation or witnessed arrest time to ROSC.

^a EMS and ED times are for out-of-hospital arrests only

We next tested the hypothesis that catheter-assisted cooling provided tighter control of patient temperature during the maintenance phase of hypothermia than did surface cooling alone. The maintenance phase was defined as the time at which 33.5°C was first reached to the time at which 33.5°C was crossed during the rewarming phase (see Fig. 2A). Comparison of the raw or averaged temperature curves for the two groups demonstrated tighter temperature control during the maintenance phase among the catheter-cooled patients (Fig. 1). This tighter control with the use of catheter-assisted hypothermia could be quantified in several ways. The percentage of time spent within the target temperature range (32.5–33.5°C) during the maintenance phase was higher for the catheter-assisted group (95.7 ± 7.9%) than it was for the surface-cooled group (36.7 ± 18.4%) (*P* < 0.0001, Mann–Whitney test; Fig. 2B). Similarly, the mean temperature error (the mean absolute value of the difference between the target temperature (33.0°C) and the temperature recorded each hour during the maintenance phase) was lower for the catheter-assisted group (0.14 ± 0.10°C) than it was for the surface cooled group (1.13 ± 0.78°C) (*P* < 0.0001, Mann–

Whitney test; Fig. 2C). The temperature error burden (the area under the curve for both overshoot below 33.0°C and undershoot above 33.0°C, in °C/h) was also different between the two groups (3.14 ± 2.13°C/h for the catheter group vs. 23.2 ± 13.1°C/h for the surface group, *P* < 0.0001, Mann–Whitney test; Fig. 2D). To determine if the greater degree of temperature error burden in the surface group was due to problems with overshoot, undershoot, or both, we separately compared the two groups according to overshoot and undershoot burdens. There was significantly greater temperature overshoot burden in the surface group (18.1 + 14.2°C/h) compared to the catheter group (1.8 + 2.4°C/h) (*P* < 0.0001, Mann–Whitney test; Fig. 2E). In contrast, no difference was detected between the two groups for temperature undershoot burden (5.1 ± 8.0°C/h for the surface group vs. 1.3 ± 1.5°C/h for the catheter group, *P* = 0.35, Mann–Whitney test; Fig. 2F). Consistent with the above findings, a greater percentage of patients in the surface group experienced overshoot to moderate to severe hypothermia (<32°C) (82.6% in the surface group vs. 10.5% in the catheter group, *P* < 0.0001, Fisher's exact test). Of note,

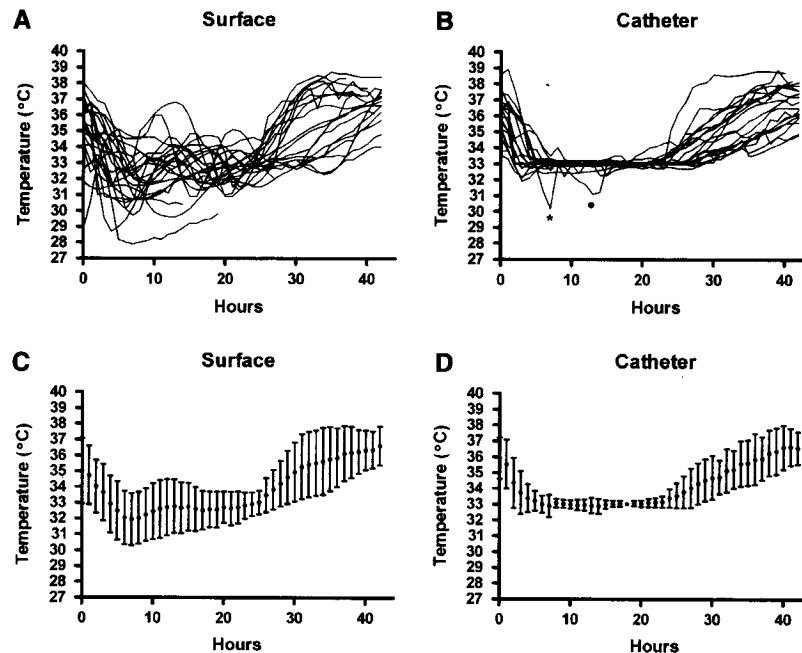


Fig. 1 Temperature curves in the surface cooled and catheter-assisted hypothermia groups. $t = 0$ for each plot is defined by the initial downward deflection in patient temperature at the start of the active cooling phase (see Methods). (A) Raw temperature curves for all patients treated with surface cooling only. (B) Raw temperature curves for all patients treated with catheter assisted hypothermia.

(Asterisks and solid circle indicate two patients in which overshoot occurred prior to the placement of a cooling catheter). (C) Mean \pm standard deviation temperature curve for all patients treated with surface cooling only. (D) Mean \pm standard deviation temperature curve for all patients treated with catheter assisted hypothermia

the two patients with overshoot to $<32^{\circ}\text{C}$ in the catheter group experienced overshoot prior to placement of the cooling catheter.

Complications in the two groups and for the overall patient population treated with therapeutic hypothermia are shown in Table 3. One common complication of hypothermia, bradycardia, was different between the two groups. While the percentage of patients experiencing any bradycardia (HR < 60) was not significantly different between the two groups (60.9% of the surface group vs. 42.1% of the catheter group, $P < 0.35$, Fisher's exact test), the percentage of time during cooling spent bradycardic was significantly higher in the surface group (15.6 + 17.8% in the surface group vs. 4.7 + 8.5 in the catheter group, $P = 0.047$, Fisher's exact test). Among patients with overshoot to $<32^{\circ}\text{C}$, 67% (14/21) experienced bradycardia; among patients without overshoot below 32°C , 30% (9/30) experienced bradycardia ($P = 0.01$, Fisher's exact test). Among patients with overshoot to $<32^{\circ}\text{C}$, the mean percentage time spent bradycardic was $15.6 \pm 18.3\%$; among patients without overshoot below 32°C , the mean percentage time spent bradycardic was $5.7 \pm 9.3\%$ ($P = 0.03$, t -test). Four patients in the surface group had a recurrent cardiac arrest while being cooled, and no patients in the catheter group had a recurrent cardiac arrest, but this difference was not significant

($P = 0.11$, Fisher's exact test). In 3 out of the 4 patients in the surface group with repeat cardiac arrest, the repeat arrest was fatal. Among the 4 patients with recurrent arrest while being cooled by surface cooling alone, the reason for use of surface cooling only was as follows: prior to catheter availability in 1 patient, coagulopathy from use of thrombolytic for PE in 1 patient, and patient already at or below goal temperature in 2 patients. Other complications, including bleeding, elevation in the international normalized ratio (INR), and in-hospital mortality, were not different between the two groups.

Discussion

In this retrospective analysis of the use of surface and catheter-assisted therapeutic hypothermia after cardiac arrest, we found clinically important differences between the two methods. Catheter-assisted cooling provided significantly better temperature control in the maintenance phase of therapeutic hypothermia, preventing overshoot into moderate to severe hypothermia. As moderate to severe hypothermia is known to be associated with greater complication rates, including bradycardia, malignant arrhythmias, coagulopathy, and bleeding, this difference in temperature overshoot may be clinically important. Indeed,

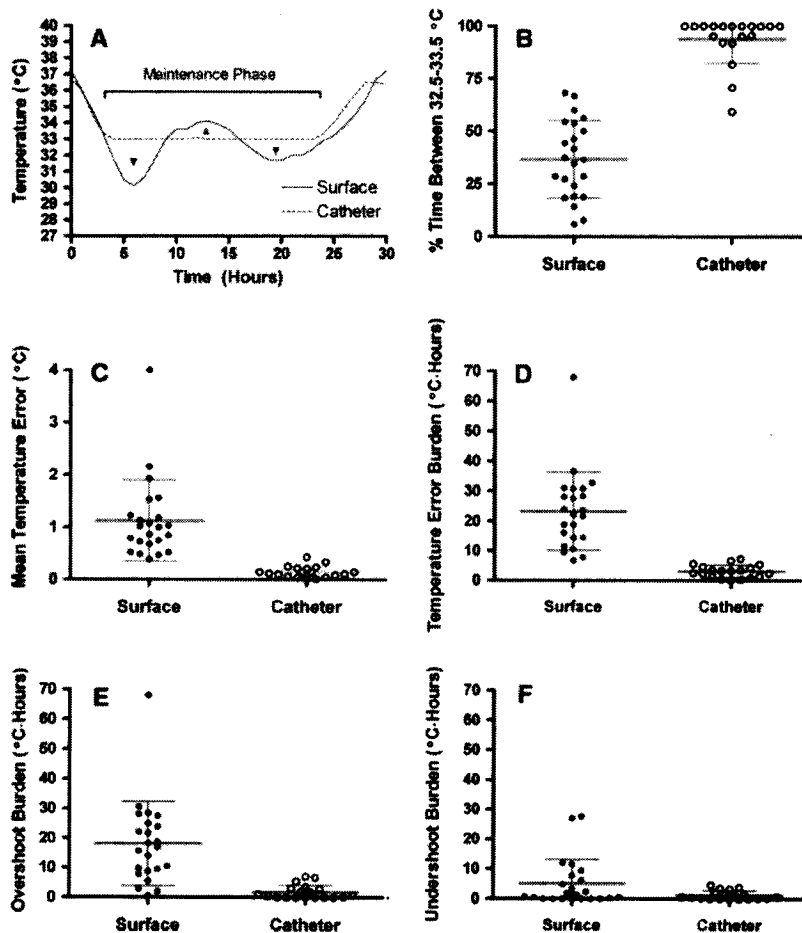


Fig. 2 Control of patient temperature during hypothermia maintenance. (A) Two representative patient temperature curves, one treated with surface cooling only and one treated with catheter-assisted hypothermia, to show the maintenance phase of therapeutic hypothermia (from the initial attainment of 33.5°C during active cooling to the time that the temperature rises above 33.5°C at the start of the rewarming phase). (B) Percentage of time spent in the goal temperature range (32.5°C–33.5°C) during maintenance in the two groups. Circles indicate individual patient values. The thick vertical gray bars indicate the mean in each group and the thin vertical gray

bars indicate the \pm standard deviation. (C) Mean temperature error during maintenance in the two groups (the mean absolute difference between patient temperature and the goal temperature of 33.5°C). (D) Temperature error burden during maintenance in the two groups (the absolute area under the curve for the difference between patient temperature and the goal temperature of 33.5°C). (E) Overshoot burden during maintenance in the two groups (the temperature error burden below the goal temperature of 33.5°C). (F) Undershoot burden during maintenance in the two groups (the temperature error burden above the goal temperature of 33.5°C)

we found that patients cooled by surface methods alone spent more time bradycardic during cooling, and we also found that temperature overshoot was associated with bradycardia. We did not find differences in the rates of coagulopathy, bleeding, or repeat arrest.

The use of a cooling catheter in general (either 10.7 F or 14 F) did not appear to produce more rapid active cooling when compared to surface cooling only. However, use of the larger (14 F) catheter did produce a >50% faster rate of active cooling than surface cooling alone. The ROSC to 33.5°C time was not different with the use of either type of catheter, possibly because of delays in initiating cooling, spontaneous rewarming in the ER, and the time required to place a cooling catheter.

The mean time overall from ROSC to 33.5°C in our series was 408 min. This time, while comparable to published trials using cooling blankets [5, 17, 18], is far longer than the 120 min median time achieved with ice packs started in the field in the Australian trial [4], which should be considered the benchmark for ROSC to goal temperature time. Several elements may have contributed to the prolonged ROSC to goal temperature time seen in our ‘real-world’ series. Despite the established hypothermia protocol at our institution, there might be an insufficient understanding of the time-critical nature of post-arrest therapeutic hypothermia. For example, the first recorded temperature among survivors of out-of-hospital arrest in our series was never from the EMS run sheet or from the

Table 3 Complications

	Surface (n = 23)	Catheter (n = 19)	Total (n = 42)	P
Overshoot to <32°C	82.6% (19/23)	10.5% (2/19) ^a	50% (21/42)	<0.0001
Mean minimum temperature	30.7 ± 1.2	32.5 ± 0.8	31.5 ± 1.3	<0.0001
INR increase in 1st 48 h	1.3 ± 3.9	0.8 ± 1.4	1.0 ± 3.0	0.69
Bleeding	4.3% (1/23)	5.3% (1/19)	4.8% (2/42)	1.0
Bradycardia	60.9% (14/23)	42.1% (8/19)	52.4% (22/42)	0.35
% time spent bradycardic	15.6 ± 17.8%	4.7 ± 8.5%	10.7 ± 15.2	0.047
Repeat code	17.4% (4/23)	0% (0/19)	9.5% (4/42)	0.11
Repeat code during cooling	17.4% (4/23)	0% (0/19)	9.5% (4/42)	0.11
Fatal repeat code	13% (3/23)	0% (0/19)	7.1% (3/42)	0.24
In-hospital mortality	65.2% (15/23)	57.9% (11/19)	61.9% (26/42)	0.75
Withdrawal of care	34.8% (8/23)	42.1% (8/19)	38.1% (16/42)	0.75
Rewarm prior to cooling	43.5% (10/23)	52.6% (10/19)	47.6% (20/42)	0.76

Data are presented either as percent of group (number in group/total in group) or as mean ± standard deviation. *P* values are for Fisher's exact test comparing surface and catheter groups for categorical data, Mann–Whitney test comparison between surface and catheter groups for minimum temperature and for % time spent bradycardic, and t-test comparison between surface and catheter groups for INR increase. INR = international normalized ratio

^a Overshoot occurred in the 2 patients indicated prior to catheter placement

first set of triage vital signs in the Emergency Department (ED). A lack of recognition of the importance of temperature control after cardiac arrest may therefore be a particular issue in the pre-hospital and ED settings. Also, SFGH is the only Level I trauma center for San Francisco, and it is therefore possible that competing time-critical cases in the ED contribute to delays in initiation of therapeutic hypothermia and inadvertent rewarming prior to hypothermia. Our finding that the addition of a smaller (10.7 F) cooling catheter did not seem to augment the rate of active cooling suggests that ice packs and cooling blankets might have been discontinued once catheter-based cooling was initiated, which would have been a deviation from our institutional protocol. Our series highlights the need to identify and improve on 'weak links' that prolong the time from resuscitation to initiation of therapeutic hypothermia, as has been done with other time-critical medical interventions such as endovascular treatment of myocardial infarction [19] and thrombolytic therapy for acute stroke [20, 21].

This study has several limitations. The assignment to surface cooling only vs. catheter-assisted cooling was made by the treating physicians and was not randomized. The assignment to non-catheter use was, in some cases, made because of medical comorbidities (coagulopathy, thrombolytics for pulmonary embolus, etc.) that might mean that the surface-only group was a sicker patient population overall. The size of catheter was similarly a choice of the treating physician, and reasons for placement of a larger or smaller catheter were not documented (but were presumably based on patient size). The relatively small number of

patients in each group may have limited our ability to detect some differences between the two cooling methods. We were only able to compare the two cooling methodologies employed at SFGH during the period under study: manually-regulated non-adherent surface cooling and this same approach augmented by one type of endovascular cooling catheter with an automatic temperature feedback system. Other cooling methods such as adherent surface cooling with an automatic temperature feedback system, gastric ice water lavage, or iced saline infusions were not in use at our institution during the time period of this analysis. The precise time at which surface and catheter cooling were begun was not consistently documented, so we cannot address whether the time required to place a cooling catheter cancels out, to some extent, any effect on the rate of hypothermia induction after the return of spontaneous circulation. Also, the lack of documentation regarding the precise start time for surface and catheter cooling required us to analyze the active rate of cooling based on the downward deflection of the temperature curve, which might have introduced bias to the comparison of the two methods. Finally, the sample size and retrospective, non-randomized nature of the present study does not allow us to address the relative impact of catheter-assisted hypothermia on survival and neurological outcomes after cardiac arrest.

As mentioned above, our study highlights some of the logistical barriers that may be encountered using therapeutic hypothermia after cardiac arrest in an academic urban hospital outside the confines of a clinical trial. Counterproductive rewarming in the ER occurred in almost

half of the patients in this series, with a mean temperature elevation of 1.4°C among these patients. This degree of rewarming is likely to result in approximately an hour of additional active cooling time, depending on the cooling method used. There were also likely delays in initiating cooling, as evidenced by the lack of a benefit of the 14 F catheter on ROSC to goal temperature despite a significantly faster active cooling time with the 14 F catheter.

The present study only compares the specific methods of ice packs with and without cooling blanket surface cooling to the same surface methods augmented by the use of an endovascular cooling catheter. Available methods for induction of therapeutic hypothermia include the use of a water-cooled mattress [1], cooling blankets [2, 22], ice packs [4, 23], an air-cooled mattress plus ice packs [5], selective cranial cooling [24, 25], ice-cold intravenous saline boluses [26], gastric ice water lavage [22], peritoneal iced saline lavage [27], adherent water-cooled pads with an automatic temperature feedback system (e.g., Arctic Sun, Medivance, Inc.) [28], alternate endovascular cooling catheter designs (e.g., CoolGard 3000 system; Alsius Corp) [29], and the use of ice-cold saline boluses followed by placement of a cooling catheter [30].

Other series have reported better control of therapeutic hypothermia after cardiac arrest using feedback controlled catheter systems when compared to ice packs and cooling blankets without feedback control. In one series of 13 patients treated with an endovascular cooling catheter after cardiac arrest, there was overall tight control of temperature across patients during the maintenance phase, but degree of overshoot or undershoot for individual patients was not directly addressed [31]. In contrast, a series of 32 patients cooled with ice packs and non-feedback cooling blankets showed extensive problems with overshoot, with 63% of patients reaching <32°C, 28% reaching <31°C, and 13% reaching <30°C [32]. In the European Resuscitation Council Hypothermia After Cardiac Arrest Registry (ERC HACA-R), patients cooled with an endovascular cooling catheter had less overshoot (mean lowest temperature 32.9°C, IQR 32.6°C to 33°C) when compared to patients cooled by other methods (mean lowest temperature 32.4°C, IQR 31°C to 32.9°C) [33]. Feedback-regulated surface cooling methods may have similar advantages in tightly controlling temperature during the maintenance phase, but a direct comparison of feedback-regulated surface cooling methods and either icepacks or endovascular methods has not yet been reported.

In studies published to date, the fastest cooling rates have been achieved with liberal use of ice packs. In one of the large randomized hypothermia trials, use of ice packs initiated in the field yielded a median temperature of 33.5°C at 120 min after ROSC⁴, and in a preliminary study by the same group, the time from ROSC to 34°C was a

mean of 74 min (range, 20–180 min) [23]. In studies using cooling blankets, median ROSC to goal temperature (33–34°C) times were 480 min [5], 349 min [17], and 414 min [18]. With the use of an endovascular cooling catheter alone, the median ROSC to goal temperature (33°C) time was 253 min [29]. Use of an ice-cold saline bolus (2000 mL 4°C NS) followed by endovascular cooling catheter placement yielded a mean ROSC to goal temperature (34°C) time of 185 min [30]. Use of a cooling helmet (Frigicap device) yielded a ROSC to 34°C median time of 180 min for bladder temperature [24]. By comparison, the overall time from ROSC to 33.5°C in our study was 408 ± 152 min, and was not different between the catheter and surface groups.

As even minimal delays in instituting post-arrest hypothermia in animal models significantly reduce the beneficial effects of the therapy [34, 35], the most rapid but safe means to lower temperature should be employed. Our data suggest that further investigation into additive approaches to inducing mild hypothermia are necessary to more acutely lower temperature in the active cooling phase while preserving the minimization of overshoot afforded by the use of an endovascular cooling catheter. For example, in appropriately selected patients, a combination of early and liberal ice pack use, iced gastric lavage, and cold IV saline boluses could be used along with timely placement of a cooling catheter to achieve a rapid induction of hypothermia with prevention of overshoot. Our data also suggest that a larger cooling catheter size should be routinely used unless anatomical considerations, such as very small femoral veins on ultrasound, argue for the use of a smaller catheter in a particular patient.

Disclosure

Conflict of Interest Disclosures: J. Claude Hemphill holds stock and stock options in Cardium Therapeutics (parent company of Innercool Therapies) and has served as a consultant and member of the scientific advisory board of Innercool Therapies. David Bonovich and Alexander Flint have nothing to disclose.

References

1. Williams GR Jr, Spencer FC. The clinical use of hypothermia following cardiac arrest. *Ann Surg* 1958;148(3):462–8.
2. Benson DW, Williams GR Jr, Spencer FC, Yates AJ. The use of hypothermia after cardiac arrest. *Anesth Analg* 1959;38:423–8.
3. Feldman E, Rubin B, Surks SN. Beneficial effects of hypothermia after cardiac arrest. *JAMA* 1960;173:499–501.
4. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346(8):557–63.

5. Group HS. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346(8):549–56.
6. Holzer M, Bernard SA, Hachimi-Idrissi S, Roine RO, Sterz F, Mullner M. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. *Crit Care Med* 2005;33(2):414–8.
7. American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 7.5: Postresuscitation Support. *Circulation* 2005;112(24_suppl):IV-84–8.
8. Hazinski MF, Nadkarni VM, Hickey RW, O'Connor R, Becker LB, Zaritsky A. Major changes in the 2005 AHA Guidelines for CPR, ECC: reaching the tipping point for change. *Circulation* 2005;112(24 Suppl):IV206–11.
9. Nolan JP, Morley PT, Hoek TL, Hickey RW. Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advancement Life support Task Force of the International Liaison committee on Resuscitation. *Resuscitation* 2003;57(3):231–5.
10. Bernard S. Therapeutic hypothermia after cardiac arrest: now a standard of care. *Crit Care Med* 2006;34(3):923–4.
11. Bernard SA. Therapeutic hypothermia after cardiac arrest. Hypothermia is now standard care for some types of cardiac arrest. *Med J Aust* 2004;181(9):468–9.
12. Rincon F, Mayer SA. Therapeutic hypothermia for brain injury after cardiac arrest. *Semin Neurol* 2006;26(4):387–95.
13. Topjian A, Nadkarni V. Cooling after cardiac arrest: have we reached the tipping point? *Crit Care Med* 2006;34(7):2017–8.
14. Merchant RM, Soar J, Skrifvars MB, et al. Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest. *Crit Care Med* 2006;34(7):1935–40.
15. Abella BS, Rhee JW, Huang KN, Vanden Hoek TL, Becker LB. Induced hypothermia is underused after resuscitation from cardiac arrest: a current practice survey. *Resuscitation* 2005;64(2):181–6.
16. Sanders AB. Therapeutic hypothermia after cardiac arrest. *Curr Opin Crit Care* 2006;12(3):213–7.
17. Zeiner A, Holzer M, Sterz F, et al. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. *Hypothermia After Cardiac Arrest (HACA) Study Group. Stroke* 2000;31(1):86–94.
18. Yanagawa Y, Ishihara S, Norio H, et al. Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. *Resuscitation* 1998;39(1–2):61–6.
19. Moscucci M, Eagle KA. Reducing the door-to-balloon time for myocardial infarction with ST-segment elevation. *N Engl J Med* 2006;355(22):2364–5.
20. Grotta JC, Burgin WS, El-Mitwalli A, et al. Intravenous tissue-type plasminogen activator therapy for ischemic stroke: Houston experience 1996 to 2000. *Arch Neurol* 2001;58(12):2009–13.
21. Gottesman RF, Alt J, Wityk RJ, Llinas RH. Predicting abnormal coagulation in ischemic stroke: reducing delay in rt-PA use. *Neurology* 2006;67(9):1665–7.
22. Felberg RA, Krieger DW, Chuang R, et al. Hypothermia after cardiac arrest: feasibility and safety of an external cooling protocol. *Circulation* 2001;104(15):1799–804.
23. Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Ann Emerg Med* 1997;30(2):146–53.
24. Hachimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: a clinical feasibility study. *Resuscitation* 2001;51(3):275–81.
25. Callaway CW, Tadler SC, Katz LM, Lipinski CL, Brader E. Feasibility of external cranial cooling during out-of-hospital cardiac arrest. *Resuscitation* 2002;52(2):159–65.
26. Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. *Resuscitation* 2003;56(1):9–13.
27. Xiao F, Safar P, Alexander H. Peritoneal cooling for mild cerebral hypothermia after cardiac arrest in dogs. *Resuscitation* 1995;30(1):51–9.
28. Mayer SA, Kowalski RG, Presciutti M, et al. Clinical trial of a novel surface cooling system for fever control in neurocritical care patients. *Crit Care Med* 2004;32(12):2508–15.
29. Holzer M, Mullner M, Sterz F, et al. Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and Bayesian approach. *Stroke* 2006;37(7):1792–7.
30. Kliegel A, Losert H, Sterz F, et al. Cold simple intravenous infusions preceding special endovascular cooling for faster induction of mild hypothermia after cardiac arrest—a feasibility study. *Resuscitation* 2005;64(3):347–51.
31. Al-Senani FM, Graffagnino C, Grotta JC, et al. A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard System and Icy catheter following cardiac arrest. *Resuscitation* 2004;62(2):143–50.
32. Merchant RM, Abella BS, Peberdy MA, et al. Therapeutic hypothermia after cardiac arrest: Unintentional overcooling is common using ice packs and conventional cooling blankets. *Crit Care Med* 2006;34(12 Suppl):S490–4.
33. Arrich J. Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med* 2007;35(4):1041–7.
34. Kuboyama K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. *Crit Care Med* 1993;21(9):1348–58.
35. Nozari A, Safar P, Stezoski SW, et al. Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. *Circulation* 2006;113(23):2690–6.