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Determinants of Effective Cooling during Endovascular Hypothermia

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Abstract

Therapeutic hypothermia is a promising neuroprotective therapy with multiple mechanisms of action. We demonstrated the feasibility of thrombolysis combined with endovascular hypothermia, but not all patients achieved effective cooling. We sought to identify the factors that determined effective cooling.

Methods—In 26 patients who underwent endovascular hypothermia we computed 4 measures of effective cooling: time to reach target; Area-Under-the-Curve (AUC) 34 ratio; AUC-34; and AUC-35. Using multivariate regression, we examined the effects of age, weight, starting temperature, body mass index, body surface area (BSA), gender, shivering, and total meperidine dose on the 4 outcome measures.

Results—In univariate analyses, all 4 outcome measures were significantly influenced by BSA ($p < 0.01$ in all univariate analyses). Time to reach target temperature was quicker in older patients ($p < 0.01$). Shivering and meperidine dose were highly intercorrelated ($r = 0.6$, $p < 0.01$) and both marginally influenced all 4 outcome measures. In multivariate analysis, AUC ratio and time to reach target temperature were significantly influenced by BSA ($p < 0.01$) and meperidine ($p < 0.05$); AUC-34 was influenced only by BSA ($p < 0.01$). The AUC-35 was influenced by BSA ($p < 0.01$), shivering, and total meperidine dose ($p < 0.05$).

Conclusions—The most important determinant of effective cooling during endovascular hypothermia is BSA; larger patients are more difficult to cool and maintain in therapeutic range. Older patients cool more quickly. Shivering was well controlled by the combination of meperidine, buspirone, and surface counter-warming and only minimally influenced cooling

effectiveness. Future trials of therapeutic hypothermia may include added measures to cool larger patients more effectively.

Keywords

stroke; clinical trial; hypothermia

Introduction

Therapeutic hypothermia is the most effective neuroprotectant in experimental stroke studies, and is proven effective in patients after cardiac arrest and neonatal hypoxia-ischemia^{1, 2}. Such patients are typically sedated, intubated and chemically paralyzed so comfort and shivering are not concerns. Shivering—a physiologic response to maintain homeostasis—generates heat and inhibits rapid, effective cooling to a target temperature³⁻⁵. Once at target, shivering—and increased metabolic rate—might also reduce the time a patient remains within the target temperature range due to heat generation. Stroke patients are generally awake and not sedated or intubated; homeostatic mechanisms that maintain core body temperature are much more difficult to overcome in the awake, non-paralyzed patient. Paralysis and intubation are avoided in stroke patients due to a risk of pneumonia, for example in patients undergoing cerebral vascular interventions⁶.

Endovascular therapeutic hypothermia is feasible and avoids the problems encountered in previous studies that used surface cooling, notably poor maintenance of target temperature, uncontrolled re-warming, and overshoot to lower temperatures⁷⁻⁹. Using older surface cooling methods, patients who rapidly warm may develop increased cerebral edema and intracranial pressure. Newer—perhaps more controllable—surface cooling methods have not been fully studied⁸. In the Intravascular Cooling in the Treatment of Stroke (ICTuS) trial, we developed an effective anti-shivering regimen to allow precise control of target temperature and safe, controlled re-warming without overshoot¹⁰. We combined intravenous meperidine, oral buspirone, and skin warming to control shivering and optimize patient comfort^{11, 12}. We then tested this regimen in patients who received intravenous thrombolytic therapy in the ICTuS-L (ICTuS-Longer time window) trial to determine if the combination of hypothermia, anti-shivering regimen, and thrombolysis might lead to excessive bleeding complications¹³. We found no increased incidence of peripheral or intracranial bleeding, but not all patients achieved the target temperature of 33.X°C, defined as the first temperature below 34°C. In addition, we found an increased incidence of pneumonia in the cooled patients. The causes of the increased pneumonia incidence are multi-factorial, and include meperidine-related reduced airway protection, impaired immune response during hypothermia, and stroke-related reduction of the immune response. In future studies of endovascular hypothermia, it may be important to reduce the dose of meperidine in an effort to avoid pneumonia. Reducing the meperidine dose, however, may increase the rate of shivering. Therefore, it is critical to understand the factors that limit effective cooling.

We sought to determine the role of several factors using the data from the ICTuS-L trial to identify the critical variables in cooling effectiveness. We examined the effects of age, body weight, BMI, BSA, gender, starting temperature, shivering, meperidine and buspirone on four measures of cooling efficacy in the ICTuS-L trial to better understand the factors that lead to poor cooling in some patients and improve the efficacy of future therapeutic hypothermia trials in acute stroke.

Methods

The ICTuS-L trial methodology has been described¹⁴ and the results have been published¹³. In brief, acute stroke patients aged 18 to 80 were randomized to receive normothermia or hypothermia plus an anti-shivering regimen. All patients who presented within 3 hours received intravenous rt-PA according to NINDS guidelines¹⁵. Patients who presented within 3 to 6 hours were randomized to hypothermia versus normothermia and then randomized to receive rt-PA versus no rt-PA. Since very few patients were enrolled in the 3-6 hour arms, for the present analysis all patients randomized to hypothermia were pooled. Patients were cooled with an endovascular cooling catheter (Accutrol™ cooling catheter; Celsius Control Console™; Philips/Innercool Inc.) placed in the inferior vena cava via a femoral venous sheath. Cooling began as soon as the catheter was placed; machine cooling rate was set at maximum until the target temperature was reached. We collected the radiographic images used to document placement of the cooling catheter and a single reader re-confirmed proper placement in all patients. The anti-shivering regimen included: a bolus of 1mg/kg intravenous meperidine over 10min followed by an infusion of 25mg per hour; buspirone 30mg orally or via nasogastric tube at initiation of cooling followed by 15mg every 8 hours; a warming blanket placed over the patient set a medium (38°C). Every hour the patient was examined using a modification of a shivering scale previously used¹⁶ as follows: no shivering = 0; minimal shivering = 1; visible shivering = 2; rigors = 3. If the patient exhibited shivering of any degree, the investigator administered additional meperidine (10 or 20mg) intravenously and adjusted the infusion rate upwards in 5mg/hour increments. If the patient appeared to be over sedated, based on respiratory rate or level of consciousness, the infusion rate was reduced. Each hour the maximum shivering score and total amount of meperidine administered were recorded. For this analysis, we summed the total meperidine used over 24 hours. To summarize the hourly maximum shivering scores over the 24-hour cooling period, we first calculated a total shivering score by adding up the score from each of the 24 hours (flat shivering score) calculated for each patient to give equal weight to shivering throughout the hypothermia period:

$$\sum_{0}^{23} shiv_i$$

Where *shiv* is the maximum shivering score recorded during each hour from hours 0 to 23.

To emphasize the importance of shivering early in the cooling period, we calculated a weighted average score that gave greater weight to early shivering:

$$\frac{1}{24} * \sum_{0}^{23} (24 - H_i) * shiv_i$$

where H is the hour in the study from hour 0 to hour 23 and *shiv* is the maximum shivering score recorded during each hour.

Temperatures were recorded every hour from a thermister at the tip of endovascular catheter; the cooling console recorded all temperature data electronically using an on-board data logger. To record a temperature, cooling was suspended for 2 minutes to allow thorough mixing of the core venous blood. After a core temperature was taken cooling resumed.

The target temperature in this trial was 33.X°C so that any temperature between 33.0°C and 33.9°C was considered 'at target'. We defined time-to-target as the number of minutes from cooling initiation to the first core temperature at target. To quantify the amount of time the patient's temperature remained within the target temperature range, we calculated an Area Under the Curve (AUC) using the trapezoid rule: the area between each time point was computed as a rectangle, with the difference in minutes (x-axis) as the width, and the midpoint of the difference in temperature (y-axis) as the height. The units of the AUC are therefore degree-minutes. To estimate total 'amount' of cooling, we then computed the AUC within the target range, called the AUC-34, as follows:

$$\sum_{i=1}^{24} (34 - T_i) * 60$$

where each hour from 1 to 24 included T_i , the maximum temperature recorded during that hour, and the multiplier 60 to convert hours to minutes. We computed AUC-35 similarly, using 33.0°C to 34.9°C as the target range. We then computed an AUC-34-ratio as the AUC-34 divided by the total cooling time, 24 hours.

The patient's weight and height were recorded at enrollment in kilograms and centimeters, respectively. Body mass index (BMI) was estimated using the formula (weight/

$0.0254 * \text{height}^2$). Body Surface Area (BSA) was calculated as $\sqrt{\frac{\text{weight} * \text{height}}{3600}}$. Age was recorded in years as the patient's age on the date of enrollment. We examined the variables weight, BMI, BSA, gender, age, starting temperature, total meperidine, and shivering score versus the outcome variables time-to-target, AUC-34-ratio, AUC-34 (degree-minutes) and AUC-35 (degree-minutes) using univariate linear regression. We then examined a multivariate regression model for each of the 4 outcomes to adjust for the baseline variables, to examine for independent effects, and evaluate potential interactions among selected variable. Due to the limited sample available, which precluded stepwise procedures, we focused the multivariable analyses on prespecified hypotheses.

Results

We randomized 28 patients to receive hypothermia, but in 2 patients no cooling began due to catheter placement failure or console failure. We used the remaining 26 patients for this analysis. The baseline and outcome variables are summarized in Table 1. The times to target temperature were derived from on-board data loggers recording all thermister measurements. These times are shown in Figure 1 (adapted with permission from Hemmen et al ¹³.) Since a thermister measurement requires the suspension of active cooling for 2 minutes, the cooling console software does not allow the first internal temperature before 20 to 30 minutes after cooling start, depending on the starting temperature. Due to this requirement, the fastest cooling time was 20 minutes. In Figure 1 only, the target temperature was defined as the first temperature below 34.0°C, or if the patient never reached 34°C then the lowest temperature achieved. There was little multi-collinearity in this dataset, although weight and age were modestly inversely correlated ($r = -0.36$, $p = 0.07$) and BMI correlated with BSA ($r = 0.97$, $p < 0.01$). There was little difference between the weighted and the flat shivering scores ($r = 0.92$, $p < 0.01$); the weighted shivering score was used in analyzing time-to-reach 34°C and the flat shivering score was used for all other analyses. Total meperidine dose was correlated with weighted shivering score ($r = 0.59$, $p < 0.01$) and the flat shivering score ($r = 0.61$, $p < 0.01$) as expected since meperidine dosing was driven by shivering.

Representative cooling curves are shown in Figure 2. In Panel A, a typical curve is shown for a patient who rapidly cooled and remained at target for the cooling period. In Panel B, a curve is shown for a patient who did not achieve cooling below 34°C. In Panel C, a curve is shown for a patient who rapidly cooled but escaped control and re-warmed within 6 hours.

Univariate analyses for each of the 4 outcome variables are summarized in Table 2. Time-to-target temperature was significantly influenced by age, BSA, and weight, but not BMI. Shivering and resultant meperidine use had less, but statistically significant, effect on time. AUC ratio, AUC-34 and AUC-35 were all significantly ($p<0.05$) influenced by weight and BSA (lighter patients remained in target range more easily) and gender (males were more difficult to maintain) but not BMI. While males were heavier than females (86 ± 14 versus 75 ± 14 kg, Wilcoxon Rank Sum $p=0.08$) the effect of gender and weight were independent in multivariable models that included a weight*gender interaction term; this interaction was not sufficiently powerful to retain in the final model. Several multivariate models were examined, and the best-fit models are summarized in Table 3. In these analyses, weight (and BSA) influenced all 4 outcomes after adjustment for the other baseline variables. Age significantly influenced time-to-target (older patients cooled more quickly), while meperidine dose or shivering influenced AUC ratio and AUC-35.

Discussion

Our analyses offer important insights into the determinants of cooling initiation and maintenance during endovascular hypothermia for acute stroke in awake patients. Study patients received an aggressive anti-shivering regimen including intravenous meperidine, oral buspirone, and surface skin-warming to improve shivering control¹⁷. The weight and BSA (but not BMI) of the patients influenced both the time to reach cooling target range and the total time spent within the target range: heavier patients were more difficult to cool and keep cool (Table 1 and Figure 3). The predictive difference between BSA and BMI is not surprising, as BMI may not accurately reflect total body mass in the obese; many of our patients were overweight or obese. Age influenced the time-to-target in that older patients cooled more quickly (Tables 2 and 3 and Figure 3), consistent with known impairment of temperature regulation in the aged⁴. We do not conclude, however, that cooling regimens should be adjusted in the elderly. Rather, it is to be expected that older patients will cool more quickly and achieve the target range sooner. Shivering was well controlled with the anti-shivering regimen, but shivering and resultant meperidine therapy affected cooling effectiveness independently of the weight effects (Table 3). This suggests that while body size is the single most important predictor of cooling rate, proper use of the anti-shivering regimen is important. Gender appeared to impact cooling, but in multivariable models was not significant after adjusting for weight. Shivering thresholds are known to differ by gender, and this may have impacted our results¹⁸.

We used four different outcome measures in this analysis because there are at least 2 important aspects to therapeutic hypothermia and no accepted metrics for either of them. The first aspect is the speed of cooling (time to reach target) and the second aspect is the 'dose' or amount of cooling, that is, the total amount of time spent in the therapeutic range. In the ICTuS-L trial, the target temperature was 33.X°C; we defined success as the time to the first recorded temperature below 34.0°C, that is, within a target range of 33.0°C to 33.9°C. As shown in Figure 1, many of our patients had already reached target at the time of the first measured core temperature. As shown in Figure 2-C, however, just reaching the target is not enough; the patient must stay in the therapeutic range. We computed 3 different measures to attempt to quantify this second aspect of therapeutic hypothermia. The Area Under the Curve (AUC) is intended to capture that amount of time spent below a therapeutic threshold¹⁹. The AUC-ratio compares the time spent within the range 33.0°C to 33.9°C

compared to the total time in the 24-hour cooling period. Compared to the AUC, the utility of the AUC-ratio lies in adjusting for time above the threshold, since hyperthermia is likely detrimental. The AUC below 34°C (AUC-34) and the AUC below 35°C (AUC-35) both collect the degree-minutes spent below a threshold and account for depth below the threshold as well. Since there is conflicting data to prefer deeper hypothermia over milder (i.e. 33°C vs. 35°C) we examined both measures. While the amount of shivering and meperidine influenced AUC-35, only weight significantly influenced AUC-34. This result suggests that nearly all patients can be cooled to 35°C with the anti-shivering regimen and current cooling methods, but deeper hypothermia may require additional measures to cool the larger patient. From experimental data, it is not yet clear whether 33°C provides additional neuroprotection over a target of 35°C. Notably, in the ICTuS trials we are combining hypothermia plus drugs that have known protective effects on metabolism²⁰.

These data have several important implications for future use of therapeutic hypothermia in acute stroke patients. Most importantly, shivering must be controlled to reach the target temperature; shivering increases metabolic rate and worsens outcome²⁰. Shivering typically doubles metabolic rate, although higher rates can be sustained briefly²¹. In this trial, we confirmed the efficacy of the anti-shivering regimen developed previously in the ICTuS trial (Figure 1). The use of meperidine was strongly correlated with shivering scores ($r=0.59$, $p<0.01$), indicating that titration of the meperidine infusion was critical to shivering control. The use of surface skin counter-warming and oral buspirone are also critical elements of the anti-shivering regimen, but cannot be titrated^{17, 22}. In the ICTuS-L trial an excess incidence of pneumonia was found in the hypothermia group, perhaps related to aggressive use of meperidine to control shivering: meperidine can cause vomiting and impairs the gag reflex, both of which may predispose to aspiration. The data presented here suggest that the anti-shivering regimen cannot overcome the influence of weight in determining cooling initiation, although a larger dataset will be required for confirmation. The failure to cool larger patients, combined with the risk of pneumonia, suggests that in future trials meperidine should be titrated, but only to a certain point; in heavier patients further attempts to enhance cooling with meperidine might only increase the risk of complications.

The second implication of our data is the influence of weight. The Accutrol catheter comes in two sizes, 10.7F and 14F diameter, and the larger catheter draws more heat; we used the larger catheter in patients heavier than 90Kg. Despite using this more powerful catheter, we encountered some patients in whom cooling could not be achieved, shown in Figures 2 and 3, but the reasons for cooling failure varied. In some cases, investigators failed to use the full anti-shivering regimen (omitting buspirone for example). Other causes for insufficient cooling include the possibility that the catheter was not fully inserted past the introducer sheath to achieve maximum cooling, but we examined all the radiographic images and assured proper placement in all patients in this analysis. In future studies, additional heat removal methods, such as iced saline or surface cooling, may be needed to facilitate rapid cooling of the larger patient^{23, 24}.

Our study comes with limitations. First, although ICTuS-L is the largest randomized, controlled trial of endovascular cooling for stroke patients to date, the sample sizes are relatively small, limiting the numbers of variables examined and the number of interactions explored. Specifically, stepwise methods could not be used to examine variables systematically. Based on clinical experience gained during the trial we examined those variables that appeared to influence either cooling rate or depth. These results provide suggestions for further research, but there may be other determinants of cooling initiation and maintenance. In larger trials, more confirmative data will emerge, as much larger randomized trials are needed to assess efficacy of therapeutic hypothermia for acute stroke²⁵. Second, we recorded shivering only once per hour as the maximum shivering score

observed during that hour whether the patient shivered at that score for the entire hour, or only briefly. The shivering scale has not been validated among multiple observers. Despite this, the shivering score is likely to reflect overall degree of shivering suffered by our patients. Third, the multi-variable models have total R^2 values in the range of 50 to 60%, suggesting that a large portion of the variance in the data remains unexplained. In a larger dataset we may gain further insight into other important predictors of cooling efficacy.

This analysis of the determinants of cooling efficacy in the ICTuS-L trial suggests that the most important variable in successfully initiation and maintaining therapeutic hypothermia was weight, and specifically the BSA. Shivering was well managed with the combination of intravenous meperidine (titrated), oral buspirone, and surface warming. To cool heavier patients effectively additional cooling methods, such as intravenous cold saline, may be needed.

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Figure One.

Time to Target Temperature. Histogram of the times to reach target temperature for 26 patients treated with endovascular hypothermia. Temperatures were not recorded before 20 to 30 minutes (depending on the starting temperature) so the fastest recorded time is 20 minutes. For each patient shown, the upper temperature is the lowest temperature achieved during the 24-hour cooling period; the lower temperature is the first temperature recorded below 34°C or if no such temperature was recorded, the lowest temperature achieved. The weight of each patient (kg) appears along the x-axis. Patients shown with a black bar received the standard 10.7 F catheter; the grey bars represent the larger 14 F catheter. (Adapted with permission from Hemmen et al, 2009¹³).

Figure Two.

A: Representative cooling curve for a patient who cooled quickly. The method for calculating the AUC is described in the text. This patient cooled quickly; the first temperature taken (at 99 minutes after cooling) was below the target temperature of 34°C.

B: Representative cooling curve for a patient who never achieved the target temperature.
C: Representative cooling curve for a patient who cooled to below target but could not be maintained below the target temperature.

Table One

Summary of Demographic Variables. See methods for definitions.

	Mean	SD	Min	Q1	Median	Q3	Max
Age (y)	68.88	8.12	55	61.5	69.5	75.5	80
Weight (Kg)	80.66	15.67	51.1	68.5	78.5	93.62	114
Starting Temperature (C°)	36.35	0.49	35.7	35.95	36.3	36.58	37.8
BMI	28.91	5.66	20.41	24.92	27.51	30.75	40.32
BSA	1.94	0.21	1.47	1.81	1.91	2.09	2.36
Meperidine (mg)	1227	436	295	933	1270	1542	2154
Weighted Shivering Score	6.75	5.51	0	2.67	4.92	9.55	19.17
Flat Shivering Score	11.85	10.66	0	4.25	8	16.25	38
AUC Ratio at 34°C	0.46	0.41	0	0.01	0.52	0.9	0.96
Time to reach 34°C (min)	420.6	544.6	58	62.75	120	678.2	1440
AUC below 34°C (degree-min)	433.4	453.1	0	12.93	245.9	855.1	1227
AUC below 35°C (degree-min)	1357.0	916.23	0	549.6	1483	2240	2624

Table two

Summary of Univariate Analyses. Each variable was tested for significant correlation with each of the four outcome measures using a Wilcoxon ranked sum.

Outcome	Variable	R ²	P
Time to Reach 34°C	Age	0.300	<0.01
	Weight	0.223	0.015
	BMI	0.104	NS
	BSA	0.221	0.018
	Gender	0.113	NS
	Meperidine	0.000	NS
	Buspirone	0.000	NS
	Shivering ^{**}	0.056	NS
AUC ratio under 34°C	Age	0.019	NS
	Weight	0.256	<0.01
	BMI	0.028	NS
	BSA	0.360	<0.01
	Gender	0.340	<0.01
	Meperidine	0.008	NS
	Buspirone	0.011	NS
	Shivering [*]	0.005	NS
AUC below 34°C	Age	0.019	NS
	Weight	0.193	0.025
	BMI	0.004	NS
	BSA	0.333	<0.01
	Gender	0.341	<0.01
	Meperidine	0.004	NS
	Buspirone	0.022	NS
	Shivering [*]	0.006	NS
AUC below 35°C	Age	0.052	NS
	Weight	0.229	0.013
	BMI	0.024	NS
	BSA	0.333	<0.01
	Gender	0.316	<0.01
	Meperidine	0.007	NS
	Buspirone	0.024	NS
	Shivering [*]	0.011	NS

* Flat shivering score (see methods)

** Weighted shivering score (see methods)

Table Three

Multivariable Analyses of the Tested Variables. The coefficient and significance for each variable in the final best-fit model is shown.

	Variable	Estimate	Std. Error	t value	P
Time to Reach 34°C	(Intercept)	216.4014	1411.9828	0.153	0.87973
	Age	-26.9176	11.8488	-2.272	0.03
	BSA	1307.3971	453.0722	2.886	<0.01
	Meperidine	-0.5611	0.2315	-2.423	<0.05
	Shivering**	32.9253	19.0893	1.725	NS
	(Intercept)	3.109593	1.166469	2.666	0.02
AUC-Ratio under 34°C	Age	-0.003464	0.008809	-0.393	NS
	BSA	-1.370163	0.446600	-3.068	<0.01
	Gender	-0.133555	0.165384	-0.808	NS
	Meperidine	0.000385	0.000193	1.995	NS
	Shivering*	-0.013190	0.008069	-1.635	<0.05
	(Intercept)	3774.7150	1197.7154	3.152	<0.01
AUC under 34°C	Age	-5.3761	9.9761	-0.539	NS
	BSA	-1718.9852	394.1432	-4.361	<0.001
	Meperidine	0.4721	0.1999	2.362	<0.05
	Shivering*	-18.2924	8.3288	-2.196	<0.05
	(Intercept)	6980.7695	2341.4380	2.981	<0.01
AUC under 35°C	Age	1.232	19.502	0.06	NS
	BSA	-3407.079	770.518	-4.42	<0.001
	Meperidine	1.0799	0.3907	2.764	<0.05
	Shivering*	-37.249	16.282	-2.28	<0.05

* Flat shivering score (see methods)

** Weighted shivering score (see methods)