ORIGINAL RESEARCH

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Determinants of Heat Generation in Patients Treated With Therapeutic Hypothermia Following Cardiac Arrest

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***Background*—**Therapeutic hypothermia (TH) is recommended to reduce ischemic brain injury after cardiac arrest. The variables that predict heat generation by patients receiving TH are uncertain, as is how this heat generation relates to neurologic outcome. We hypothesized that patient characteristics, medication use, inflammation, and organ injury would be associated with heat generation. We further hypothesized that neurologic outcome would be most strongly associated with heat generation.

***Methods and Results*—**Surface and intravascular cooling devices were used to provide TH in 57 consecutive cardiac arrest patients. Device water temperatures during the maintenance (33°C) phase were collected. Patient heat generation was quantified as the "heat index" (HI), which was the inverse average water temperature over a minimum of 2 hours of maintenance hypothermia. Variables measuring reduced ischemic injury and improved baseline health were significantly associated with HI. After controlling for presenting rhythm, a higher HI was independently associated with favorable disposition (OR=2.2; 95% CI 1.2 to 4.1; P=0.014) and favorable Cerebral Performance Category (OR=1.8; 95% CI 1.0 to 3.1; P=0.035). Higher HI predicted favorable disposition (receiver-operator area under the curve 0.71, P=0.029). HI was linearly correlated with arteriovenous CO_2 (r=0.69; P=0.041) but not O_2 (r=0.13; P=0.741) gradients.

***Conclusions*—**In cardiac arrest patients receiving TH, greater heat generation is associated with better baseline health, reduced ischemic injury, and improved neurologic function, which results in higher metabolism. HI can control for confounding effects of patient heat generation in future clinical trials of rapid TH and offers early prognostic information. **(*J Am Heart Assoc*. 2014;3: e000580 doi: 10.1161/JAHA.113.000580)**

Key Words: cardiac arrest • cardiopulmonary resuscitation • ischemia • prognosis

Sudden cardiac arrest (CA) affects >500 000 people in the United States annually.[1,2] Fewer than 1 in every 10 of these patients will survive to hospital discharge[3] with the majority of deaths occurring as a result of neurologic injury.[4] Since 2002, therapeutic hypothermia (TH) has emerged as the only effective post-resuscitation therapy for neurologic injury.[5–7] TH has a class I indication after ventricular fibrillation/ventricular tachycardia (VF/VT) out-of-hospital CA[7] and neonatal hypoxic-ischemic injury.[8] At present, hypothermia is being actively investigated as an adjunct in treatment of other forms of acquired brain injury[9] and myocardial infarction.[10] Thus, TH offers benefit for a number of illnesses carrying significant morbidity and mortality, and gaining an understanding to its clinical application is crucial in future clinical trials.

Several animal studies[11–14] and 2 clinical studies[15,16] have shown that faster time to target temperature results in better outcomes. However, this result has not been confirmed in 2 other clinical studies prospectively comparing early versus late initiation of TH.[17,18] Indeed some clinical studies have shown that several indirect measures of reduced patient heat generation (lower presenting body temperatures, shorter time to goal temperature, longer passive rewarming times) predict worsened outcomes.[19–21] In designing studies aimed at rapid achievement of TH, it is therefore crucial to quantify the contribution of patient-level variables in heat generation.

We hypothesized that differences in patient heat generation during TH could explain the inconsistencies between preclinical and clinical results. Furthermore, we hypothesized that patient heat generation, quantified as a "Heat Index" (HI), could be associated with patient demographics, body habitus,

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pre-existing comorbidities, and the presence of infection, inflammation, or more severe ischemic injury, and could also be influenced by delivery of adjunctive medications commonly used to suppress shivering. Based on the existing literature,[19–22] we hypothesized that greater heat generation would be associated with better neurologic outcomes and survival to hospital discharge. Therefore, the aim of this study was to determine which factors contribute to heat generation in patients receiving TH and to provide insight to clinicians for neuroprognostication and in designing future clinical trials of rapidly induced TH.

Methods

Study Population

This study used data prospectively gathered at 2 hospitals (UPMC Presbyterian and Mercy) as part of ongoing quality improvement (QI) efforts in post-resuscitation care and TH implementation. It is our institutional standard to provide therapeutic hypothermia to all comatose survivors of CA except in the setting of active hemorrhage or severe antecedent bradycardia or heart block. Data was obtained from consecutive out-of-hospital and in-hospital CA survivors who received TH and were maintained within the target temperature (33°C) for a minimum of 2 consecutive hours using either an intravascular device (ThermoGard XP; Zoll Medical) or adhesive surface cooling pads (Arctic Sun 5000; Bard Medical). As part of our QI efforts patient and water temperature data were downloaded from each device to analyze how units were performing at reaching and maintaining target cooling and rewarming temperatures. These data were linked to patient-level data on a list of variables (Table 1) with intentions to understand variations from goals. The Institutional Review Board deemed this analysis of de-identified QI data to be exempt from review.

Therapeutic Hypothermia

Standard protocols with accompanying computerized entry order sets were used in both hospitals following CA. Similar to prior work,[23] these protocols included inducing TH to 33°C as quickly as possible using maximum cooling on the devices, along with most patients receiving 2 L iced saline and ice packs applied to the neck and groin before and during induction of TH. These adjuncts were not used in any of the included patients during maintenance TH. Patients were to be maintained at 33°C for 24 hours and rewarmed to 36.5 to 37°C at a goal rate of 0.25°C/h, (maximum rate 0.5°C/h). The patients included in this report were either treated using external gel-coated pads (Arctic Sun), 2 placed on the torso and 2 on the legs, or a 3 or 4 balloon femoral venous intravascular cooling catheter (Zoll Icy or Quattro catheters). Our standard anti-shivering regimen consists of use of sedation (propofol or midazolam), occasional opioid analgesia (fentanyl or morphine infusion), and occasional neuromuscular blockade (vecuronium or rocuronium, generally used only at induction of hypothermia). Continuous neuromuscular blockade is infrequently employed in our facilities for these patients.

Measuring Heat Generation

Patients' heat generation during the maintenance phase was quantified using a "Heat Index" (HI) developed for this study. The HI was calculated as $\times 100$ the inverse average machine water temperature over the period in which patient temperature reached the target temperature of the maintenance phase (33°C) of TH for and was maintained for a minimum of 2 consecutive hours. Device water temperature is automatically recorded every minute. When TH was paused for patient transport, we did not resume this calculation until the patient was back at goal temperature. In all cases we averaged as much time as possible until rewarming began, which was indicated by a change in the goal temperature on the machine. HI as calculated directly quantifies patient heat generation since a higher HI indicates a lower water temperature was required to maintain the patient at 33°C.

Outcome Assessment

Our primary outcome endpoint was discharge disposition, which strongly correlates with other measures of neurologic outcome[24] and is ultimately based on the patient's functional status at discharge. Other outcomes assessed were discharge Pittsburgh Cerebral Performance Category (CPC) and survival. CPC[24] was defined using strict criteria such that patients with CPC 1 or 2 must be able to perform all activities of daily living and be able to return to work independently or in a sheltered environment. CPC and disposition were dichotomized as favorable or unfavorable. Favorable disposition was defined as discharge to home or acute rehabilitation, while unfavorable disposition was discharge to an advanced care or skilled nursing facility, hospice or death. A CPC of 1 or 2 was considered favorable whereas a CPC of 3 to 5 was unfavorable.

Additional Data Collection

Clinical, laboratory, and pharmacological data (Table 1) from the QI database was abstracted if it related to 1 of 6 predetermined patient characteristics: (1) demographics, (2) body habitus, (3) patient health at time of CA, (4) presence of infection or inflammation, (5) measures of ischemic injury severity, and (6) medication use to prevent shivering. A full list

Table 1. Variables Included Within the Quality Improvement (QI) Database

Variable	Explanation
Demographics	
Hospital	University of Pittsburg Medical Center (UPMC) Presbyterian, Mercy, Shadyside or Montefiore
Hospital unit	Intensive care unit name
Sex	
Age	
Living situation prior to arrest	Independent, dependent at home, nursing home, in hospital, psychiatric institute, or other
Weight	
Body mass index	
Body surface area	
Cardiac arrest	
Time of arrest	Time of day
Location of arrest	Out of hospital, in emergency department, or in hospital
Arrest witnessed or monitored	
Cause of arrest	Respiratory, myocardial infarction, arrhythmia, trauma, pulmonary embolism, or hypothermia
Cardiopulmonary resuscitation (CPR)	No CPR, untrained CPR, or trained CPR
Time from cardiac arrest (CA) to CPR	
Duration of CPR	
Presenting rhythm	
Number of defibrillations	
Time to defibrillation	
Type of resuscitative drugs used	No drugs, epinephrine, norepinephrine, vasopressin, atropine, sodium bicarbonate, amiodarone, dopamine, dobutamine, lidocaine, or other
Location of return of spontaneous circulation (ROSC)	OHCA- on scene, OHCA-off scene, IHCA
Time to ROSC	
Time to hospital	
Intrafacility transport	
First Glasgow Coma Scale (GCS)	
First FOUR Score	
Pittsburgh CA Category (PCAC)	Category 1 to 4 within 6 h of ROSC (Ref 22)
Hypothermia	
Primary cooling device	Device used during all phases of cooling
Secondary cooling device	Optional devices used at initiation
Emergency department cooling device	Optional devices used at initiation
Pre-hospital cooling	Was iced saline given?
Ice packs	No used, before cooling device, during cooling device, or used but unknown when
Cold fluid	No used, before cooling device, during cooling device, or used but unknown when
Time from CA to cold fluids	
Volume of cold fluids	

Continued

Table 1. Continued

Variable	Explanation
Pressure bag or infusion	
Pump infusion rate	min/L
Temperature measurement type	Axillary, bladder, brain, ear, esophageal, oral, or rectal
Time from CA to first cooling device	
Patient temperature at start of cooling	
Mean therapeutic hypothermia (TH) target temperature of device	
Patient temperature difference from start of TH and 34°C	
Time from start of TH to 34°C	
Time from CA to 34°C	
Time to reach target temperature	Never reached, ≤12 h, >12 h
Time from beginning of TH to target temperature	
Mean cooling rate (°C/h)	
Mean warming rate with a rise in target temperature (°C/h)	
Duration of TH (<34°C)	
Time from target temperature to rewarming	
Day 1: percent of time patient temperature is >0.5°C below target temperature	
Day 1: percent of time patient temperature is >1.0°C below target temperature	
Day 1: percent of time patient temperature is >0.5°C above target temperature	
Day 1: percent of time patient temperature is >1.0°C above target temperature	
Day 1: total percent of time patient temperature is within target temperature range	
Day 2: percent of time patient temperature is >0.5°C below target temperature	
Day 2: percent of time patient temperature is >1.0°C below target temperature	
Day 2: percent of time patient temperature is >0.5°C above target temperature	
Day 2: percent of time patient temperature is >1.0°C above target temperature	
Day 2: total percent of time patient temperature is within target temperature range	
Day 3: percent of time patient temperature is >0.5°C below target temperature	
Day 3: percent of time patient temperature is >1.0°C below target temperature	
Day 3: percent of time patient temperature is >0.5°C above target temperature	
Day 3: percent of time patient temperature is >1.0°C above target temperature	
Day 3: total percent of time patient temperature is within target temperature range	

Continued

Table 1. Continued

Variable	Explanation
All days: percent of time patient temperature is >0.5°C below target temperature	
All days: percent of time patient temperature is >1.0°C below target temperature	
All days: percent of time patient temperature is >0.5°C above target temperature	
All days: percent of time patient temperature is >1.0°C above target temperature	
All days: total percent of time patient temperature is within target temperature range	
Duration of time patient temperature below 30°C	
Lowest temperature reached	
Rewarming	
Initial patient temperature	Measures at start of rewarming
Mean rewarming target temperature of device	
Time from start temperature to target temperature	
Mean rewarming rate (°C/h)	
Time above 1.0°C of target temperature in first 24 h	
Duration of fever (>37.8°C) or fever management	
Fever management	Were measures used to prevent fever?
Hypothermia stopped early	Yes, due to complications; Yes, limitation of care; No
Interventions and labs	
Coronary angiography	
Stenting	
Lowest heart rate	Following ROSC
Highest heart rate	Following ROSC
Lowest mean arterial pressure (MAP)	Following ROSC
Highest MAP	Following ROSC
Lowest troponin	Following ROSC
Highest creatine kinase MB	Following ROSC
Highest creatine phosphokinase	Following ROSC
Lowest hemoglobin	Following ROSC
Lowest white blood count	Following ROSC
Highest white blood count	Following ROSC
Initial creatinine	Following ROSC
Highest creatinine	Following ROSC
Initial blood urea nitrogen	Following ROSC
Initial lactate	Following ROSC
Highest lactate	Following ROSC
Lowest magnesium	Following ROSC
Lowest glucose	Following ROSC
Highest glucose	Following ROSC
Lowest potassium	Following ROSC

Continued

Table 1. Continued

Variable	Explanation
Lowest phosphorus	Following ROSC
Day 1: total volume fluids in	
Day 1: total volume fluids out	
Day 2: total volume fluids in	
Day 2: total volume fluids out	
Day 3: total volume fluids in	
Day 3: total volume fluids out	
Blood gas and respiratory	
Initial pH	Following ROSC
Lowest pH	Following ROSC
Highest pH	Following ROSC
Initial pO_2	Following ROSC
Lowest pO_2	Following ROSC
Arteriovenous pO_2 gradient	Following ROSC
Initial pCO_2	Following ROSC
Arteriovenous pCO_2 gradient	Following ROSC
Initial HCO_3	Following ROSC
Initial $pSaO_2$	Following ROSC
Initial base deficit	Following ROSC
Initial base excess	Following ROSC
Highest FiO_2	Following ROSC
Days on ventilator	
Color of secretions	Within 24 h of rewarming
Time of secretions	No secretions, during cooling, or during rewarming
Infection suspected	
Infection	Documented infection based on positive culture or imaging plus clinical diagnosis/treatment noted in medical record
Positive culture results	Negative, bacterial, viral, fungal, or parasite
Time of positive culture results	Negative, during cooling, or during rewarming
Medication	
Day started on antibiotics	
Days given antibiotics	
Days magnesium >8 mg	
Days given skin counter warmer	
Fentanyl	Over initial 24 h following CA
Propofol	Over initial 24 h following CA
Aspirin	Over initial 24 h following CA
Acetaminophen	Over initial 24 h following CA
Midazolam	Over initial 24 h following CA
Lorazepam	Over initial 24 h following CA
Alprazolam	Over initial 24 h following CA
Rocuronium	Over initial 24 h following CA

Continued

Table 1. Continued

Variable	Explanation
Vercuronium	Over initial 24 h following CA
Morphine	Over initial 24 h following CA
Hydromorphine	Over initial 24 h following CA
Ketamine	Over initial 24 h following CA
Pressors	
Dobutamine	mg/h over induction phase
	mg/h over maintenance phase
	mg/h over rewarming phase
Epinephrine	mg/h over induction phase
	mg/h over maintenance phase
	mg/h over rewarming phase
Norepinephrine	mg/h over induction phase
	mg/h over maintenance phase
	mg/h over rewarming phase
Vasopressin	units/h over induction phase
	units/h over maintenance phase
	units/h over rewarming phase
Milrinone	mg/h over induction phase
	mg/h over maintenance phase
	mg/h over rewarming phase
Phenylephrine	mg/h over induction phase
	mg/h over maintenance phase
	mg/h over rewarming phase
Dopamine	mg/h over induction phase
	mg/h over maintenance phase
	mg/h over rewarming phase
Outcomes at discharge	
Pittsburgh cerebral performance category (CPC)	CPC 1 to 5
Discharge location	Died, home, acute rehabilitation, nursing home, hospice, other
Mini-mental state examination (MMSE)	Maximum score 30
GCS	3 to 15
Days in hospital	
Survival	Yes/no

IHCA indicates in hospital cardiac arrest; OHCA, out of hospital cardiac arrest.

of the variables included in this study and how they were defined is stated in Table 2. CA data routinely collected include the location of arrest (out-of- or in-hospital), gender, the presenting rhythm (dichotomized as VF/VT or non-VF/VT), and Pittsburgh CA category, a post-arrest injury severity score.[22] This score is based on the neurological examination, hemodynamics, and ventilator settings within 6 hours of arrest and is described elsewhere.[22] Using this simple 4-point scale, patients with the lowest CA category (I) had expected survival to discharge of ≈80% (60% with good neurologic outcome) as opposed to category IV patients who had survival <10% (<5% with good neurologic outcome). In patients who had paired arterial and superior vena cava central venous blood gases available within 30 minutes of one another, arteriovenous oxygen (A-VO_2) and carbon dioxide (A-VCO_2) gradients were calculated as they have been shown to correlate with cardiac output and metabolic energy expenditure.[25,26] These were obtained as we hypothesized that higher

Table 2. Clinical, Laboratory, and Pharmacological Data Hypothesized to be Associated With Patient Heat Generation

Variable	Explanation
Demographics	
Sex	
Age	
Location of arrest	In hospital cardiac arrest (IHCA) or out of hospital cardiac arrest (OHCA)
Presenting rhythm	Dichotomized to ventricular fibrillation (VF)/ventricular tachycardia (VT) or non-VF/VT
Body habitus	
Weight	Weight
Body mass index	Body mass index
Body surface area	Body surface area
Patient health at time of cardiac arrest	
Comorbidities	Dichotomized to none/few, or moderate/many
Lowest white blood count	Following return of spontaneous circulation (ROSC)
Measures of ischemic injury severity	
Time to ROSC	
Patient temperature at start of cooling	
Pittsburgh cerebral performance category (CPC)	Favorable (1 to 2) or unfavorable (3 to 5)
Disposition	Favorable (home/acute rehabilitation) or unfavorable (other)
Pittsburgh CA category (PCAC)	Category 1 to 4 within 6 h of ROSC
Days in hospital	
Survival	Yes/no
Lowest heart rate	Following ROSC
Highest heart rate	Following ROSC
Lowest mean arterial pressure (MAP)	Following ROSC
Highest MAP	Following ROSC
Lowest troponin	Following ROSC
Highest creatine kinase MB	Following ROSC
Highest creatine phosphokinase	Following ROSC
Lowest hemoglobin	Following ROSC
Initial creatinine	Following ROSC
Highest creatinine	Following ROSC
Initial blood urea nitrogen	Following ROSC
Initial lactate	Following ROSC
Highest lactate	Following ROSC
Lowest glucose	Following ROSC
Highest glucose	Following ROSC
Lowest potassium	Following ROSC
Initial pH	Following ROSC
Lowest pH	Following ROSC
Arteriovenous pO_2 gradient	Following ROSC
Arteriovenous pCO_2 gradient	Following ROSC
Initial base deficit	Following ROSC
Medication use to prevent shivering (cumulative dose in mg)	
Fentanyl	Over initial 24 h following CA
Propofol	Over initial 24 h following CA
Aspirin	Over initial 24 h following CA
Acetaminophen	Over initial 24 h following CA
Midazolam	Over initial 24 h following CA
Lorazepam	Over initial 24 h following CA
Vercuronium	Over initial 24 h following CA
Presence of infection or inflammation	
Infection present	Documented infection based on positive culture or imaging plus clinical diagnosis/treatment noted in medical record
Highest white blood count	Following ROSC
Initial patient temperature	Measured at the start of cooling

These variables were included in the regressions analysis for heat index.

heat generation was the result of higher metabolic rate and thus carbon dioxide generation presumably due to a higher hypothalamic/pituitary mediated set point. Both arteriovenous oxygen and carbon dioxide gradients have been demonstrated to correlate with cardiac output[26] but only carbon dioxide differences correlate with metabolism and heat generation.[25]

Statistical Analysis

Univariate linear regressions determined the association of each of the grouped variables (Table 2) with HI. Variables associated with HI in the univariate analyses ($P<0.05$) were included in a multivariable backward stepwise linear regression to determine independent association with HI and are reported as coefficients with 95% confidence intervals (95%

Table 3. Binary Logistic Regressions Examining the Association Between Known Predictors of Outcome Following Cardiac Arrest and Each Endpoint

	Disposition		Survival		Cerebral Performance Category	
	Odds Ratio (95% Confidence Interval)	*P* Value	Odds Ratio (95% Confidence Interval)	*P* Value	Odds Ratio (95% Confidence Interval)	*P* Value
Age	0.98 (0.94, 1.02)	0.359	1.01 (0.98, 1.05)	0.492	1.00 (0.96, 1.04)	0.894
Sex	0.99 (0.27, 3.72)	0.991	1.54 (0.52, 4.55)	0.434	1.03 (0.30, 3.56)	0.965
Rhythm (VF/VT, non-VF/VT)	9.60 (2.14, 43.05)	0.003	4.56 (1.39, 14.97)	0.012	5.44 (1.45, 20.40)	0.012
Location of arrest (IHCA, OHCA)	0.77 (0.19, 3.04)	0.704	0.22 (0.07, 0.72)	0.012	0.44 (0.12, 1.57)	0.204
PCAC	0.42 (0.20, 0.86)	0.018	0.14 (0.04, 0.43)	0.001	0.45 (0.22, 0.90)	0.024

IHCA indicates in hospital cardiac arrest; OHCA, out of hospital cardiac arrest; PCAC, Pittsburgh CA category; VF, ventricular fibrillation; VT, ventricular tachycardia.

CI). Univariate binary logistic regressions determined the association of HI with each outcome endpoint expressed as an odds ratio (OR) with 95% CI. A series of univariate analyses determined the association of known predictors of outcome of CA with the primary endpoints (Table 3). To avoid over fitting the model, the strongest associated predictor was included in a bivariate binary logistic regression as a control to determine the independent association of HI with each endpoint, also expressed as an odds ratio (OR) with 95% CI. The area under the receiver-operator curve (ROC) determined the predictive strength of HI for each outcome. Mann-Whitney U test determined differences in median HI between favorable versus unfavorable outcome cohorts for each endpoint. Chi square analysis compared the proportion of patients with favorable and unfavorable discharge disposition based on Pittsburgh CA category.[22] Correlation between HI and A-VO_2 and A-VCO_2 was determined based on Pearson's regression. In all cases 2-tailed $P<0.05$ was considered significant. Regressions were performed using SPSS v19 (IBM Inc) and other analyses using Prism v6.01 (GraphPad Software, Inc).

Results

A total of 76 consecutive, comatose post-CA patients were treated with TH using one of the designated devices between October 2011 and September 2012. Of these, 19 patients were excluded from the study due to the target temperature of the machine being set to a temperature other than 33°C (n=5), inadequate time at 33°C due to truncated cooling (n=3), or frequent (>10% of total time) interruptions of cooling (n=2), improper programming of the cooling device (n=7), or the patient not maintaining 33°C despite full protocol execution (n=2). To avoid bias we examined the 2 patients excluded due to inadequate time at goal temperature despite appropriate protocol use by using the available maintenance data. One patient maintained at goal for only 106 minutes had an HI of 6.93 and survived with favorable CPC. He was discharged back to the nursing home from which he came. The other patient was maintained at goal for 67 minutes with HI of 2.93. This patient died.

Thus, 57 patients remained for the final analysis. A total of 36 (63%) patients died before hospital discharge. Patient demographics are shown in Table 4. Patients were cooled using the Arctic Sun 5000® (n=20), and ThermoGard® Icy (n=18) and Quattro (n=19) catheters. We found minimal variation in the mean HI (Figure 1) or ranges for each device indicating similar cooling efficiencies ($P=0.371$), therefore the data were pooled for analysis.

Patient Level Variables Associated With Heat Generation

To test our hypothesis that various patient-level variables (Table 2) could account for fluctuations in heat generation, we performed univariate linear regressions to determine the association of these variables with the HI. Six of the analyzed variables had some association with HI (Table 5). Of these 6, only 3 were independently associated with HI ($P<0.05$) in a multivariable step-wise backward linear regression. Increased heat generation was associated with higher minimum WBC count (ie, less leukopenia), a marker of poor health or immunosuppression, higher initial lactate, a marker of ischemia severity, and higher initial 24-hour cumulative propofol dosage (Table 6). We were unable to analyze several medications (alprazolam, rocuronium, morphine, hydromorphine, and ketamine), which may potentially alter heat generation due to their underutilization (<10 patients having received the medication). Surprisingly, patient size did not associate with HI (BMI: $P=0.440$; BSA: $P=0.417$; weight: $P=0.858$).

Table 4. Patient Demographics and Characteristics

	Overall Population (n=57)	Favorable Disposition (n=11)	Unfavorable Disposition (n=46)
Age (SD)	59 (17)	55 (12)	60 (18)
Male	31 (54%)	6 (55%)	25 (54%)
OHCA	39 (68%)	7 (64%)	32 (70%)
Presenting rhythm			
VF/VT	19 (33%)	9 (82%)	10 (22%)
PEA	17 (30%)	1 (9%)	16 (35%)
Asystole	18 (32%)	1 (9%)	17 (37%)
Unknown	3 (5%)	—	3 (6%)
Favorable CPC	13 (23%)	9 (82%)	4 (9%)
Survival	21 (37%)	11 (100%)	10 (22%)

CPC indicates cerebral performance category; OHCA, out of hospital cardiac arrest; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.

Association Between Heat Generation and Outcomes

To test the hypothesis that greater heat generation predicts better neurologic outcome, we performed a univariate binary logistic regression between HI and our endpoints. HI was associated (Figure 2A) with favorable disposition (OR=2.26; 95% CI: 1.19, 4.29; *P*=0.013) and CPC (OR=1.91; 95% CI: 1.08, 3.37; *P*=0.026), while a trend was observed with survival (OR=1.67; 95% CI: 0.97, 2.88; *P*=0.067). Our analysis of the known predictors of outcome after CA showed presenting rhythm, dichotomized as presentation with or without VF/VT, had the strongest association with the endpoints (Table 3). After adjustment for presenting rhythm, HI remained independently associated with favorable disposition and CPC (Figure 2B) in bivariate logistic regression. A sensitivity analysis performed defining "good outcome" to include patients who were admitted from a nursing home and discharged to a similar nursing home (n=2) did not alter these associations. A separate sensitivity analysis excluding patients with a clinical diagnosis of sepsis (n=2) or fever (n=4) antecedent to hypothermia induction also did not alter these results.

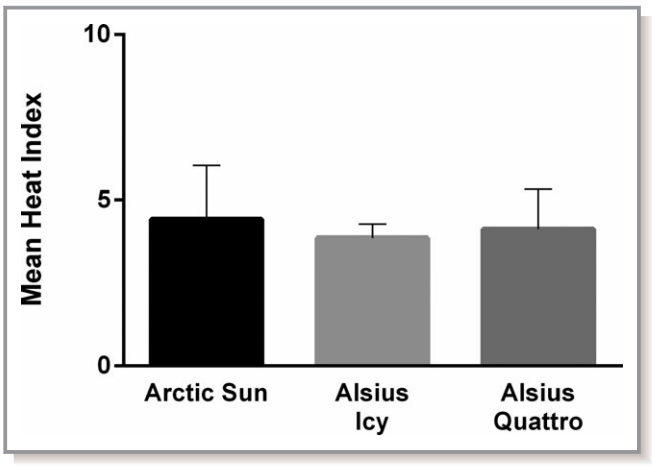

Figure 1. Mean heat generation by cooling device. Mean±SD of HI for each device during the maintenance phase of TH with target temperature set at 33°C. The HI did not differ significantly between groups (*P*=0.371). HI indicates heat index; TH, therapeutic hypothermia.

Table 5. Univariate Predictors of Heat Generation

	Unstandardized Coefficient (95% Confidence Interval)	*P* Value
Lowest hemoglobin, mg/dL	0.186 (0.060, 0.312)	0.005
Lowest WBC, $\times 10^9$	0.068 (0.000, 0.135)	0.049
Initial lactate, mmol/L	−0.119 (−0.188, −0.051)	0.001
Maximum glucose, mg/dL	−0.028 (−0.050, −0.006)	0.014
Propofol, mg	0.011 (0.002, 0.020)	0.019
Acetylsalicylic acid, mg	0.028 (0.001, 0.056)	0.041

Variables associated with heat index in univariate linear analyses. Minimum hemoglobin and white blood count (WBC) are the lowest values observed following return of spontaneous circulation, while maximum glucose is the highest value observed. Initial lactate is the earliest recorded value after return of spontaneous circulation. Propofol and acetylsalicylic acid are recorded as the cumulative dosage over the initial 24 hours following cardiac arrest.

HI distribution differed significantly (*P*=0.029) between patients with favorable (median HI=4.63) and unfavorable (median HI=3.80) disposition (Figure 3A). HI predicted (Figure 3B) favorable disposition (AUC=0.71, *P*=0.029) with optimal discrimination at a cut-off of HI=4.45, which had a sensitivity of 0.636 and specificity of 0.826 for predicting favorable disposition (likelihood ratio=3.66). Analyses for the endpoints of CPC (favorable CPC median HI=4.45, unfavorable CPC median HI=3.80, AUC=0.677, *P*=0.055) and survival (survivors median HI=4.19, nonsurvivors median HI=3.73, AUC=0.626, *P*=0.116) yielded similar trends.

Table 6. Independent Predictors of Heat Generation

	Unstandardized Coefficient (95% Confidence Interval)	*P* Value
Minimum WBC, $\times 10^9$	0.072 (0.013, 0.130)	0.018
Initial lactate, mmol/L	−0.099 (−0.165, −0.033)	0.004
Propofol, mg	0.009 (0.001, 0.017)	0.025

Variables independently associated with heat index in a backward multivariable model. WBC indicates white blood count.

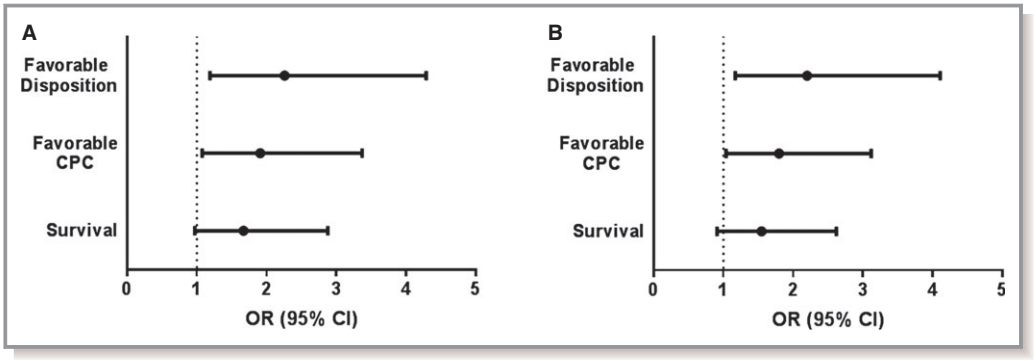

Figure 2. Association between heat index (HI) and outcomes. A, OR and 95% CI for each endpoint with HI, with favorable disposition and CPC demonstrating a significant association. B, OR and 95% CI for each endpoint with HI after adjusting for presenting rhythm, the major factor associated with CA outcome (Table 3). This adjustment minimally altered associations. CA indicates cardiac arrest; CPC, cerebral performance category; OR, odds ratio.

Heat Index Measures Metabolic Rate

In order to corroborate the theory that HI was indeed measuring metabolic rate, we examined its correlation with arteriovenous carbon dioxide (A-VCO_2) and oxygen (A-VO_2) gradients. Others have demonstrated that A-VCO_2 is correlated with both metabolic rate (CO_2 generation) and cardiac output whereas A-VO_2 tends to be primarily a measure of cardiac output.[26] Consistent with the hypothesis that HI is measuring metabolic rate, HI correlated well with A-VCO_2 (Spearman's rho=0.68; P=0.043) but not with A-VO_2 (Spearman's rho=0.32, P=0.406) (Figure 4).

Differences in Heat Generation After Adjustment for Injury Severity

Based on the results above, it is clear that clinical trials of more rapid cooling would need to adjust for baseline neurologic injury or be seriously confounded by this interaction. We therefore looked to see how strongly the association between heat generation was mitigated after adjustment for injury severity after CA. Our recently reported Pittsburgh CA Category (PCAC) is a simple 4-point injury severity score,[22] which categorizes CA survivors based in large part on their early neurologic exam and cardiopulmonary injury. Higher PCAC corresponds to worsened injury with increasing mortality and worsened neurologic function. Adding PCAC as a continuous variable in a bivariate logistic regression removed the association between HI and favorable disposition.

A univariate linear regression between HI and PCAC demonstrated a strong negative association (B=−0.561; 95% CI: −0.920, −0.202; P=0.003) with higher HI tracking with lower PCAC (ie, less injury). When we plotted patient disposition by PCAC, there was a trend to more favorable disposition in patients with HI above the regression line (8/27) compared with those below it (3/29; OR=3.65; 95% CI

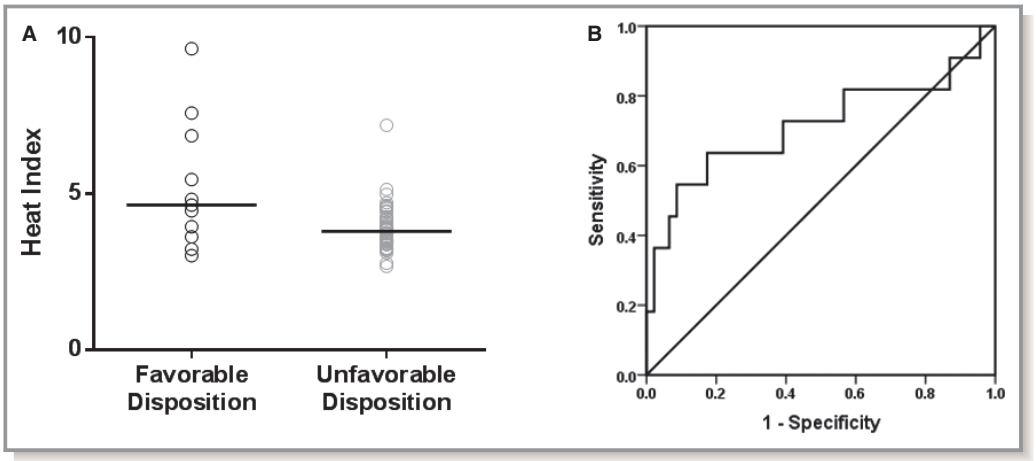

Figure 3. Association between heat index (HI) and favorable disposition. A, Distribution of HI within the primary endpoint demonstrates a higher median HI in patients with favorable compared to unfavorable disposition (P=0.029). B, HI significantly predicts favorable disposition with an area under the receiver operator curve of 0.71 (P=0.029).

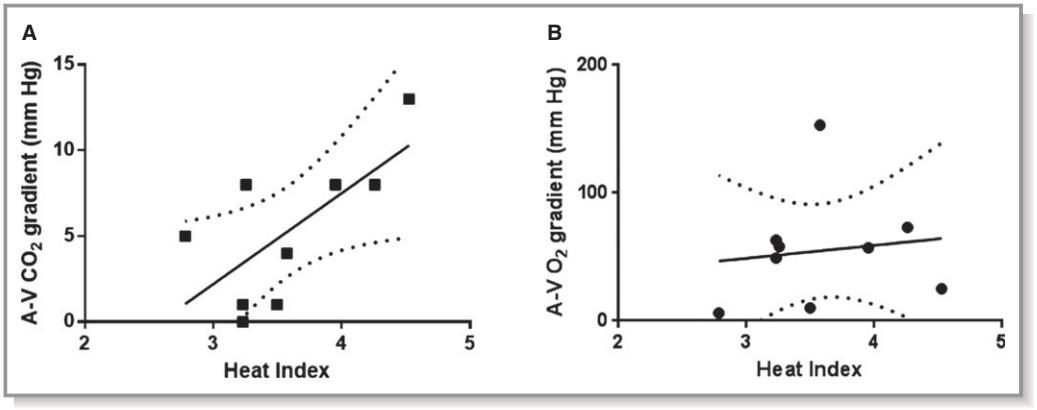

Figure 4. Correlation between heat index and arteriovenous gradients. Heat index was significantly correlated with the (A) arteriovenous carbon dioxide gradient (A-VCO_2; Spearman's rho=0.68; *P*=0.043) but not (B) arteriovenous oxygen gradient (A-VO_2; Spearman's rho=0.32, *P*=0.406). The linear regression line and 95% confidence intervals are also plotted for each correlation.

0.085, 15.6; *P*=0.081) (Figure 5). Thus, the diminishing effect that early categorization of injury severity has on the association of HI with outcomes is likely a result of the 2 variables both measuring injury severity.

Discussion

There are several important findings of this study, which is the first to quantify heat generation in cardiac arrest survivors receiving therapeutic hypothermia. First, of an extensive list of variables analyzed, only 3 had independent associations with greater heat generation: a lower initial lactate level, a higher minimum WBC count, and a higher 24 hour cumulative propofol dose. Second, greater heat generation was associated with neurologically intact survival. Finally, these data suggest that greater heat generation is the result of higher metabolic rates in less injured patients. Heat index is therefore a quantitative prognostic factor that can be obtained early in treatment of cardiac arrest patients even when sedation and neuromuscular blockade used adjunctively with TH clouds the neurological exam making prognostication difficult.[27,28]

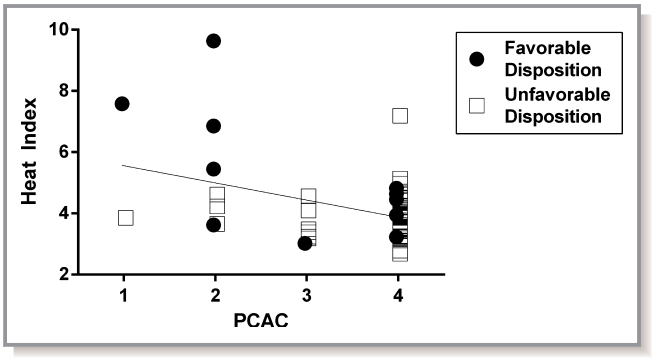

Figure 5. . Association between heat generation and post-arrest injury severity score. Plotted is the regression line that correlates heat index (HI) to the Pittsburgh cardiac arrest category (PCAC). Points lying above the line represent patients with a higher than expected HI for that category and those below the line represent a lower than expected HI. The solid points represent good outcomes and the open points bad outcomes. HI was strongly associated with the PCAC, *P*=0.003. A HI greater than that predicted based on PCAC trended towards higher likelihood of favorable disposition (*P*=0.081).

Several studies have shown an association between elevated initial lactate levels and both mortality and worsened neurologic outcomes in cardiac arrest patients.[29–31] Therefore, it is not surprising that a higher HI is also associated with lower initial lactate level. This finding and the association between HI with post-arrest injury severity (PCAC) may be useful in alerting clinicians to the fact that the patient being treated with therapeutic hypothermia will likely be easier or harder to cool. The higher propofol requirement in patients with higher HI is likely a reflection of this as propofol is commonly used in shivering prevention.[32] Although we do not know of any papers documenting leukopenia as a risk factor for worsened post-CA outcome, this plus the univariate association between HI and anemia likely speak to patients with lower baseline health having worsened outcomes. Because other measures such as albumin and pre-arrest functional status were not available to us, this is only speculative and requires future validation.

At least 2 other groups[19,21] have reported that poikilothermia on presentation after ROSC is associated with worsened survival. Benz-Woerner and colleagues[19] reported that longer time to rewarming was associated with non-survival. Haugk and colleagues[21] reported rapid time to target temperature (34°C) was associated with unfavorable neuro-

logic outcomes after CA. These results suggest patients with more severe neurologic injury are generating less heat and are therefore easier to cool and harder to rewarm.

The correlation between HI and arteriovenous carbon dioxide gradients corroborate the hypothesis that the measured HI reflects metabolic rate with lower heat generation present in more severely injured CA patients. We can only speculate on the physiologic mechanism of this effect. One potential etiology is that more severe global brain injury impacts the hypothalamus, which impairs thermoregulation.[33] The hypothalamus is not one of the well-characterized, selectively vulnerable (to ischemia) regions of the brain[34] and thus may only be affected in more severe cases. Alternatively, mitochondrial dysfunction after cardiac arrest[35–37] and hence systemic ability to generate heat may limit heat generation and predicts worsened survival.[36] Given the differential sensitivities of various tissue types to ischemia, and the relative resistance to ischemia by muscle[38] where most heat generation occurs, compared with the brain, where it is regulated, we favor the former hypothesis.

An important finding of our study is the independent and quantitative prognostic value of HI. This effect persisted even after controlling for the most important known association with CA outcomes, namely the presenting rhythm. Admittedly the predictive value of comparing median HI between groups is modest with a likelihood ratio of 3.6. What adds to its value in clinical practice is the ability to use it at a time when neuroprognosis is nearly impossible, namely during hypothermia when most patients are sedated and perhaps paralyzed. The PCAC is limited to these constraints and requires a fair degree of expertise to assign effectively; therefore, it may be difficult to implement at most institutions. The objective nature of HI will allow it to be calculated with minimal expertise on all patients, regardless of their level of sedation, rendering it a valuable early predictor of injury severity. Additionally, the quantitative nature of HI makes it more powerful in more extreme cases than the group medians. In this report, the median difference in HI between those with favorable versus unfavorable neurologic outcome translated to a nearly 5°C difference in water temperature throughout maintenance phase. Though not linear, mean water temperature increases from 16.6 to 20°C and 25 to 33°C (corresponding to HI decrease from 6 to 3) are each associated with a 2.2-fold increase in odds of poor neurologic outcome. Thus in cases where low (<3) or high (>6) HI is present the value is substantial. Given the increasing use of hypothermia in post-resuscitation care frequently mediated by devices where water temperature is available,[39] this provides clinicians an additional early marker of prognosis. When using HI in conjunction with PCAC, another early prognostic marker, we saw greatest discernment in the lower injury severities where outcomes are often hardest to predict. In more severe cases, the outcome is often manifest.

Our results are also important in the planning of randomized clinical trials aimed at achieving more rapid initiation of hypothermia and achievement of goal temperature. Several trials of this sort have been performed with hopes of reducing reperfusion injury to the brain. Although this approach has yielded good results in animal models,[11,12,14] these results have not been consistently replicated clinically.[17,18] Animal models deliver similar degrees of ischemia, resulting in a more homogenous injury severity such that the rapidity of cooling depends only on the therapeutic cooling methods used. In the clinical setting where injury is heterogeneous, patients' heat generation will vary substantially so discerning the benefit of external hypothermic therapies is challenging without an adjustment for this patient level variable. The use of HI is the only quantitative method to perform such a post-hoc adjustment. Our findings regarding the correlation between HI and arteriovenous CO_2 gradients, which can be obtained even in the field, permit a means to estimate heat generation permitting stratification prior to randomization in trials testing rapid hypothermia.

There are limitations to this study. The study population is small, though it is comprised of patients from 2 centers, which increases generalizability. The sample size may explain the limited number of associations we observed and larger studies may detect weaker associations. Though the data collection on HI and many peri-arrest variables were collected prospectively, other data elements (such as drug dosing and blood gases) were gathered retrospectively. Thus, there is a reliance on accurate record keeping and data entry, which is not always present. As much as possible, we used objective lab measures and for the calculation of HI all data were directly downloaded from the devices, which should mitigate inaccuracies. We also note that continuous neuromuscular blockade is rarely employed in these facilities. Facilities using continuous neuromuscular blockade may yield differing results and potentially a significant association with decreased heat generation. CPC assessment at discharge is limited by the evaluations provided in physician's reports, which are inherently subjective in nature.[40] Hence our use of a slightly more objective endpoint for neurologic outcome, the discharge location, which is more clearly dictated by the patient's functional status.

Conclusion

Heat generation is independently associated with neurologic outcome in patients successfully resuscitated from cardiac arrest, and shows a strong association with initial illness severity. Markers of better baseline health and reduced

ischemic injury were associated with greater heat generation. Our findings demonstrate one potential reason for the inability to translate more rapid cooling to improved clinical outcomes and provide a means to control for this important confounding variable in future clinical trials.

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Disclosures

None.

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Determinants of Heat Generation in Patients Treated With Therapeutic Hypothermia Following Cardiac Arrest

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