Concordance of Brain and Core Temperature in Comatose Patients After Cardiac Arrest

Patrick J. Coppler, BA,^{1,2} Keith A. Marill, MD,¹ David O. Okonkwo, MD, PhD,³
Lori A. Shutter, MD,³⁻⁵ Cameron Dezfulian, MD,⁵ Jon C. Rittenberger, MD, MS,¹
Clifton W. Callaway, MD, PhD,¹ and Jonathan Elmer, MD, MS^{1,5};
on behalf of the Pittsburgh Post-Cardiac Arrest Service*

Comatose patients after cardiac arrest should receive active targeted temperature management (TTM), with a goal core temperature of 32–36°C for at least 24 hours. Small variations in brain temperature may confer or mitigate a substantial degree of neuroprotection, which may be lost at temperatures near 37°C. The purpose of this study was to define the relationship between brain and core temperature after cardiac arrest through direct, simultaneous measurement of both. We placed intracranial monitors in a series of consecutive patients hospitalized for cardiac arrest at a single tertiary care facility within 12 hours of return of spontaneous circulation to guide postcardiac arrest care. We compared the absolute difference between brain and core (esophageal or rectal) temperature measurements every hour for the duration of intracranial monitoring and tested for a lag between brain and core temperature using the average square difference method. Overall, 11 patients underwent simultaneous brain and core temperature monitoring for a total of 906 hours of data (Median 95; IQR: 15–118 hours per subject). On average, brain temperature was 0.34°C (95% confidence interval [CI] 0.31–0.37) higher than core temperature. In 7% of observations, brain temperature exceeded the measured core temperature $\geq 1^\circ\text{C}$. Brain temperature lagged behind core temperature by 0.45 hours (95% CI = –0.27–1.27 hours). Brain temperature averages 0.34°C higher than core temperature after cardiac arrest, and is more than 1°C higher than core temperature 7% of the time. This phenomenon must be considered when carrying out TTM to a goal core temperature of $<36^\circ\text{C}$.

Keywords: monitoring, hypothermia, cardiac arrest, brain injury, neurocritical care, intracranial monitoring

Introduction

CARDIAC ARREST IS THE MOST common cause of death in the United States and the majority of patients who succumb after return of spontaneous circulation (ROSC) die from sequelae of brain injury (Coppler *et al.*, 2015; Mozaffarian *et al.*, 2015; Elmer *et al.*, 2016). To minimize secondary brain injury, guidelines recommend active targeted temperature management (TTM) of comatose postcardiac arrest patients to a core temperature of 32–36°C for at least 24 hours after ROSC (Callaway *et al.*, 2015). Since the publication of the large TTM trial (Nielsen *et al.*, 2013), targeting a core temperature of 36°C has become increasingly common (Leary *et al.*, 2015; Rittenberger *et al.*, 2015; Deye *et al.*, 2016). Unfortunately, although the brain is the target end organ for TTM-induced protection, only core temperature is usually measured and the relationship between brain and core temperature after cardiac arrest is poorly described.

In other populations with severe acquired brain injury, core temperature is systematically lower than brain temperature (Childs and Lunn, 2013; Karaszewski *et al.*, 2013).

Preclinical evidence suggests that reductions of brain temperature by 1°C from 37°C to 36°C may be neuroprotective (Jackson *et al.*, 2015), and that these benefits are not achieved with active normothermia (37°C) (Logue *et al.*, 2007). These data raise concern that the neuroprotective benefits of TTM may be reduced when targeting a core temperature of 36°C, if the unmeasured brain temperature were significantly higher. The purpose of this study, therefore, was to quantify the relationship between brain and core temperature in comatose postcardiac arrest patients through direct, simultaneous measurement of both. We hypothesized that core temperature would substantially underestimate brain temperature across a range of core temperatures. Secondarily, we hypothesized that brain temperature would lag behind core temperature during periods of dynamic temperature change.

¹Department of Emergency Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

²Department of Physician Assistant Studies, University of the Sciences, Philadelphia, Pennsylvania.

³Departments of Neurosurgery, ⁴Neurology, and ⁵Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

*The list of the Pittsburgh Post-Cardiac Arrest Service researchers can be found under Acknowledgments at the end of the article.

Materials and Methods

The University of Pittsburgh Institutional Review Board approved this study. In brief, we identified a series of patients treated after cardiac arrest at a single tertiary care center between 2013 and 2015 who had intracranial monitors placed within 12 hours of ROSC to guide clinical care. We measured baseline severity of postcardiac arrest illness using a previously validated illness severity scale (Coppler *et al.*, 2015). We excluded subjects who had cardiac arrest or had brain monitors placed because of severe trauma or a primary neurological process such as catastrophic cerebrovascular accident. Our neuromonitoring package included placement of a right frontal intracranial access bolt (Licox® IMC Bolt Fitting, Integra LifeSciences; or QFlow 500™ Titanium Bolt, Hemedex, Inc.), through which intracranial pressure, temperature, and tissue oxygen probes were placed in the subcortical white matter. We measure intracranial temperature with either a Licox (Integra LifeSciences) or Raumedic® Neurovent PTO (Raumedic) catheter. Core temperature was measured by either a rectal or esophageal temperature probe. We performed TTM using a CoolGard 3000® endovascular catheter (Alsium Corporation) or Arctic Sun® (Mediance, Bard Medical) surface cooling pads, and targeted a core temperature of 33°C for 24 hours followed by rewarming at 0.25°C/h to a goal of 37°C, which we maintained for at least 5 days after ROSC.

Statistics

We used descriptive statistics to summarize population characteristics, then compared brain and core temperature measurements every hour for the duration of intracranial monitoring within each patient and for the overall population. We tested for a lag between brain and core temperature using the average square difference method. The sum of the squared difference in temperature between each hourly measurement divided by the number of measurements was computed while varying the lag between the two temperature signals between −3 and +3 hours. The minimum of the seven resulting values corresponded to the optimal lag between the two signals for each patient. Computations were programmed in Matlab R2014a (The Mathworks). We calculated the mean lag for the 11 included patients and bootstrapped its 95% confidence interval using the BCa method with 10,000 bootstrap samples in SPSS 23 (IBM).

Results

Overall, 11 patients underwent simultaneous brain and core temperature monitoring for a total of 906 hours (Median 95; IQR: 15–118 hours per subject). The majority of subjects had an asystolic initial rhythm and presented with severe brain injury (Table 1). Esophageal core temperature was monitored in 64% of patients and most subjects (73%) were cooled using an endovascular device. Median time from arrival to placement of intracranial monitoring was 7 hours (IQR: 5.5–8.5 hours).

On average, brain temperature exceeded core temperature by 0.34°C (95% confidence interval [CI]: 0.31–0.37°C) (brain mean temperature −34.81°C; 95% CI: 34.68–34.95; core mean temperature −34.46°C; 95% CI: 34.33–34.59; Figs. 1 and 2). Individual patient data did not reveal any differences in brain–core gradient between patients with rectal and esophageal tempera-

TABLE 1. SUBJECT DEMOGRAPHICS

Subject characteristics	N = 11
Age, years	47 ± 10
Male sex	6 (55%)
Out-of-hospital cardiac arrest	11 (100%)
Initial rhythm (%)	
VT/VF	2 (18)
PEA	3 (27)
Asystole	5 (46)
Unknown	1 (9)
Pittsburgh cardiac arrest category (%)	
I	0 (0)
II	1 (9)
III	0 (0)
IV	10 (91)
Core temperature monitoring site (%)	
Rectal	4 (36)
Esophageal	7 (64)
Cooling device	
CoolGard 3000®	9 (73%)
Arctic Sun®	2 (27%)
Arrival to brain monitoring interval, hours	7 ± 3
Survival to hospital discharge	1 (9%)

PEA, pulseless electrical activity; VT/VF, ventricular tachycardia/ventricular fibrillation.

ture measurements, nor between patients with endovascular or surface cooling (Fig. 2). In 7% of observations, brain temperature exceeded core temperature by at least 1°C. The bias for measurements of brain temperature to be higher than core temperature was nonsignificantly higher at higher temperatures based on the Bland–Altman plot (Fig. 3). Brain temperature lagged behind core temperature by 0.45 hours (95% CI: −0.27–1.27 hours).

Discussion

To our knowledge, this is the first report to compare brain and core temperature in human cardiac arrest patients. We found that during active temperature management, core temperature consistently underestimated brain temperature, often by a substantial degree. This phenomenon has also been observed after brain

FIG. 1. Histogram of total hours of observation and differences between brain and core temperature.

FIG. 2. Box and whisker plot of individual patient data and differences between brain and core temperature.

trauma and stroke (Karaszewski *et al.*, 2009; Childs and Lunn, 2013). Since the landmark TTM trial showing equivalent effects of treatment at 33°C versus 36°C on patient outcomes (Nielsen *et al.*, 2013), clinical practice has shifted toward targeting 36°C in comatose survivors of cardiac arrest (Callaway *et al.*, 2015; Leary *et al.*, 2015; Deye *et al.*, 2016). The TTM trial demonstrated equivalent patient outcomes at a population level, yet even within the context of this trial the 95% error bars in the 36°C cohort crossed 37°C (Nielsen *et al.*, 2013). Clinical practice outside of the context of a robust trial may be less precise, and patients treated with a target core temperature of 36°C are at greater risk of exceeding 37°C than patients treated with a lower target core temperature (Rittenberger *et al.*, 2015). Given the discrepancy we demonstrate between brain and core temperature, our results highlight the importance of vigilant prevention of even small rises in core temperature above 36°C to prevent unintended cerebral normothermia or fever during TTM.

Our work has several limitations. We present single center observational data including some of the most severe brain-injured cardiac arrest patients. The generalizability of our findings to less severe brain-injured postcardiac arrest patients is unknown. It may be that in a more mildly injured cohort, brain metabolism is less severely impaired and there is actually more cerebral thermogenesis, or that homeostasis is better preserved and there is less of a difference. In addition, the site of core temperature measurement and the device used for TTM were not consistent across patients. This va-

FIG. 3. Bland–Altman plot of absolute difference in core and brain temperature and relative core temperature.

riety likely reflects current clinical practice among cardiac arrest centers (Coppler *et al.* unpublished data 2016). Finally, with regard to detection of a lag between brain and core temperature, hourly measurements may be too infrequent and relatively insensitive to identify a lag that may exist on the order of minutes. However, we feel that such a brief lag, if it exists, is unlikely to be clinically relevant.

Conclusion

Brain temperature exceeds core temperature in comatose patients after cardiac arrest, sometimes by more than 1°C. Small elevations in core temperature above 36°C may risk brain normothermia and reduce the neuroprotective effect of TTM.

Acknowledgments

The Pittsburgh Post-Cardiac Arrest Service researchers are Jon C. Rittenberger, MD, MS; Clifton W. Callaway, MD, PhD; Francis X. Guyette, MD, MPH; Ankur A. Doshi, MD; Cameron DeZfulian, MD; Jonathan Elmer, MD, MS; Bradley J. Molyneaux, MD, PhD; and Lillian Emlet, MD, MS. Source of funding: Dr. Elmer's research time is supported by the NHLBI 5K12HL109068; Dr. DeZfulian's research time is supported by the NINDS KO8NS069817; and Dr. Elmer's research time is supported by the NHLBI 5K12HL109068.

Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:

Jonathan Elmer, MD, MS
Department of Emergency Medicine
University of Pittsburgh
Iroquois Building, Suite 400A
3600 Forbes Avenue
Pittsburgh, PA 15213

E-mail: elmerjp@upmc.edu