# Energy Expenditure in Patients Undergoing Targeted Temperature Management at 36°C After Cardiac Arrest, the Effect of Shivering and Ability to Maintain Goal Temperature

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## ABSTRACT

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Survivors of cardiac arrest undergo targeted temperature management (TTM) in the intensive care unit as a strategy to promote neurologic recovery and prevent further cellular injury from post-cardiac arrest syndrome (PCAS). During TTM, core body temperature is most often lowered to either 33°C or 36°C for approximately 24 hours. Since two landmark studies published in 2002 demonstrated a survival benefit of inducing hypothermia to 33°C, TTM has become a mainstay for post-cardiac arrest care. More recently, TTM at 36°C has gained popularity following a large randomized trial showing no difference in survival or neurologic outcome benefit for TTM at 36°C compared to that provided at 33°C. As TTM at 36°C is a newer strategy, less evidence exists related to the physiologic changes that occur at this "ultra-mild" hypothermic temperature. One of the effects of lowering body temperature is a reduction in

energy expenditure (EE), which is believed to contribute to the protective effect of TTM. An important side effect of TTM is shivering, which can increase EE by 400% as a mechanism to raise body temperature. Both the increase in body temperature and energy demands may attenuate the benefits of TTM. TTM at 33°C has been shown to decrease EE 20-35%, but the change in EE at 36°C for post-cardiac arrest patients is not known.

TTM can be initiated and maintained using surface cooling pads that circulate water within the pads placed on the body to regulate core temperature. The surface cooling device responds to a patient's core temperature by either increasing or decreasing the temperature of the circulating water to maintain 36°C. The acceptable variability in the targeted temperature is ±0.5°C. Compliance with maintaining body temperature within the acceptable range has been shown to be more difficult at a target temperature of 36°C compared to 33°C, although the effect on outcomes is unclear. One reason for poor compliance is patient heat generation, such as occurs during shivering. To date, there is little evidence evaluating the impact of shivering on the ability to maintain 36°C during TTM. Additionally, the change in surface pad water temperature in response to changes in body temperature has not been well described. This dissertation aims to address key gaps in knowledge related to understanding the change in EE for patient receiving TTM at 36°C following cardiac arrest, and the effect of shivering on EE. Additionally, this dissertation describes the relationship between water temperature of the cooling device and body temperature, as well as relationship between temperature variability and shivering.

We conducted a prospective observational case-series study of consecutive patients following out of hospital cardiac arrest to evaluate patterns of EE during the course of TTM 36°C. A total of three patients were included. We found that EE at 36°C was similar to that of other critically ill patients with and without brain injury. In addition, we observed that two patients with dynamic EE and temperature changes survived to hospital discharge with good neurologic outcome, and the patient with little temperature variability did not survive. This finding is in alignment with previous studies on the association with heat generation (increased EE) and improved outcomes.

We then conducted a retrospective cohort study of patients with cardiac arrest who received TTM at 36°C using surface cooling pads at Harborview Medical Center in Seattle, Washington. A total of 186 patients were included. We found that there was a strong correlation between device water temperature and body temperature. For every 0.1°C change in body temperature, there was a 4.3°C change in water temperature. Additionally, we found that shivering was significantly associated with having an increased proportion of temperature measurements > 36 ±0.5°C, and significantly associated with survival to hospital discharge. This finding supports growing evidence supporting the relationship with the ability to shiver and improved outcomes.

The studies within this dissertation aimed to add to the knowledge of caring for patients during TTM at 36°C.

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# DEDICATION

*To my loving husband, without whom this dissertation would not be possible*

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# CHAPTER 1: Introduction

Sudden cardiac arrest affects more than 500,000 Americans per year with a mortality of 50-90%.[1,2] For those who survive the initial cardiac arrest and achieve return of spontaneous circulation (ROSC), survival with favorable neurologic recovery depends on early healthcare-driven interventions to preserve neurologic function and prevent further cellular injury from post-cardiac arrest syndrome (PCAS).[3-7] The only evidence-based intervention known to mitigate the effects of PCAS is initiation of targeted temperature management (TTM), which is an active process to first lower, and then maintain core body temperature for a defined period of time.[8-10] Since two landmark trials published in 2002 demonstrated a survival benefit of inducing hypothermia to 32-34°C for 12-24 hours, TTM has become a mainstay for post-cardiac arrest care.[11,12] More recently, TTM at 36°C (termed ultra-mild hypothermia)[13] has received broader clinical acceptance following a large randomized trial showing no survival or neurologic outcome benefit for TTM at 33°C compared to 36°C.[8] As TTM at 36°C is a newer strategy, less evidence exists related to the physiologic changes that occur at this ultra-mild hypothermic temperature. Considering this lack of knowledge, it is critical to investigate the effectiveness of TTM at 36°C, and develop strategies to deliver optimal patient care specific to this contemporary targeted temperature.

## *Post-Cardiac Arrest Syndrome*

Survivors of the initial cardiac arrest face potential for secondary injury as reperfusion following a period of total-body hypoxia initiates cellular injury pathways, and can cause permanent disability or death.[4,5] PCAS is a term used to describe the pathophysiologic response to cellular injury following a cardiac arrest, and is characterized by a triad of brain injury, myocardial dysfunction, and a systemic ischemia-reperfusion response. A potential fourth criterion is the presence of precipitating pathology, such as an untreated coronary occlusion or ongoing metabolic disturbance. All components of PCAS are present following ROSC. However, the degree to which cellular injury or death occur depends on several factors including; an individual's underlying health, length of the cardiac arrest, timing of life-saving interventions such as chest compressions and defibrillation, and access to interventions such as TTM and coronary reperfusion following ROSC.[3-5]

*Targeted Temperature Management*

After achieving ROSC, patients receive interventions to reestablish homeostasis, which is necessary for survival. In addition, these patients often undergo TTM as in intervention to moderate the deleterious effects of PCAS. TTM is thought to elicit a protective effect against PCAS by preventing fever, blunting the inflammatory response, and reducing energy expenditure (EE) and oxygen consumption.[4,14,15] TTM includes three phases; induction (active total-body cooling to a goal temperature [GT] as quickly as possible), maintenance (maintaining GT for approximately 24 hours) and slow rewarming to normothermia (to approximately 37°C).[3,16] TTM can be accomplished using surface or intravascular cooling methods, with some institutions adding intravascular cold crystalloids during induction.[8,17,18] Surface cooling includes the use of ice packs, cooling blankets or cooling gel pads. Intravascular cooling involves the placement of a central venous catheter that circulates cold fluid within the catheter lumen allowing for heat exchange through indirect contact with circulating blood. The use of surface cooling pads and intravascular cooling catheters are considered advanced cooling methods, and are most frequently used in developed countries with no difference in patient outcomes between the two devices.[18-21] However, intravascular cooling catheters have been shown to have a faster time to GT, and maintain GT more precisely compared with all other cooling methods.[21]

A major component of patient care during TTM is the management of side effects. Modifying core body temperature alters temperature-dependent physiologic processes, thus altering assessment and laboratory findings. Similarly, observed side effects are also temperature dependent. It is expected that side effects will differ at 33°C compared to 36°C (Table 1), with lower temperatures being associated with more pronounced side effects. Not all side effects are present for every patient, and may depend on severity of PCAS, preexisting pathophysiology, degree of neurologic injury and demographic factors such as age and gender.

**Table 1. Side Effects of TTM Comparing 36°C to 33°C**

| Side Effect[3,9,22-25] | Present at 36°C | Present at 33°C |
|---|---|---|
| Hypovolemia (from cold diuresis) | Unknown | Yes |
| Arrhythmias (bradycardia) | Yes | Yes |
| Cardiovascular changes (peripheral vasoconstriction) | Potential | Yes |
| Electrolyte disturbances (decreased serum potassium, magnesium, phosphate and calcium) | Unknown | Yes |
| Alterations in serum laboratory values (increased lactate, acidosis, suppressed immune function) | Potential | Yes |
| Coagulopathy | Potential | Yes |
| Shivering | Yes | Yes |
| Insulin resistance | Potential | Yes |
| Increased risk of infection | Unknown | Yes |
| Skin impairment (from peripheral vasoconstriction) | Potential | Potential |
| Delayed drug clearance | Unknown | Yes |

### *Shivering During TTM*

One common and expected side effect of TTM is shivering. Shivering occurs when body temperature drops below approximately 35.5°C, which is referred to as the shivering threshold.[26,27] Hypothalamic signaling initiates shivering by increasing muscle tone and initiating rhythmic muscular contractions in an effort to generate heat and raise body temperature. Increases in heat and energy production resulting from shivering can reach 200% to 600% above baseline, and oxygen consumption can increase upwards of 200% above baseline.[26,28-31] Particularly for patients with PCAS, the potential 6-fold and 2-fold increases in EE and oxygen consumption, respectively, may further induce cellular injury and negate the potential benefits of TTM. In addition, shivering may inhibit the ability to reach or maintain GT due to a rise in body temperature from excess heat generation. Shivering has also been associated with decreased brain tissue oxygenation, increased intracranial pressure, and increased cardiac output and heart rate; all of which have potentially clinically important implications for neurologic recovery following cardiac arrest.[28,32,33] Although hospital TTM protocols frequently include anti-shivering strategies, the clinical and pathophysiologic impact of shivering during TTM is not well understood. Most pharmacologic agents aimed at preventing and treating shivering have known negative consequences to patient recovery, and may also interfere with appropriate neurologic assessment and prognostication.[34-37]

Shivering can occur at any point during TTM and at either GT. Shivering is seen in higher frequency when core body temperature is rapidly decreased, or when temperatures are within the shivering zone of approximately 33.5°C to 35.5°C.[10,27] At core body temperatures below 33.5°C, the shivering response is suppressed, and is usually absent at temperatures ≤ 33°C.[10,27,38] Hypoxic brain injury, such as occurs with cardiac arrest, can alter the hypothalamic set point causing shivering to occur at higher body temperatures.[39] However, those individuals with severe brain injury may lose their shiver response altogether.[40] Although the physiologic changes as a result of shivering have been described, neither shivering severity nor duration have been evaluated across the totality of TTM, or at a GT of 36°C.

The most common tool to measure shivering is the Bedside Shivering Assessment Scale (BSAS).[26] The BSAS is a 1-item, 4-point scale that requires clinicians to observe the patient for two minutes; including visual inspection and palpation of the neck, thorax, arms and legs (Table 1). The clinician then rates shivering on a scale from zero to three, with zero indicating no shivering, and each subsequent numerical value corresponding to increasing shivering severity. A higher BSAS score is associated with distinct increases in EE for critically ill, neurologically injured patients.[26] Although shivering severity was associated with step-wise increases in EE, the authors only measured EE at one time point and included multiple types of brain-injured patients.

### *Energy Expenditure During TTM*

EE is a measurement of total cellular metabolic activity and is expressed as kilocalories per day.[41-43] Total EE includes components of basal energy expenditure (BEE), diet-induced thermogenesis, and physical activity. BEE is the minimal amount of energy needed to maintain basic physiological homeostasis, and makes up greater than 80% to 90% of total EE during critical illness.[44] As BEE requires strict measurement criteria, resting energy expenditure (REE) is most often used in clinical settings as an alternative to BEE. Numerous factors contribute to EE during TTM and include; age, sex, body composition, illness severity, circulating catecholamines, body temperature, medications and the presence of shivering.[44,45] It is estimated that for every 1°C reduction in body temperature, EE will decrease by approximately 8%, and cerebral metabolism by 6-8%.[9,46]

Few studies have evaluated the effects of EE during TTM at any goal temperature, with or without shivering. In a study of 25 post-cardiac arrest patients undergoing TTM at 33°C, REE was evaluated at five time points (during the maintenance phase of TTM at 33°C, during rewarming at 34.5°C, at 36°C, 36.5-37.5°C, and at 48 hours after the cardiac arrest) using indirect calorimetry (IC) to examine the correlation between REE and body temperature.[47] REE was resulted as the mean RRE over a 30 minute steady state period. The authors found an average reduction in REE of 20% at 33°C compared to 36°C, and a 7.3% reduction in REE comparing 36.8°C to 36°C. On average, there was a 6.6% reduction in REE for every 1°C reduction in body temperature below 36°C. Shivering was not assessed or included in the analysis as all patients received continuous paralytic administration. Another study measured EE using IC (via a calorimeter module on the mechanical ventilator) in seven patients undergoing TTM at 33°C after cardiac arrest to estimate energy requirements.[48] EE was recorded continuously, and values were the respiratory quotient was 0.7-1.0 were included. There was an average reduction in EE of 34.4% at 33°C compared to 36°C. The authors purposefully avoided inclusion of data where shivering was suspected, thus EE during shivering was not included.

Validation of the BSAS represents one of the few studies evaluating EE and shivering in brain injured patients, however the study was not specific to TTM or post-cardiac arrest patients.[26] To date, no study has evaluated the change in EE during TTM at 36°C, and no study has evaluated the impact of shivering on EE over the course of TTM.

### *Dissertation Elements*

This dissertation aims to address key gaps in knowledge related to understanding the change in EE for patient receiving TTM at 36°C following cardiac arrest. Additionally, this dissertation explores the impact of shivering on EE as well as ability to maintain the targeted temperature. Here, we provide a brief overview of each chapter.

### **Chapter 2. Methods for Estimating Energy Expenditure in Critically Ill Adults**

There are numerous methods available to assess EE, few which are practical in the clinical setting. This chapter examines existing methods for estimating EE in critically ill adults, with and without mechanical ventilation. This chapter describes the benefits and limitations of each method and includes practical considerations for use. The methods covered in the review include predictive equations used to estimate energy needs, end tidal carbon dioxide measurements, the Fick method and indirect calorimetry.

### **Chapter 3. Energy Expenditure During Targeted Temperature Management at 36°C**

TTM at 36°C has become a popular targeted temperature in recent years despite remaining gaps in knowledge regarding the neuro-protective effects, if any, of this ultra-mild hypothermic temperature. One way in which TTM is thought to protect against PCAS is by decreasing EE, which in turn decreases oxygen demand, inflammatory activation and free radial production.

These protective mechanisms have been observed at temperatures of 32-34°C, but little is known if these same benefits exist at 36°C. Chapter 3 presents a study that describes patterns of energy expenditure during TTM at 36°C from the maintenance phase through rewarming. Additionally, this study explores the change in EE associated with clinical observations of shivering, and the effect of changes in EE on core body temperature.

### Chapter 4. Temperature Variation During Targeted Temperature Management at 36°C After Cardiac Arrest: Effect of Shivering and Changes in Water Bath Temperature

TTM can be initiated and maintained using surface cooling pads that circulate water within the pads placed on the body to regulate a patient's core temperature. The surface cooling device responds to a patient's core temperature by either increasing or decreasing the temperature of the circulating water to maintain patient GT. Patient heat generation, such as during shivering, may greatly affect the response of the cooling pad temperature by decreasing the water temperature in an effort to respond to increased EE and heat production seen during shivering. To date, the change in surface-pad water temperature in response to heat generation from shivering has not been well described. Additionally, there is little evidence evaluating the effect of shivering on the ability to maintain GT during TTM. The aims of this study were to describe the relationship between surface cooling water temperature and core body temperature, and to describe the association between shivering and body temperature variation during TTM at 36°C.

### Chapter 5. Conclusion

This chapter provides a synthesis of key findings from all dissertation activities. In addition, this chapter will discuss remaining gaps in knowledge and next steps needed to address the identified gaps.

# CHAPTER 2: Methods for Estimating Energy Expenditure in Critically Ill Adults

Title: Methods for Estimating Energy Expenditure in Critically Ill Adults

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# Abstract

Energy expenditure (EE) is the summation of all metabolic activity within the body at a given time. EE is comprised of basal energy expenditure, diet-induced thermogenesis and physical activity, with basal energy expenditure making up greater than 80% of total EE during critical illness. Critically ill adults have alterations in EE due to illness severity, administration of metabolism-altering medications, and underlying pathologic conditions. Assessment of EE is most often used to estimate caloric needs for hospitalized patients, but may also be useful in understanding disease states and the metabolic impact of clinical interventions. Several methods for determining EE are available for use in critically ill adults including predictive equations, exhaled carbon dioxide, the Fick method and indirect calorimetry. Each approach requires differing equipment and patient data, and is driven by the need for static versus dynamic measurements. Although indirect calorimetry is considered the gold standard for measuring EE, use is often limited by equipment availability, cost and expertise needed to obtain accurate measurements. It is therefore necessary to consider alternative methods to assess EE when indirect calorimetry is unavailable. The purpose of this review is to examine methods for evaluating EE in critically ill adults and discuss the benefits and limitations of each method with practical considerations for use.

## Introduction

Energy expenditure (EE) is an assessment of cellular metabolic activity in the body, and can be expressed as kilocalories or kilojoules per day.[41-43] During critical illness, EE may be affected by many factors including severity of illness, an individual's underlying health, and pharmacologic interventions used.[49,50] Assessment and monitoring of EE is useful in this population for determining caloric need, and to evaluate the metabolic effect of interventions during patient care. In the intensive care unit (ICU), EE can be estimated for both mechanically ventilated and non-ventilated patients. The choice of method for EE assessment should be carefully considered based on the indication for use, available equipment and the availability of patient information required for measurement. Knowledge of each method's components and limitations are also important considerations. The purpose of this review was to examine relevant methods for evaluating EE in critically ill adults and discuss the benefits and limitations of each method with practical considerations for use.

## Energy Expenditure

Total daily EE encompasses three main components: basal energy expenditure (BEE), diet-induced thermogenesis and physical activity. BEE, or basal metabolic rate, represents the lowest rate of energy expended to maintain basic autonomic function when an individual is at rest.[44] In healthy individuals, BEE comprises approximately 70% of total EE.[44,51] For hospitalized patients, BEE makes up greater than 80% to 90% of total EE, particularly for those who are immobile and critically ill.[44] BEE varies widely between individuals based on age, sex, body composition, hormonal balance, circulating catecholamines, genetics and is altered by level of fitness, body temperature, medications, and severity of illness.[44,45] Diet-induced thermogenesis, or the thermogenic effect of food, is the amount of energy required to digest nutrients and makes up about 10% of total EE.[51,52] As physical activity for most critically ill patients is minimal, the amount of energy expended is a small portion of total daily EE.

To accurately determine BEE, measurements require precise conditions, such as following 12 hours of fasting after eight hours of sleep in a recumbent position with minimal interruptions. Therefore, measurement of BEE is not practical in most clinical settings. Alternatively, resting energy expenditure (REE) measures EE at rest, but is more accessible given the requirements for measurement are less restrictive compared to BEE. REE is generally within 10% of BEE for healthy individuals.[44,52] While REE and BEE are often used interchangeably, the difference in the rigor of measurement is an important distinguishing factor.

EE can be estimated in critically ill adults using predictive equations or calculated from components of metabolism. Predictive equations are mostly based on regression models of individual characteristics such as age, sex, weight and height, and are discussed in detail below. In contrast, EE can also be calculated from measurement of oxygen consumption (VO2) and carbon dioxide production (VCO2) using the Weir equation, with or without urinary nitrogen (Table 1). VO2 can be measured by subtracting the volume of expired oxygen from the volume of inspired oxygen, or from the difference in arterial and mixed venous oxygen saturation. Carbon dioxide is produced as a byproduct of metabolic reactions and is largely eliminated via the respiratory tract. VCO2 can be measured as the volume of expired CO2 (in liters per minute). Urinary nitrogen excretion represents protein oxidation, and usually contributes less than 5% of EE.[41] Most often, nitrogen is excluded from EE assessment, but may represent a larger proportion of EE in persons with high protein catabolic states, such as those with a prolonged critical illness.[44,53] The ratio of VCO2 to VO2, referred to as the respiratory quotient (RQ), provides information related to substrate-specific oxidation and energy balance. In general, a RQ of >1.0 represents lipogenesis, and an RQ of <0.7 represents lipolysis.[44] An RQ between 0.7 and 1.0 indicates mixed substrate metabolism.

There are a number of additional approached for measuring EE including calculations from heart rate, direct heat loss, doubly labeled water, activity logs, kinematic measurements, electromyography, total collection systems and direct calorimetry. These approaches are either not relevant, or have not been validated for routine use in the ICU, and are therefore not included in this review.

### *Indications for Use of Energy Expenditure*

Energy expenditure is a surrogate measure for the patient's cellular metabolic activity, and can be used for a variety of purposes during critical illnesses. First, EE is most often used to predict caloric needs for hospitalized patients.[49,50] For nutritional support, EE is usually assessed as the mean value of a short time interval (10-30 minutes) to estimate total daily caloric requirements. Second, values obtained from EE measurements can be used to estimate substrate-specific oxidation of proteins, carbohydrates and fats.[54] Substrate-specific oxidation can assist in determining the optimal amount of macronutrients needed to individualize the nutrition support regimen. To fully assess macronutrient needs however, additional tests, such as urea nitrogen balance, are required. Third, EE may be measured as a means of understanding how disease states or acute illness affects metabolism. Identifying metabolic changes associated with altered, and often dynamic physiologic states, may be an important tool to better recognize condition-specific metabolic patterns and evaluate the potential influences of commonly applied strategies designed to improve clinical outcomes.[26,47,55] Finally, EE can be assessed to evaluate the metabolic effect of specific medications or interventions. For example, during targeted temperature management following cardiac arrest, core body temperature is reduced to 32°-36°C for approximately 24 hours.[3] One side effect of lowering body temperature is shivering, which can sharply increase EE and may attenuate the benefits of targeted temperature management.[26] In this setting, assessment of EE can be used to detect the presence of shivering, or assist in understanding the effectiveness of anti-shivering treatment strategies.[26] A limitation of EE is that it reflects total body metabolism, and targeting metabolic alterations of one organ or body system is not possible. The choice of EE assessment method is driven by the equipment available, need for accuracy of true patient EE, need for static or continuous measurement and the intended use of EE values.

## Methods to Assess Energy Expenditure

### *Predictive Equations*

More than 200 equations have been proposed to estimate EE, most of which have not been validated for use in critically ill patients.[56] Some of the most commonly used predictive equations in critical care are the Harris-Benedict equation, American College of Chest Physician (ACCP) weight-based method, Mifflin-St Jeor (Mifflin) equation, Ireton-Jones equations, and the Penn State equation (Table 2).[49,57-66] The primary purpose of predicted equations are to estimate REE at steady states to guide nutritional therapy in conjunction with national nutrition recommendations.[42]

When compared to actual measurement of EE using indirect calorimetry (IC) for critically ill patients in the ICU, predictive equations have largely been shown to have poor agreement (>10% variability) in predicting REE compared to measured values.[45,57,60,67-71] This is especially evident when stratified by body mass index (BMI), age and illness severity.[71-73] Obesity is a major confounding factor in determining predictive equation bias (over or under predicting measured values) and accuracy. As many hospitalized patients are obese, are in varying states of illness and diverse in age and gender distribution, it is challenging to apply any single equation to all critically ill patients.[60,72,74,75] It is therefore necessary to carefully consider which equation is best suited for the population of interest. For example, the energy needs of ventilated patients with burn injuries may be very different than a stable medical patient. One equation with higher demonstrated accuracy (70 to 75%) when compared to measured EE is the Penn State equation, although results very by patient age and obesity status.[63,71,76] The Academy of Nutrition and Dietetics recommends using the Penn State equation in critically ill adults with mechanical ventilation when actual measurement of EE is not available, whereas the American Society for Enteral and Parenteral Nutrition guidelines do not recommend any one equation.[42,77]

### Benefits and Limitations of Predictive Equations

Predictive equations are easily accessible via online calculators, and largely do not require complex patient data collection or invasive monitoring to estimate REE. While predictive equations are practical, their use in correctly predicting REE in critically ill patients is limited. Choosing the optimal equation for the population of interest may also present challenges, especially when there is a risk for over-estimation of caloric need. Estimating excessive caloric requirements has been associated with complications such as increased rates of infection.[78] Additionally, most equations have been shown to over or under predict REE for people at extremes of weight, for older adults and for non-Caucasians.[44,58,74] Patient-specific illnesses, such as acute kidney injury, can also cause predicted equations to be inaccurate compared to measured EE.[54] The most promising predictive equation for critically ill adults is the Penn State equation; however, this only provides a static estimation of REE and would not be appropriate for understanding acute fluctuations in energy production. As critically ill patients likely have highly variable metabolic expenditures over the course of their hospital stay, predictive equations should be used with caution as a surrogate for measured EE in this population. Further, predictive equations should not be used when the goal is understanding dynamic components of EE through stages of an intervention or illness.

### *Exhaled Carbon Dioxide*

Recently, it has been hypothesized that using VCO2 alone could be used to estimate EE. VCO2 can be measured using end-tidal carbon dioxide (ETCO2), also referred to as capnography. ETCO2 is the maximal concentration of expired CO2 at the end of each breath, and can be displayed as a total volume over one minute (VCO2).[79,80] ETCO2 is often used during mechanical ventilation to monitor acute changes in breathing or physiologic states. ETCO2 may be integrated within a mechanical ventilator, or as a standalone system. Although it is possible to measure ETCO2 in spontaneously breathing patients, measurement values are shown to be inaccurate, and therefore are not recommended to estimate EE.[81,82]

Using VCO2 to estimate EE, either a fixed or a nutritionally-based RQ (which takes into account macronutrient utilization) should be employed.[83-86] In either case, the Weir equation is modified to replace VO2 with VCO2/RQ to calculate EE. In a study of 79 pediatric mechanically ventilated patients, steady state EE from IC was used to derive a mean RQ (0.89).[84] A subsequent validation group of 94 mechanically ventilated patients was used to test the accuracy of the modified equation compared to both a predicted equation and measured EE. Compared to measured EE, the modified Weir equation was found to be more accurate (bias -0.6%, limits of agreement -14.4% to 13.1%) compared to the predictive equation (bias 0.1%, limits of agreement -40.5% to 40.6%), but demonstrated greater variability as the measured RQ moved further above or below 0.89. Similar results were found in a study of mechanically ventilated adults where mean 24-hour EE from IC was compared to EE derived from simultaneous ventilator-derived CO2 and predictive equations.[85] In this study, a nutritionally-based RQ was determined by calculating macronutrient intake (assumed a RQ of 1 for carbohydrates, 0.7 for fats and 0.8 for protein), so was not a fixed value. The RQ was a weighted average of total macronutrient intake over 24 hours. Similar to the pediatric study, the modified Weir equation using ventilator-derived CO2 was more accurate compared to predictive equations (61% compared to 31-54%), and had an acceptable bias of 7.7% when compared to EE from IC.[84] However, a retrospective study of 278 mechanically intubated adults comparing both a fixed and nutritionally based RQ to IC found that approximately 23% of VCO2 derived EE values were greater than the 10% variability threshold for both RQ calculations.[86] When accuracy was compared at a 5% variability threshold, approximately 54% of values were outside the range for both RQ calculations.

Benefits and Limitations of Exhaled Carbon Dioxide

Expired CO2 may be a promising method to estimate EE in critically ill patients and it is easily obtained using non-invasive monitoring. Additionally, many hospital systems already have ETCO2 technology, and several ventilator models offer built-in ETCO2 capabilities. Conversely, VCO2 may not allow for enough flexibility to account for the wide range of physiologic complexities and metabolic fluctuations that occur during illness trajectories, and correlation with measured EE is variable between studies.[80,84,86] Altered adsorption of nutrients, or differences in fed versus fasting states may increase RQ variability leading to inherent inaccuracies in the modified equation using a fixed or calculated RQ. Although early results are encouraging, further research is needed before global adoption of VCO2 is used to estimate EE in clinical settings. Additionally, this method has not been validated for use in understanding clinical states, or sensitivity to acute metabolic fluctuations.

*Fick Method*

The Fick equation was originally developed as a way to estimate cardiac output using oxygen consumption principles.[60] Reversing the equation, it is possible to estimate EE from measured cardiac output, hemoglobin, arterial oxygen saturation and mixed venous oxygen saturation, thus called the Fick method.[87,88] The Fick method is sometimes referred to as “respiratory indirect calorimetry”, and is limited to patients with a pulmonary artery catheter due to the need for mixed venous oxygen measurements. To estimate EE, the following equation is used where CO is cardiac output, Hb is hemoglobin concentration, SaO2 is the percent of oxygen bound to hemoglobin, and SvO2 is central venous oxygen saturation:

$$EE= CO \times Hb \times (SaO2-SvO2) \times 95.18$$

When compared to IC, correlation and agreement of the Fick method to estimate EE is highly variable between studies, and has largely fallen out of favor as a method for estimating EE in more recent years.[67,89-92] Additionally, it is unclear whether the Fick method truly represents total body EE, or actually over-represents pulmonary metabolism.

### Benefits and Limitations of the Fick Method

In patients with an existing pulmonary artery catheter, assessment of EE using the Fick method is easy to calculate using frequently obtained patient measurements. For the majority of patients in the ICU today, pulmonary artery catheters are used infrequently and it would not be advantageous to place for EE assessment alone. Additionally, EE calculations may be prone to inaccuracies if cardiac output and mixed venous oxygen saturation are incorrectly measured. Due to inconsistencies in accuracy and requirement of invasive monitoring, the Fick method is not recommended for routinely assessment of EE in critically ill adults. Although, the Fick method is sometimes still used in research applications as a comparator to IC.[93]

### *Indirect Calorimetry*

Calorimetry is the measurement of the amount of energy produced from both endothermic and exothermic activities resulting from metabolism of fats, carbohydrates and proteins.[94,95] The breakdown of these substrates during metabolism consumes oxygen, and releases CO2 and heat. Direct calorimetry measures actual heat loss and is the most exact method for measuring EE, but requires extensive equipment and expertise that is not practical for use in clinical settings.[49,94] Conversely, IC is a widely used method to assess EE in hospitalized patients. IC measures exhaled carbon dioxide and oxygen to calculate EE (Table 1). IC is considered the gold standard method for measuring EE in hospitalized patients to determine caloric needs, and is sometimes referred to as a “metabolic cart” study.[49,50] IC provides highly specific information regarding EE, oxygen consumption and substrate-specific utilization. There are several IC devices on the market that can be used for both mechanically ventilated and spontaneously breathing patients.

### Closed and open circuit indirect calorimeters

There are two types of IC systems, closed and open circuit. In a closed circuit, the patient breathes from a closed air system of known volume to measure VCO2 and VO2. Closed circuits are rarely used in clinical practice currently. Open circuit IC on the other hand, is widely used in modern devices. In open circuit systems, the patient inhales ambient air and the expired gases are analyzed using either dilution, mixing chambers or breath-by-breath systems. Dilution methods use a bias gas, usually room air, to move the patient's exhaled air through the circuit for sampling. The bias flow is of known concentration and volume and is not included in EE analysis. Mixing chamber systems homogenize the patient's exhaled air and the gases are sampled from the chamber. Breath-by-breath systems sample the patient's expired air for each breath, and EE is usually displayed as a function of the average EE over several breaths.

As it is difficult to measure the difference between the volume of inspired and expired air, open circuit IC uses the Haldane transformation to estimate the volume of inspired air from exhaled volumes (Table 1).[56,95] The Haldane transformation assumes the volume of nitrogen is constant between inhalation and exhalation to calculate inspired volumes. As the denominator is '1-FiO2', higher fraction of inspired oxygen (FiO2) values cause the denominator to approach zero and result in a VO2 of infinity. Calculations with FiO2 > 0.6 have been shown to have higher error rates, and VO2 cannot be accurately calculated at a FiO2 of approximately ≥ 0.85, depending on the device used.[49,95]

Open circuit IC can be used for both spontaneously breathing and mechanically ventilated patients. For spontaneously breathing patients, expired gasses can be captured using a mouthpiece, face mask, face canopy or face tent.[44] Some models pump a constant flow of air through the system, while others allow the patient to breathe ambient air. Care must be taken to avoid allowing patients to rebreathe expired CO2. If this occurs, EE calculations will be inaccurate due to misassumptions from VCO2 calculations. For mechanically ventilated patients, an open-circuit IC system is required to allow for measurement of variable FiO2. IC devices use either sampling ports attached to both the inspiratory and expiratory limbs of the ventilator, or connect at a single point near the patient's endotracheal tube.[52,56] Often a single standalone system is capable of assessing EE for both spontaneously breathing and mechanically ventilated patients.

### Gas Analyzers

VCO2 is most often measured using nondispersive infrared sensors that consist of a spectroscopic sensor to measure adsorption of the infrared wavelength specific to CO2.[41,96] Attenuation of the CO2 wavelength determines concentration. Oxygen is more challenging to measure, and most modern devices use either a paramagnetic or galvanic O2 sensor. Paramagnetic sensors rely on the paramagnetic properties of oxygen whereby O2 is attracted to a magnetic field within the analyzer, and the amount of pressure or current displaced is proportional to the concentration of oxygen within the gas mixture.[41,97] Galvanic fuel oxygen sensors use a flow of electrons that is proportional to the concentration of oxygen.[97]

### Benefits and Limitations of Indirect Calorimetry

IC is considered the gold standard to assess energy expenditure in critically ill adults as it provides the most accurate assessment of EE.[42] IC can be used for both spontaneously breathing and mechanically ventilated patients, and is the only plausible method for assessment of acute fluctuations in EE, or measurement of EE over prolonged periods.

Patients with a chest tube and air leak, pneumothorax or a respiratory rate > 35 breaths per minute would likely render IC measurements inaccurate. For mechanically ventilated patients, having a positive end expiratory pressure greater than 12 mm Hg, ventilator humidification, concomitant inhaled nitric oxide, having controlled mechanical ventilation rates with patient-initiated breaths, or leaks in the ventilator system will decrease measurement accuracy.[50,56,98] As each IC device varies, it is imperative for the provider to be knowledgeable of and trained in the use of the selected equipment when performing the test and interpreting the results.

When studies have compared IC devices to one another, there is large variability in agreement of EE values.[99-101] Inconsistency in agreement between devices could be due to the location of gas sampling on the ventilator circuit, or reflect differences in mixing chamber compared to breath-by-breath analysis. Studies with non-simultaneous comparisons may reflect metabolic fluctuations and not true device inaccuracies. Historically, modern IC devices have been compared to the Deltatrac II, which has long been considered the most accurate IC device. With improved technology of modern IC devices, it is reasonable to question the continued practice of comparing agreement and device validity to the Deltatrac II, particularly because the Deltatrac II is no longer manufactured or supported. [101,102] Additionally, when level of agreement between devices is compared without a reference or definitive measure of EE, it is difficult to determine if either device reflects true EE or is just a function of technique. The observed variability in agreement of true IC values highlights the importance for clinicians to critically evaluate each IC device prior to use and have a thorough understanding of proper technique and measurement limitations.

Despite inherent device variability, IC is still considered the gold standard to assess EE in hospitalized and critically ill patients when determining caloric requirements. It is plausible that IC would also be the preferred method for measuring EE in relation to assessment of real-time fluctuations in metabolic rates, and has been used for this purpose in several clinical studies.[17,26,47,98,103] Although useful for understanding EE, IC represents total body metabolic activity, and therefore does not provide information related to organ-specific differences in matabolism. Additionally, IC devices are sensitive to measurement error, require user expertise and can be time consuming to set up. Finally, IC devices are expensive, often costing more than $40,000, which is a major limiting factor for routine use in clinical settings.

## Conclusion

Assessment of EE in critically ill adults is an important component of nutritional therapy and may be useful in understanding metabolic influences of pathophysiological conditions and acute metabolic impacts of interventions. Several methods can be used to estimate EE, and each requires careful consideration to determine which approach is appropriate and feasible for the given scenario. Largely, predictive equations should not be used in critical care as they have been found to consistently be inaccurate across multiple comparisons. Additionally, predictive equations do not respond to fluctuations in patient condition and would not be useful in measuring or responding to acute changes in EE. Newer methods for estimating EE, such as exhaled VCO2 with a derived RQ may allow for continuous and inexpensive assessment of EE, but results are preliminary and in need of further validation. IC remains the gold standard and can be used for both mechanically ventilated and spontaneously breathing patients. IC also allows for the assessment of substrate-specific metabolism. Although IC use can be technically challenging with a risk for bias estimates, it is the preferred tool to measure EE whenever possible. Assessment of EE in clinical care may deepen the understanding of critical illness and the effect of interventions on metabolism, as well as aid in providing accurate information regarding caloric needs.

## TABLES

Table 1. Equations used to calculate EE from expired gasses

| Equation | Purpose | Calculation |
|---|---|---|
| Weir Equation | To determine EE using expired CO2 and O2 | With urinary nitrogen:<br>$EE\ (kcal/day) = [(3.94 \times VO2) + (1.11 \times VCO2)]1.44 – 2.17(UN)$<br>Excluding urinary nitrogen:<br>$EE\ (kcal/day) = [(3.94 \times VO2) + (1.11 \times VCO2)]1.44$ |
| Respiratory Quotient | Determine substrate utilization<br>RQ glucose = 1<br>RQ lipid = 0.69<br>RQ protein = 0.81 | $RQ= VCO2 / VO2$<br>(using Haldane transformation) |
| VO2 | Determine O2 consumption | $Vi(FiO2) – Ve(FeO2)$ |
| VCO2 | Determine CO2 consumption | $Ve(FeCO2) – Vi(FiCO2)$ |
| Haldane transformation | Estimate Vi when using open circuit indirect calorimetry | (1) $Vi = (FeN2 / FiN2)Ve$<br>(2) $FeN2 = 1 - FeO2 - FeCO2$<br>(3) $FiN2 = 1- FiO2 - FiCO2$<br>(4) $VO2 = [(1 – FeO2 – FeCO2) x (FiO2 – FeO2[Ve] / (1 – FiO2)$ |

Vi = volume of inspired air

Ve = volume of expired air

Fi = fraction of inspired gas

Fe = fraction of expired gas

Table 2. Predictive Equations Commonly Used for Critically Ill Adults

| Equation | Calculation in kcal/day |
|---|---|
| Harris-Benedict[59] | Male: 66.473 + (13.7516 x weight[1]) + (5.003 x height[2]) – (6.755 x age[3])<br>Female: 655.0955 + (9.5634 x weight[1]) + (1.8496 x height[2]) – (4.6756 x age[3]) |
| ACCP[58,61] | BMI < 25: ABW[6] x 25<br>BMI ≥ 25: IBW[7] x 25 |
| Mifflin-St Jeor[64] | Male: (10 x weight[1]) + (6.25 × height[2]) - (5 × age[3]) + 5<br>Female: (10 x weight[1]) + (6.25 × height[2]) - (5 × age[3]) - 161 |
| Ireton-Jones[65,66] | Mechanically ventilated: 1,784 – (11 x age[3]) + (5 x weight[1]) + (244 if male) + (239 if trauma present) + (840 if burn present)<br>Spontaneously breathing: 629 – (11 x age[3]) + (25 x weight[1]) − 609 (when BMI >27 $kg/m^2$) |
| Penn State[62,63] | 2003: 0.85(Harris-Benedict equation) + (175 x Tmax[4]) + (33 x $V_E$[5]) – 6,433<br>2010 (≥60 years old, BMI ≥30$kg/m^2$): 0.71(Mifflin-St Jeor equation) + 85(Tmax[4]) + 64($V_e$[5]) - 3085 |

1 = kg, 2 = cm, 3 = in years, 4 = maximum temp in Celsius, 5 = minute volume in liters per minute

6= Actual Body Weight = weight in kg on hospital admission

7 = Ideal Body Weight =

Men: 50kg + (2.3kg per inch > 60 inches)

Women: 45.5kg + (2.3kg per inch > 60 inches)

Table 3. Benefits and Limitations of Methods for Estimating Energy Expenditure

| Method | Benefits | Limitations | Applications |
|---|---|---|---|
| Predictive Equations | • Easily accessible equations<br>• No cost | • Often inaccurate during critical illness, especially when stratifying by BMI and age<br>• Not adaptable for dynamic physiologic states | • Use when IC not available<br>• Penn State equation may be most accurate, depending on the population |
| Exhaled CO2 (EtCO2) | • Often integrated in existing ventilators<br>• Low cost | • Limited studies validating usefulness<br>• Complex calculation of EE with nutritional RQ | • May be a viable option to estimate EE pending further research |
| Fick Method | • Easily available calculation<br>• Can measure dynamic EE measurements | • Limited use of pulmonary artery catheters<br>• May over-represent pulmonary artery metabolism | • May be of use when pulmonary artery catheter is in place and IC not available<br>• Not widely used method in clinical care |

| | | | |
|---|---|---|---|
| Indirect Calorimetry | • Gold standard and most precise measure of EE<br>• May be integrated in new mechanical ventilators<br>• Useful in ventilated and non-ventilated patients | • Costly<br>• Technically challenging | • Can be used to determine caloric requirements, or to evaluate clinical states or interventions |

# CHAPTER 3: Energy Expenditure During Targeted Temperature Management at 36°C: A Case Series

Title: Energy Expenditure During Targeted Temperature Management at 36°C: A Case Series

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# Abstract

Patients undergoing targeted temperature management (TTM) after cardiac arrest have a reduction in energy expenditure (EE), which is one proposed mechanism that mitigates the effects of post-cardiac arrest syndrome. Although TTM at 36°C has gained popularity in recent years, little is known about the reduction in EE at this ultra-mild hypothermic temperature. We conducted an observational case-series describing patterns of EE for out-of-hospital post-cardiac arrest patients undergoing TTM at 36°C. EE was measured continuously from TTM maintenance through rewarming using indirect calorimetry. A total of 3 males (ages 67, 44, and 62 years) were included in the study. Mean steady state EE during the maintenance phase was 2066 ±72 kcal/day (temperature range 34.8-36.4°C), 2209 ±70 kcal/day (temperature range 35.8-36.2°C) and 1958 ±119 kcal/day (temperature range 35.7-36.5°C) for patients #1, #2 and #3 respectively. Following rewarming, mean steady state EE was 2359 ±122 kcal/day (difference of 150 kcal/day compared to 36°C) and 1629 ±23 kcal/day (difference of -329 kcal/day compared to 36°C) for patients #2 and #3 respectively (patient #1 not available). Factors such as shivering and medication administration had the greatest impact on EE. Patient #1 had 335 minutes (43.1%) of shivering, patient #2 had no shivering and patient #3 had 70 minutes (8.5%) of shivering during the study period. Although temperature-dependent changes in EE were observed, it is unclear if differences in EE at 36°C compared to normothermia are clinically meaningful.

## Introduction

Targeted temperature management (TTM) is indicated for survivors of cardiac arrest as a neuroprotective strategy to reduce the deleterious effects of post-cardiac arrest syndrome (PCAS).[3,5] PCAS is a triad of neurologic injury, myocardial dysfunction and a systemic reperfusion response.[5] A potential fourth criteria is the presence of persisting conditions, such as an untreated coronary lesion. If left untreated, PCAS can lead to significant morbidity and death. TTM is one of the only evidence-based strategies known to mitigate aspects of PCAS.

TTM includes three phases; (1) lowering of core body temperature to the targeted temperature, (2) maintaining the targeted temperature for a specific period of time (usually 24 hours) and (3) slow rewarming to normothermia.[104-106] The recommended targeted temperature is between 32-36°C, with most institutions choosing either 33°C or 36°C.[3,8] One of the effects of lowering body temperature is a reduction of energy expenditure (EE), which is believed to contribute to the protective effect of TTM.[5] It is expected that for every 1°C reduction in body temperature, EE will decrease by approximately 8%.[9] TTM at 33°C following cardiac arrest has been shown to reduce EE by approximately 20-35%.[47,48]

Numerous factors contribute to EE during TTM and include age, sex, body composition, illness severity, circulating catecholamines, body temperature, medications (especially vasopressors, sedatives, analgesics, neuromuscular blocking agents and dextrose-containing solutions) and the presence of shivering. An important and expected side effect of TTM is shivering.[104,107] Shivering occurs at a body temperature below approximately 35.5°C as a thermoregulatory mechanism to generate heat, ultimately raising body temperature.[108] Shivering is known to sharply increase EE and can occur during all phases of TTM.[26,32] Both the increase in body temperature and energy demands may attenuate the benefits of TTM, and therefore is thought to be essential to recognize and treat shivering. However, previous research evaluating the metabolic impact of shivering in brain injured patients did not include TTM at 36°C for post-cardiac arrest patients, and only measured EE at a single time point.[26] The duration and frequency of shivering and the impact on EE was therefore not captured. Of studies that did include either continuous or multiple measures of EE during TTM, the periods where shivering occurred were purposely excluded from analysis.[47,48]

As many institutions employ TTM at 36°C, it is important to understand how this relatively recent targeted temperature impacts EE. Currently, little evidence exists as to the expected reduction of EE in this population. Additionally, to better treat and develop tools for early recognition of shivering, it is necessary to investigate the temporal nature of shivering over the course of TTM and not just at single time points. The purpose of this study was to describe patterns of EE for post-cardiac arrest patients receiving TTM at 36°C, and to explore the impact of shivering on EE.

## Methods

This prospective observational study was performed at a tertiary medical center in Portland, OR. Consecutive patients meeting inclusion criteria from November 2017 to February 2018 were included in the study. Patients were included if they were ≥18 years old, undergoing TTM following out-of-hospital cardiac arrest and were mechanically ventilated. Exclusion criteria were positive end-expiratory pressure >10 cm H2O, presence of a chest tube or pneumothorax, use of a high-frequency percussive ventilator, continuous paralytic infusion at time of study enrollment, anticipated survival < 24 hours and family refusal.

Patients were recruited from the cardiovascular critical care unit. The investigator was notified by the unit charge nurse when the admission of a patient meeting inclusion criteria was pending. The investigator then determined eligibility and study enrollment. This study was approved by the institutional review board (IRB) at the University of Washington with a waiver of informed consent. However, verbal consent was obtained from a family member whenever possible per the approved IRB protocol.

### *TTM Protocol*

Patients received care at the discretion of the medical team, and TTM was managed using hospital protocols. In general, TTM was initiated in the emergency department using ice packs to the groin and axilla followed by insertion of an intravascular cooling catheter (Quattro®, Zoll, Sunnyvale, United States) that circulates iced-cold water within the catheter's lumen to regulate core body temperature using a temperature management system (Thermogard®, Zoll, Sunnyvale, United States). TTM was maintained for 24 hours after goal temperature was reached, then rewarming occurred to 37°C at 0.25°C/hour. Core body temperature was monitored using a temperature-sensing indwelling urinary catheter (Infection Control 400 Series Temperature-Sensing Foley Catheter, C. R. Bard, Inc., Covington, GA). All patients received continuous sedation using propofol titrated to a Richmond Agitation Scale Score of -4 until rewarming was complete. If required, pain was managed using fentanyl titrated to a Critical Care Pain Observation Tool score of < 3. Patient goals during TTM were mean arterial pressure ≥ 65mmHg, urine output ≥ 30 ml/kg/hr, blood glucose 140-180 mg/dL, serum magnesium > 2 mg/dL and serum potassium 3.5-5 mM/L. Patients did not receive nutritional support during TTM but they did receive continuous propofol infusion, which provides 1.1 kcal/ml as a lipid-containing solution. Additionally, patients may have received dextrose-containing intravenous solutions.

Shivering was assessed by the bedside nurse at least hourly using the Bedside Shivering Assessment Scale (BSAS).[26] Additionally, the investigator recorded presence of shivering every 15 minutes during the study. Total shivering time was reported as the number of minutes from documentation of a BSAS > 0 to documentation of BSAS of 0 as a proportion of total study time.

The change in EE associated with shivering was determined by the mean difference in EE when BSAS was 0 compared to when BSAS was > 0 for each patient.

All patients were to receive buspirone 30mg every 8 hours until rewarming complete, and counterwarming using a forced air warming device (3M™ Bair Hugger™ Normothermia System). If shivering was detected, treatment was at the discretion of the medical team. Interventions could have included magnesium administration, increase in continuous sedation, meperidine or administration of a neuromuscular blocking agent.

### *Measurement of Energy Expenditure*

EE was calculated using the modified Weir equation and Haldane transformation from volume of exhaled carbon dioxide (VCO2) and volume of oxygen consumed (VO2) using the Ultima Series™ (MGC Diagnostics®, Saint Paul, MN) indirect calorimeter (IC).[56,109] The Ultima Series™ uses breath-by-breath measurements to display the average of the last five breaths after dropping the highest and lowest values. VCO2 was measured using non-dispersive infrared technology (range 0-15%; accuracy ± 0.1%), and VO2 was measured using a galvanic fuel cell (range 0-100%; accuracy ± 1%). All volumes were corrected to ambient temperature and pressure. The medical team was blinded to IC recordings.

Steady state measurements of EE are intended to approximate resting EE when little variation in EE and patient care are present. Steady state measurements were calculated when VO2 and VCO2 varied by ≤ 10%, and the respiratory quotient varied by < 5% over at least a 10-minute period.[56,110] In addition, no changes to ventilator settings, medication rates or administration of medications occurred in the 1 hour preceding steady state measurements.

### *Study Procedure*

The IC was calibrated prior to each use according to manufacturer’s instructions. Following patient enrollment, the DirectConnect™ metabolic flow sensor was connected between the endotracheal tube and the ventilator tubing (Figure 1). EE was then measured continuously from study enrollment through the TTM rewarming phase. Gas sensing was recalibrated every 4 hours, when a break in the closed tubing system occurred or following respiratory care that limited gas exchange (such as endotracheal suctioning). A drift was noted if there was a > 10% difference in EE following recalibration. If condensation occurred within the sensor, the Directconnect™ metabolic flow sensor was replaced, and the device recalibrated before resuming testing.

During the study period, an investigator was present to record all patient care activities (nursing care, medication administration, etc.) in real time to allow for alignment of EE measurements with the precise time of the activity. Core body temperature recordings were extracted from the temperature management device. Additional information was obtained from the medical record.

### *Statistical Analysis*

Data were analyzed using descriptive statistics and graphical visualization. Patient characteristics were presented as counts, relative frequencies, means and standard deviations (SD) as appropriate. Results were inspected for accuracy, and recorded values falling outside of a plausible physiologic range were excluded. EE values were plotted as the average EE over 1 minute with corresponding body temperature. If data were missing, mean substitution of the previous and subsequent datum was used (< 3% missing data). Analyses were performed using R language (version 1.0.136) and Microsoft Excel® 2016.

## Results

A total of three patients met inclusion criteria. Patient #1 (Figure 2), a 67-year-old male, had a witnessed ventricular fibrillation (VF) arrest (Table 1) with bystander cardiopulmonary resuscitation (CPR). The approximate length of the arrest was 45 minutes. Data were recorded from approximately hour 0 of TTM to hour 13 for a total of 778 minutes. Mean EE during maintenance was 2912 ± 630 kcal/day (steady state EE 2066 ± 72 kcal/day; temperature range 34.8-36.4°C) (Table 2). Total time with BSAS > 0 was 335 minutes (43.1%). Mean difference in EE during periods of shivering (3145 ± 516 kcal/day) compared to no shivering (2602 ± 636 kcal/day) was 543 kcal/day. The study ended early due to IC malfunction.

Patient #2 (Figure 3), a 44-year-old male, had a witnessed pulseless electrical activity arrest lasting 59 minutes with no bystander CPR. Data were recorded from approximately hour 11 of TTM to hour 27 for a total of 845 minutes. Mean EE prior to reaching the targeted temperature was 2121 ± 123 kcal/day (temperature range 35-35.7°C). Mean EE during maintenance was 2172 ± 302 kcal/day (steady state 2209 ± 70 kcal/day; temperature range 35.8-36.2°C) and 2421 ± 259 kcal/day (steady state 2359 ± 122 kcal/day; temperature range 36.8-37°C) following rewarming. No shivering was observed during TTM.

Patient #3 was a 62-year-old male with an unwitnessed VF arrest and no bystander CPR. The length of arrest was approximately 20 minutes. Data were recorded from approximately hour 13 of TTM to hour 27 for a total of 820 minutes. Mean EE during maintenance was 2370 ± 387 kcal/day (steady state 1958 ± 119 kcal/day; temperature range 35.7-36.5°C) and 1649 ± 49 kcal/day (steady state 1629 ± 23 kcal/day; temperature range 36.8-37°C) following rewarming. Total time with BSAS > 0 was 70 minutes (8.5%).

## Discussion

EE is a surrogate measure for total body metabolism. It is believed that one way in which TTM confers benefit is by decreasing metabolism and oxygen demand as a component to mitigate some aspects of PCAS. Reduced EE (and, in turn, reduced oxygen consumption) during TTM has been associated with decreased cerebral oxygen demand and cellular hypoxia.[7,9,111] In previous studies of patients with a targeted temperature of 32-34°C, EE ranged from approximately 1200-1900 kcal/day, with an overall reduction in EE of 20-35% compared to normothermia.[26,47,48] In this case series, mean EE during the maintenance phase was 2337 kcal/day (range 1205-3705), which is similar to reported EE in other critically ill populations.[57,112] Even when we evaluated steady state measurements, which limit EE variability, mean EE (2078 kcal/day) was within the reported range from previous studies of normothermic patients with brain injury.[26] As there have been no demonstrated differences in neurologic outcomes when targeting 36°C compared to 33°C[8], it is plausible to consider that other factors are responsible for mitigating PCAS at 36°C besides EE. Our results highlight the need for additional investigation related to the mechanistic benefits of TTM at 36°C.

Shivering, a known side effect of TTM, is associated with increases in temperature and EE.[9,26,27] In the present study, periods of nurse-documented shivering were also associated with increased EE (500-600 kcal/day) compared to periods of non-shivering. Although it is often suggested that shivering requires aggressive treatment to retain tight temperature control, patients (patient #1 and #3) that exhibited dynamic changes in EE (with or without shivering) survived with a good neurologic outcome, and the patient (#2) who had little temperature variation and no shivering did not survive. The association between the ability to shiver or generate heat and improved outcomes are in alignment with similar findings from other studies.[40,43,113] Although shivering should not be left unopposed, it does raise the question as to importance of preemptively instituting aggressive interventions (such as paralytics) that eliminate the shiver response to allow for tight temperature control.

There were several limitations to this study. First, the small sample size limits generalizability and results may not reflect EE from a wider sample. Second, alternate medication and anti-shivering regimens may produce differing results. Finally, it is possible that EE measurements may have had inherent inaccuracies given the length of the study period. To limit inaccuracies in measurements, we frequently recalibrated the IC device, as well as changed the flow sensors if condensation was observed. No significant discrepancies (>10% difference in average EE) were noted following recalibration. Further research with a larger and more diverse population is warranted.

## Conclusion

Changes in temperature are linked to changes in EE, but it is unclear if targeting a 1°C reduction in body temperature for TTM at 36°C provides a clinically important reduction in metabolism.

## TABLES

Table 1. Summary of Patient Characteristics and Features of TTM Care from Induction Through Rewarming

| | Patient #1 | Patient #2 | Patient #3 |
|---|---|---|---|
| Age (years) | 67 | 44 | 62 |
| Sex | Male | Male | Male |
| Race | Caucasian | African American | Asian |
| Body Surface Area ($m^2$) | 2.11 | 2.41 | 1.86 |
| Initial Rhythm | VF | PEA | VF |
| Witnessed | Y | Y | N |
| Bystander CPR | Y | N | N |
| Length of arrest in minutes | 45 | 59 | 20 |
| Seizure Activity during TTM | N | N | N |
| RASS[a] Score, range | -2 to -4 | -4 to -5 | +1 to -5 |
| Propofol dose (mcg/kg/min), mean (range) | 30 (20-40) | 35 (35) | 22.7 (10-40) |
| Serum Magnesium (g/dL) at 36°C, mean (range) | 2.1 (2.1) | 3.0 (3.0) | 1.8 (1.6-2.0) |

| | | | |
|---|---|---|---|
| Survival | Y | N | Y |
| CPC[b] Score at Hospital Discharge | 2 | - | 2 |

[a] Richmond Agitation Scale Score

[b] Cerebral Performance Categories Scale

Table 2. Steady State and Mean Energy Expenditure in kcal/day by TTM Phase

| Case | Induction (mean ±SD) | Maintenance (mean ±SD) | Rewarming (mean ±SD) | Normothermia (mean ±SD) | Difference (Normothermia – Maintenance) |
|---|---|---|---|---|---|
| Patient #1 | | | | | |
| Overall | - | 2912 ±630 | - | - | - |
| SS* | | 2066 ±72 | | | |
| Patient #2 | | | | | |
| Overall | 2121 ±123 | 2172 ±302 | 2468 ±222 | 2421 ±259 | 249 |
| SS | | 2209 ±70 | - | 2359 ±122 | 150 |
| Patient #3 | | | | | |
| Overall | - | 2370 ±387 | 1809 ±260 | 1649 ±49 | -721 |
| SS | | 1958 ±119 | - | 1629±23 | -329 |

SS= steady state

## FIGURES

Figure 1. Attachment of DirectConnect™ metabolic flow sensor to mechanical ventilator tubing

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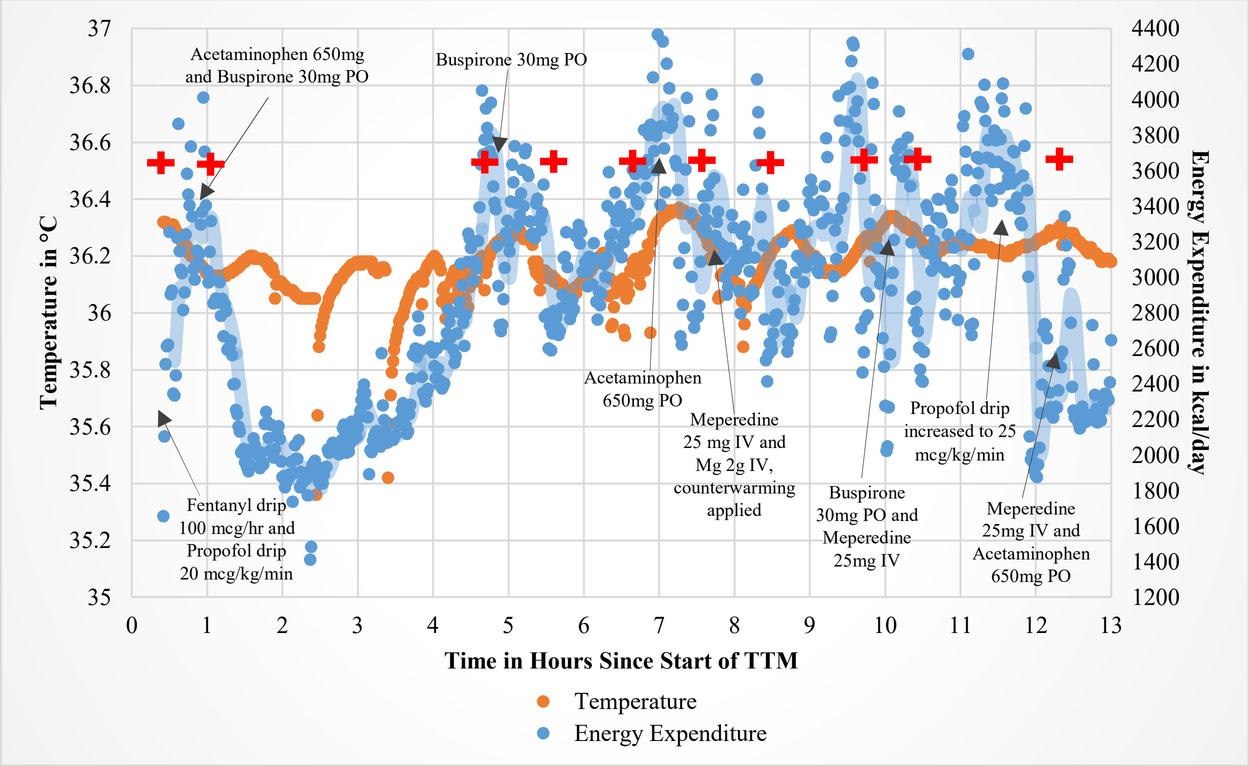
Figure 2. Patient #1



✚ = Positive shivering documentation

Figure 3. Patient #2

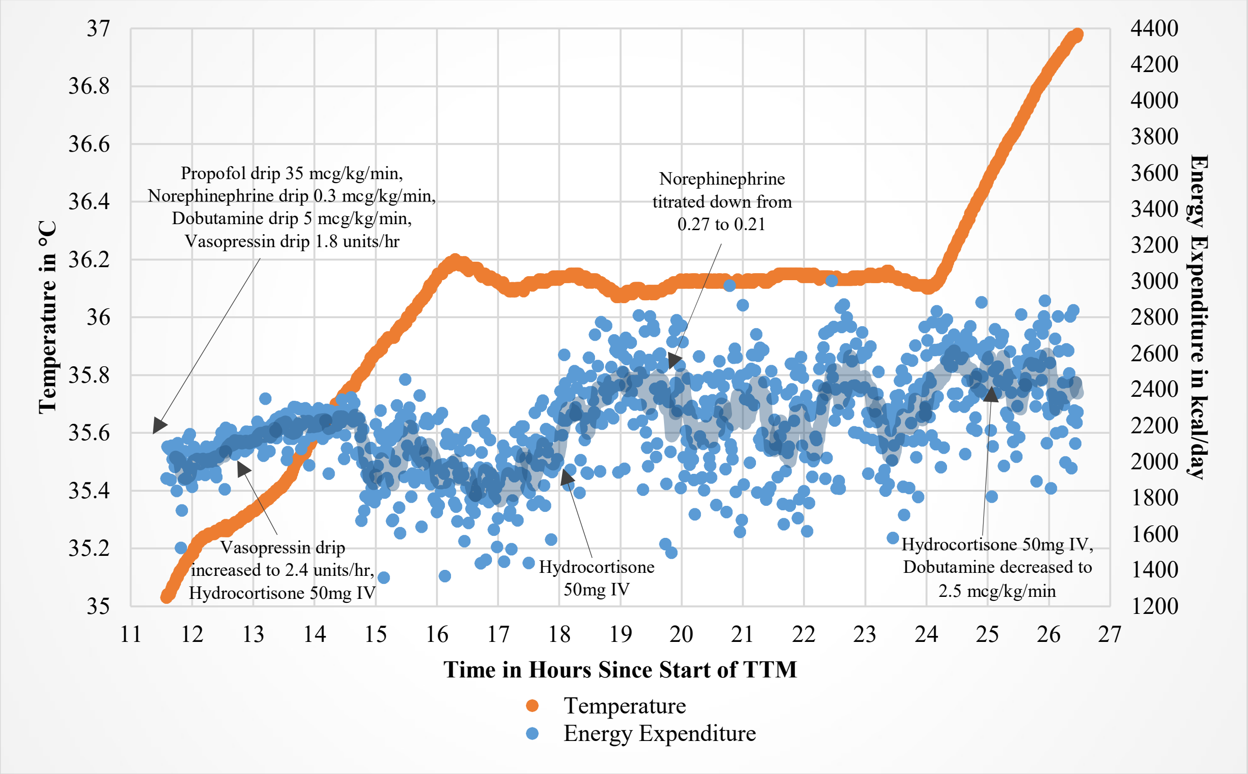
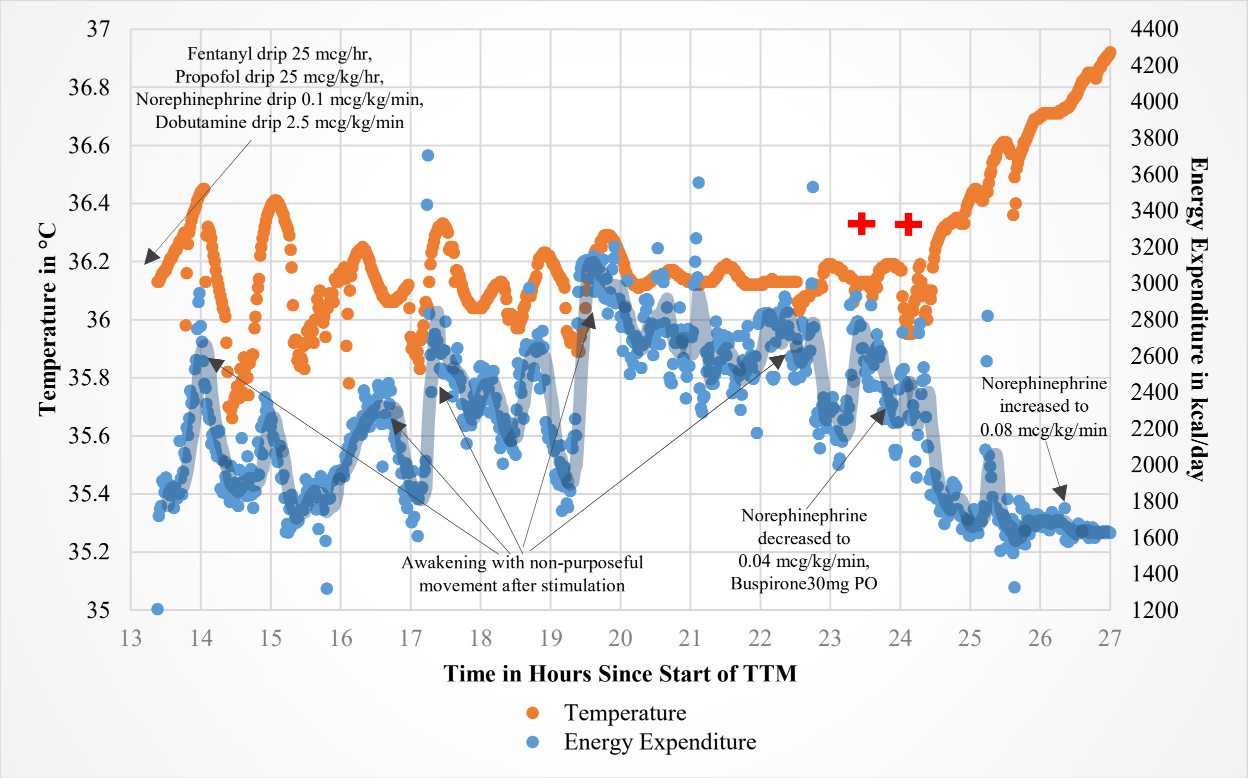


Figure 4. Patient #3



# CHAPTER 4: Temperature Variation During Targeted Temperature Management at 36°C After Cardiac Arrest: Effect of Shivering and Changes in Water Bath Temperature

# Title: Temperature Variation During Targeted Temperature Management at 36°C After Cardiac Arrest: Effect of Shivering and Changes in Water Bath Temperature

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Key words: targeted temperature management, cardiac arrest, induced hypothermia, shivering

Target journal: Resuscitation
Paper formatted in the style of the target journal

## Abstract

**Background**: Compliance with targeted temperature management (TTM) at 36°C may be an important factor in reducing morbidity and mortality after cardiac arrest. Changes in water bath temperature ($T_{Bath}$) of cooling devices may provide an early indication of impending body temperature fluctuations, especially during shivering. This study described the relationship between $T_{Bath}$ and core body temperature, and the association between shivering and body temperature variation ($T_{Var}$) during TTM at 36°C.

**Method**: This was a retrospective cohort study of post-cardiac arrest patients during the maintenance phase of TTM at 36°C using Arctic Sun® 5000 surface cooling device at Harborview Medical Center from November 2014 and June 2017. Generalized estimating equations were used to describe the relationship between $T_{Bath}$ and body temperature, and linear regression was used to evaluate the association between percent of time with $T_{Var} > 36\pm0.5°C$ and number of shivering events.

**Results**: A total of 186 patients were included. A mean increase in body temperature of 0.1°C was associated with a decrease in $T_{Bath}$ of -4.3°C (95%CI: -5.43, -3.24). Lower $T_{Bath}$ was associated with shivering ($p < 0.001$, 95%CI: -.52, -.16). Patients with $T_{Var}$ were more likely to have a shockable rhythm at time of arrest (p=0.02; 95%CI: -9.70, -.86) and an increased number of shivering events during the maintenance phase of TTM (p=0.03; 95%CI: 0.05, 0.85), but not survival to discharge (p=0.94; 95%CI: -3.26, 3.02). Having at least one shivering event was associated with an almost 2-fold increase in survival to hospital discharge (OR 1.99; p= 0.04; 95%CI: 1.03, 3.88).

**Conclusion**: Monitoring changes in $T_{Bath}$ could allow for early recognition of shivering. Patients with shivering were more likely to have $T_{Var}$ and improved survival to hospital discharge.

## Introduction

Targeted temperature management (TTM) at 36°C for post-resuscitative care after cardiac arrest has become increasingly utilized following a large clinical trial demonstrating no difference in neurologic outcomes compared to TTM at 33°C (32-34°C).[8] National guidelines recommend targeting a goal temperature (GT) between 32-36°C.[3] Despite the rise in popularity of TTM at 36°C,[114,115] many facets of clinical care remain uncertain. One area of investigation is the need for tight temperature control and understanding the role of temperature variation ($T_{Var}$) on patient outcomes. The Emergency Neurological Life Support guidelines recommend temperature variation of less than ± 0.5°C.[116,117] Compliance with tight temperature control has been shown to be more difficult when targeting 36°C compared to 33°C, although the effect of poor compliance on outcomes is unclear.[115,118]

Monitoring water bath temperature ($T_{Bath}$) of cooling devices may allow for early recognition of changes in body temperature from excess heat generation.[43] Advanced cooling methods (surface pads or intravascular catheters) use temperature control systems that regulate body temperature by adjusting circulating $T_{Bath}$ either within pads or a catheter. When excess heat is generated from the patient, the device responds by lowering $T_{Bath}$ in an effort to maintain the targeted temperature. Conversely, when body temperature drops below the targeted temperature, $T_{Bath}$ increases. The change in $T_{Bath}$ occurs at a much faster and proportionally larger rate than the change in body temperature.[107] Therefore, being able to identify what change (or pattern of changes) in $T_{Bath}$ are associated with body $T_{Var}$ outside of the GT range could allow for early interventions to maintain tight temperature control.

Shivering is a common and expected side effect of TTM and occurs as a thermoregulatory control mechanism in response to body temperatures dropping below the hypothalamic set point.[9,26,27] Shivering is known to decrease brain tissue oxygenation, increase intracranial pressure, and increase cardiac output and heart rate; all of which have potentially important implications for recovery following cardiac arrest.[28,32,33] Although the ability to shiver may indicate less neurologic damage,[40] increased body temperature resulting from shivering could partially negate the neuroprotective effects of TTM. As the purpose of shivering is to increase body temperature, it is reasonable then to anticipate that $T_{Bath}$ would decrease during periods of shivering. Therefore, the purpose of this study was to describe the relationship between $T_{Bath}$ and core body temperature, and to evaluate the role of shivering on the ability to maintain TTM at 36°C.

## Methods

This was a retrospective cohort study of adult post-cardiac arrest patients at Harborview Medical Center, a Level-1 Trauma Center and Post-Cardiac Arrest Receiving Center with 413 beds in Seattle, WA. Patients from November 2014 to June 2017 were included in the study if they were ≥ 18 years old, received TTM at 36°C using surface cooling hydro-coated gel pads following a cardiac arrest and completed at least the hospital-defined maintenance phase of TTM. Patients were excluded if there were < 10 water temperatures recorded, or if they did not complete 24 hours of TTM. This study was approved by the institutional review board at the University of Washington.

Data were obtained from the medical record and included: age, sex, race, body mass index (BMI) (from weight on arrival to the intensive care unit), location of arrest (in-hospital or out-of-hospital), initial rhythm (shockable or non-shockable), presence of a witness to the arrest, bystander cardiopulmonary resuscitation (CPR), length of cardiac arrest (from time of emergency services arrival to return of spontaneous circulation or from code report), cause of cardiac arrest (cardiac, respiratory or other), length of hospitalization, survival, cerebral performance categories scale (CPC) score at hospital discharge, discharge disposition, body temperature, $T_{Bath}$, medications administered during TTM, seizure activity diagnosed by electroencephalogram (EEG) and presence of shivering.

*TTM Protocol*

Patient management during TTM was guided by hospital protocol and the patient care team. In general, TTM was initiated using surface cooling gel pads with a temperature management system (Arctic Sun®, Bard Medical, Colorado, United States) for 24 hours. Gel pads were selected based on patient's size according to manufacturer's recommendations. The Arctic Sun® temperature management system uses a proportional, integral derivative formula to systematically adjust the water temperature using a pre-programmed algorithm and adjusts water temperature in response to body temperature every 1 minute to maintain the programmed GT [107,119]. Temperature measurement accuracy is ± 0.2°C, with precision of 0.1°C and a maximum water velocity of 5 L/min. $T_{Bath}$ range is 3°C to 45°C.

Core body temperature was monitored using an esophageal temperature sensing probe (Level 1® Esophageal Stethoscope with Temperature Sensor, Smiths Medical, St. Paul, MN). Sedation included propofol or midazolam infusion, and pain was managed using fentanyl intravenous (IV) boluses. Rewarming occurred following approximately 24 hours at 36°C at a rate of 0.3°C/hr to a temperature of 37°C. Normothermia was then maintained for an additional 48 hours.

Shivering was assessed using either a binary code, or using the Bedside Shivering Assessment Scale (BSAS) (The BSAS was added in fall of 2016).[26] For the purposes of this study, a shivering event was defined as documentation of positive shivering during a 15-minute interval. All patients received acetaminophen 650mg orally every 6 hours and counterwarming using a forced air warming blanket (3M™ Bair Hugger™ Normothermia System). If shivering was detected, a sedation bolus was given with an increase in the continuous infusion. If shivering continued, an IV bolus or continuous infusion of vecuronium or cisatracurium was used to stop shivering. Other medications used to manage shivering may have included magnesium or buspirone.

### *Data Management*

For the purposes of this study, the maintenance phase was defined as the first time body temperature was 36 ± 0.2°C following the first recorded $T_{Bath}$ in the medical record until the start of rewarming. Data were organized in 15 minutes intervals from the start to the end of the maintenance phase. In the case that more than one value for $T_{Bath}$ or body temperature occurred during a 15-minute interval, the mean of recorded values was used. If there was a recorded $T_{Bath}$ without a corresponding body temperature within an interval, mean imputation of the adjacent body temperatures was used as this occurred in < 5% of cases. Data were considered missing if there was no recorded $T_{Bath}$ within the 15-minute interval. If more than one documentation of shivering occurred within a 15-minute interval, the maximum recorded shivering value was used. $T_{Var}$ was defined as a body temperature greater than 36 ± 0.5°C during the maintenance phase. Data were inspected for accuracy, and values falling outside of a plausible physiologic range were excluded.

### *Statistical Analysis*

Patient characteristics were presented as counts, relative frequencies, means and standard deviations (SD) as appropriate. To model the relationship between body temperature and $T_{Bath}$, weighted linear and cubic spline interpolation (2/3 linear, 1/3 spline) was used to allow for model flexibility and close approximation to patterns of recorded values. Both univariate and multivariate generalized estimating equations (GEE) were used to evaluate the relationship between body temperature and $T_{Bath}$. Covariates for GEE included age, sex, BMI, presence of shivering and use of neuromuscular blocking agents (NMBA). Multivariate linear regression was used to evaluate the relationship between amount of time with $T_{Var}$ as a proportion of total time during maintenance phase and presence of shivering. Covariates for linear regression included age, sex, race, BMI, location of cardiac arrest, initial rhythm, initiation of bystander CPR, cause of cardiac arrest, use of NMBAs and survival. Length of cardiac arrest was not included in the analyses given > 40% missing data. Data were analyzed using STATA (version 14, StataCorp LP, College Station, TX) and R language for computer programming (version 1.0.136). All analyses were 2-sided, with a significance level at $\alpha < 0.05$.

## Results

Of a potential 237 post-cardiac arrest patients during the study period, 186 met inclusion criteria. Table 1 summarizes sample characteristics and features of the cardiac arrest event. Notably, patients with at least one documented $T_{Var}$ were more likely to have had a shockable rhythm than those with no $T_{Var}$ (shockable rhythm-$T_{Var}$: n=54, 43.5%; no $T_{Var}$ n=12, 19.4%; p=0.002). Similarly, there was significantly more shivering in the $T_{Var}$ group ($T_{Var}$: n=83, 66.9%; no $T_{Var}$ n=28, 45.2%; p=0.01), but presence or absence of $T_{Var}$ was not associated with a difference in survival at discharge ($T_{Var}$: n=41, 33.1%; no $T_{Var}$ n=17, 27.4%; p=0.54).

### *Water Bath Temperature*

There was a significant negative correlation between body temperature and $T_{Bath}$ (r= -.45; p<0.001; 95%CI -0.46, -0.44) (Figure 1). The correlation between a $T_{Bath}$ and body temperature was highest when $T_{Bath}$ was lagged one 15-minute interval (r= -0.46). On average, a 0.1°C increase in body temperature was associate with a -4.3°C (95%CI: -5.43, -3.24) decrease in $T_{Bath}$ both for the univariate and multivariate model. Higher $T_{Bath}$ was associated with older age (p=0.03, 95%CI: 0.004, 0.073), while lower $T_{Bath}$ was associated with having a higher BMI (p=0.002, 95%CI: -.187, -.044) and shivering (p<0.001, 95%CI: -.518, -.158). Adjacent 15-minute intervals where body temperature did not change and was outside of 36 ± 0.2°C (goal range of surface cooling device during maintenance phase) resulted in an additional change in water temperature of 0.4°C.

### *Temperature Variation*

There was a significant association between a higher proportion of time with $T_{Var}$ and increased number of shivering events (p=0.03; 95%CI: 0.05, 0.85) as well as having a shockable rhythm (p=0.02; 95%CI: -9.70, -.86), but not survival to hospital discharge (p=0.94; 95%CI: -3.26, 3.02). Age, sex, race, BMI, location and cause of cardiac arrest and use of NMBAs were not significantly associated with $T_{Var}$. Having at least one shivering event was associated with an almost 2-fold increase in survival (OR 1.99; p=0.04; 95%CI: 1.03, 3.88). Figure 2 displays the difference in body temperature (2a) and $T_{Bath}$ (2b) between patients with and without $T_{Var}$. Among those with $T_{Var}$, there were 876 (7.6%) documented body temperatures < 35.5°C, and 345 (3.0%) documented body temperatures > 36.5°C.

## Discussion

This was a retrospective study describing the relationship between $T_{Bath}$ and core body temperature for patients undergoing TTM at 36°C after cardiac arrest. We observed an approximate 4.3°C change in water temperature for each 0.1°C change in body temperature. The surface cooling device responded to changes in body temperature almost immediately, and $T_{Bath}$ was correlated with a change in body temperature within 15 minutes. Monitoring changes in $T_{Bath}$ temperature may allow clinicians to anticipate a trend in body temperature before the patient moves out of a clinically acceptable GT range. As an example, shivering is known to cause excess heat generation and raise body temperature.[26,107] Currently, the BSAS is the most widely accepted tool to assess for shivering.[26,120,121] The BSAS relies on a clinician to physically assess and recognize shivering through observation. If a clinician is not present, or when sub-clinical shivering occurs that may be imperceptible to the clinician,[122] recognition of shivering would consequently be missed even though heat generation is occurring. As cooling devices receive continuous feedback on additional components of heat generation (such as $T_{Bath}$ inflow and outflow temperature),[107] it is plausible that changes in water temperature would occur prior to clinician recognition of shivering. For example, in this study, if a patient's body temperature increased from 36°C to 36.2°C, there would be an associated decrease in $T_{Bath}$ of 8-10°C. Although the body temperature is still within clinically acceptable range, the proportionally larger change in $T_{Bath}$ could trigger the clinician to more closely monitor the patient and implement appropriate interventions. We have presented a beginning estimate as to the expected change in $T_{Bath}$ as body temperature changes. Future studies should include collecting data directly from cooling devices to further refine this estimate.

Having $T_{Var}$ was not associated with a difference in survival. This finding may be in part because there was a high proportion of patients with a non-shockable rhythm (64.5%) and an overall high mortality (68.8%). Non-shockable rhythms have been associated with worse outcomes and may not reflect a wide population of post-cardiac arrest patients.[8,106,123] Nevertheless, our findings suggest that $T_{Var}$ did not negatively impact survival. Recently, Uber and colleagues reported patients with increased heat generation during induction of TTM had better outcomes than those who reached the target temperature more quickly (less heat generation).[113] Additionally, Murnin et al. found a significant relationship between increased heat generation and improved neurologic outcomes.[43] In contrast, we did not find a significant relationship between $T_{Var}$ and survival to discharge. This may be a reflection of the difference in definitions. We used body temperature as a measure of heat generation, while both Uber and Murnin calculated a heat index (100 x inverse of average $T_{Bath}$). In addition, both of these studies included only patients with a GT of 32-34°C, so there may be differences when evaluating patients with TTM at 36°C. Finally, although patients in our study with $T_{Var}$ had temperatures >36.5°C (3.0% of temperatures), it was more frequently noted that body temperatures were < 35.5°C (7.6% of temperatures). This difference in the proportion in extremes of observed $T_{Var}$ may indicate that heat generation causing temperatures > 36.5°C occurred less often in our study, or could be a reflection of differences in pharmacologic management (greater sedation or paralytic use diminishes capacity for heat generation). As shivering was associated with $T_{Var}$, it is likely that aggressive anti-shivering interventions were instituted prior to excessive heat generation causing a rise in body temperature >36.5°C. Abrupt cessation in shivering may have been related to a subsequent abrupt reduction in body temperature given that $T_{Bath}$ was lower in the patients with $T_{Var}$. Future studies of heat generation and temperature variability should include TTM at 36°C.

We also observed a negative association between bystander CPR and $T_{Var}$, This finding is likely due to the way in which bystander CPR data were reported. There was no difference in $T_{Var}$ for patients with a witnessed compared to an unwitnessed arrest, which suggests that a subset of patients received bystander CPR following an unwitnessed arrest. Although bystander CPR improves the likelihood of survival, the unknown length of downtime may have been a greater factor.[124]

Significantly more patients with $T_{Var}$ shivered. Although $T_{Var}$ was not associated with survival, having at least one episode of shivering was. Our findings are in alignment with previous studies that report an increase in survival with the ability to shiver.[40,122] Historically, many studies report the use of continuous paralytic infusions during TTM to prevent shivering and maintain tight temperature control.[11,12,125,126] Despite the use of paralytics in 69.9% of patients, we report a higher proportion of patients who shivered (59.7%) compared to other studies including TTM at 36°C.[8,114,115] This result may be due to differences in NMBA administration or reporting of shivering. One strength of this study is that we evaluated the number of shivering events ("shiver burden"), which differs from other reports of TTM outcomes. We observed shivering as a cyclical pattern where some patients had only one recorded shivering event, while others had multiple recorded events. Including shiver burden may be an important consideration for future studies as there may be differences between individuals who have an increasing number of shivering events compared to only one.

### *Limitations*

This was a retrospective observational study which limits generalizability. Additionally, the large proportion of patients presenting with non-shockable rhythm and overall high mortality may have biased results. A larger sample with a more heterogeneous population may produce different outcomes. We only included patients who completed the TTM maintenance phase in order to capture the greatest number of water temperatures. This may have biased our sample to include patients who had to survive at least 24 hours, although this did allow us to compare patients who received a similar dose of TTM. Finally, we interpolated the relationship between $T_{Bath}$ and body temperature from recorded values. It is possible that we did not describe the true relationship between $T_{Bath}$ and body temperature, particularly as temperature control devices consider more than just patient body temperature when adjusting water temperature.[107] To limit imprecision, we used conservative estimates for interpolation and visually inspected each patient's $T_{Bath}$ and temperature curve for model fit. In addition, we included all recorded values in the model with enough flexibility to not significantly over or under estimate interpolated values.

### Conclusion

In this sample of post-cardiac arrest patients undergoing TTM at 36°C, we observed a 4.3°C change in water temperature for every 0.1°C change in body temperature. Monitoring changes in water temperature could allow clinicians to recognize and intervene earlier for events such as shivering, which result in heat generation. Our results are consistent with the premise that shivering is associated with $T_{Var}$ and improved survival. Future investigation is needed to examine the role of shiver burden on outcomes, and the role of heat generation for TTM at 36°C.

## TABLES

Table 1. Patient and Event Characteristics, including differences by presence of temperature variability. * denotes group difference p<0.05.

| Characteristic | Total (N=186) | No Temp Variability (n=62) | Temp Variability (n=124) | p-value |
|---|---|---|---|---|
| Sex, n(%) | | | | |
| Male | 131 (70.4) | 45 (72.6) | 86 (69.4) | 0.78 |
| Female | 55 (29.6) | 17 (27.4) | 38 (30.6) | |
| Age (years), mean±SD | 53.8 ±15.7 | 54.1 ±19.4 | 53.8 ±13.6 | 0.89 |
| BMI, mean±SD | 27.2 ±7.5 | 26.0 ±8.0 | 27.9 ±7.1 | 0.12 |
| Race, n(%) | | | | 0.52 |
| Caucasian | 127 (68.3) | 45 (72.6) | 82 (66.1) | |
| African American | 27 (14.5) | 8 (12.9) | 19 (15.3) | |
| Asian | 13 (67.0) | 6 (9.7) | 7 (5.6) | |
| Other | 19 (10.2) | 3 (4.8) | 16 (12.9) | |
| Location of Cardiac Arrest, n(%) | | | | 0.17 |
| Out of hospital | 164 (88.2) | 51 (82.3) | 113 (91.1) | |
| In-hospital | 19 (10.2) | 9 (14.5) | 10 (8.1) | |
| Other | 3 (1.6) | 2 (3.2) | 1 (0.8) | |
| Initial Rhythm, n(%) | | | | 0.002* |
| Shockable | 66 (35.5) | 12 (19.4) | 54 (43.5) | |
| Non-Shockable | 120 (64.5) | 50 (80.6) | 70 (56.5) | |
| Cause of Cardiac Arrest, n(%) | | | | 0.01* |
| Cardiac | 59 (31.7) | 10 (16.1) | 49 (39.5) | |
| Resp | 38 (20.4) | 13 (21.0) | 25 (20.2) | |
| Other | 54 (29.0) | 24 (38.7) | 30 (24.2) | |
| Unk | 35 (17.7) | 15 (24.2) | 20 (16.1) | |
| Witnessed, n(%) | 103 (55.4) | 36 (58.1) | 67 (54.0) | 0.74 |
| Bystander CPR, n(%) | 116 (62.4) | 46 (74.2) | 70 (56.5) | 0.02* |
| Length of CA from EMS arrival¥ (minutes) mean±SD | 19.2 ±13.7 | 14.9 ±10.3 | 21.1 ±14.6 | 0.03* |
| Shivering | | | | |
| Yes, n(%) | 111 (59.7) | 28 (45.2) | 83 (66.9) | 0.01* |
| Shivering episodes, mean±SD | 2.4 ±3.2 | 1.26 ±1.97 | 2.96 ±3.55 | 0.001* |
| Paralytic Use, n(%) | 130 (69.9) | 39 (62.9) | 91 (73.4) | 0.19 |
| EEG, n(%) | 148 (79.6) | 50 (80.6) | 98 (79.0) | 0.95 |

|  |  |  |  |  |
|---|---|---|---|---|
| Epileptic seizures (diagnosed via EEG), n(%) | 33 (17.7) | 13 (21.0) | 20 (16.1) | 0.54 |
| Length of Hospitalization, mean±SD | 12.7 ±20.1 | 13.0 ±16.2 | 12.6 ±21.9 | 0.90 |
| Discharge Disposition, n(%) |  |  |  | 0.54 |
| Home | 26 (14.0) | 5 (8.1) | 21 (16.9) |  |
| SNF/Rehab | 23 (12.4) | 9 (14.5) | 14 (11.3) |  |
| AMA | 5 (2.7) | 2 (3.2) | 3 (2.4) |  |
| Outside hospital | 4 (2.2) | 1 (1.6) | 3 (2.4) |  |
| Deceased | 128 (68.8) | 45 (72.6) | 83 (66.9) |  |
| CPC at discharge, n(%) |  |  |  | 0.35 |
| 1-2 (good) | 47 (25.3) | 12 (19.4) | 35 (28.3) |  |
| 3-4 (poor) | 11 (5.9) | 5 (8.1) | 6 (4.8) |  |
| Survival, n(%) | 58 (31.2) | 17 (27.4) | 41 (33.1) | 0.54 |

[¥] 40% missing data

## FIGURES

Figure 1. Scatter Plot of $T_{Bath}$ and Patient Body Temperature

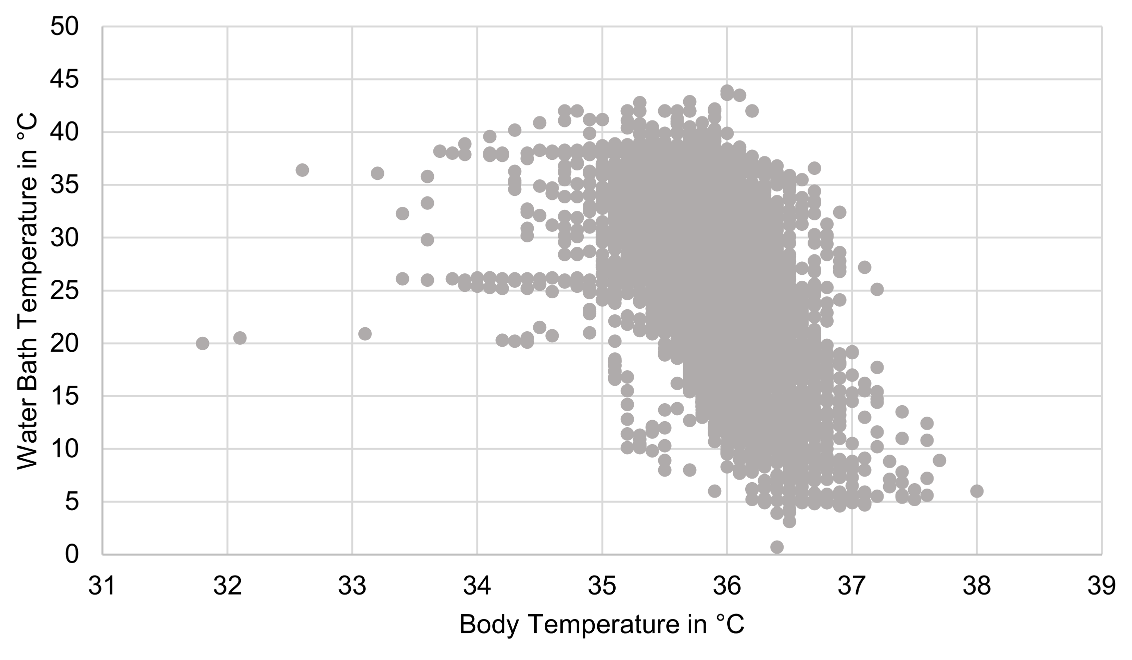
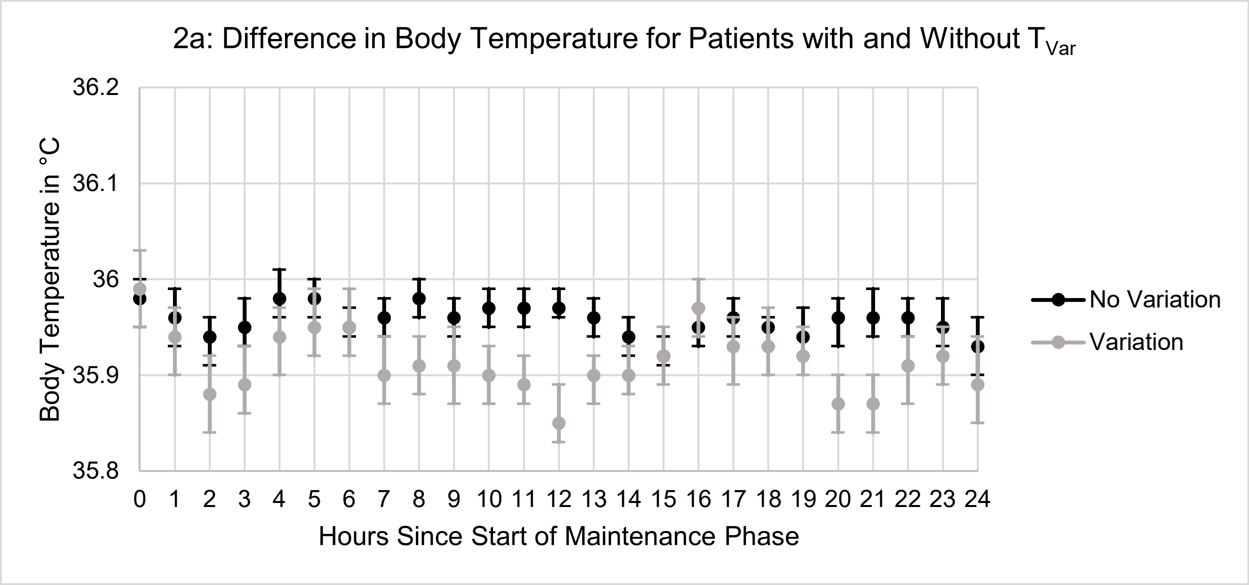
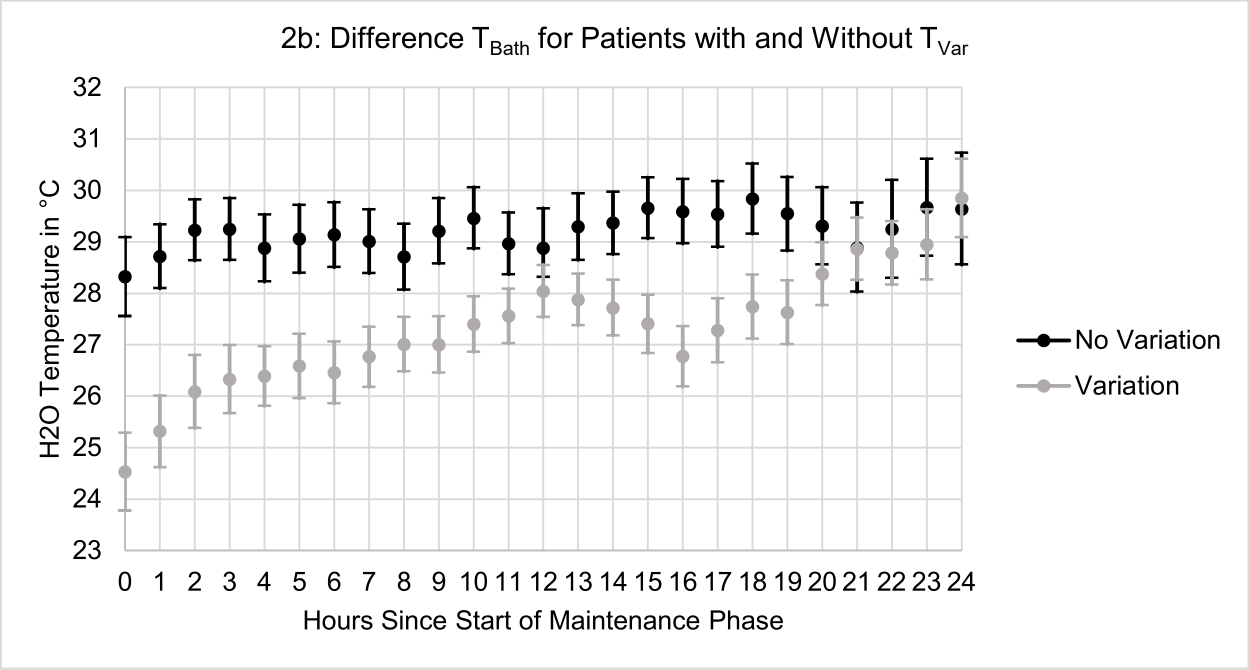


Figure 2. Difference in Body Temperature and $T_{Bath}$ for Patients with and Without $T_{Var}$


2a: Difference in Body Temperature for Patients with and Without $T_{Var}$


2b: Difference $T_{Bath}$ for Patients with and Without $T_{Var}$

Data presented as the hourly average temperature (Body or $T_{Bath}$) and 95% confidence interval

# CHAPTER 5: Conclusion

Sudden cardiac arrest affects more than 500,000 Americans annually and carries a high mortality. For those that do survive the initial arrest and achieve return of spontaneous circulation, care is continued in the intensive care unit (ICU). Targeted temperature management (TTM) is the only known evidence-based intervention to mitigate the effects of post-cardiac arrest syndrome (PCAS). In this dissertation, we included several approaches to better understand how TTM at 36°C affects patients, and discussed the effect of patient characteristics and assessment findings on the ability to maintain TTM at 36°C.

In Chapter 3, we used energy expenditure (EE) as a measure of metabolism to describe the changes in EE at 36°C. Recruitment during this prospective study was challenging. We anticipated enrolling six patients, but were only able to enroll three, even after extending the study for an additional month. Using the information gathered from chapter two, it may be more feasible to conduct future similar studies using ventilator-integrated EE where an investigator would not have to necessarily be present at the time the patient arrived in the ICU. We found that although not many qualifying patients were missed during the study period, staff in the ICU were busy and often forgot to contact the investigator until several hours after the patient's arrival. Using ventilator-integrated EE, measurements would occur automatically and are downloaded directly to the electronic health record (EHR). Another challenge of this study was that we had to align three separate entities to one common time variable. For example, we extracted body temperature from the cooling device which was not always programmed to the correct time. We then had to match the corrected time from the cooling device to the time stamp from the EHR, as well as the EE measurement device, which was done post-hoc. In the future, it would be beneficial to ensure all devices were set with the correct date and time prior to enrolling patients, and recognize how each study device records measurements in terms of time.

In Chapter 4, we described the relationship between cooling device water temperature and patient body temperature, as well as described the effect of shivering on temperature variability. We used retrospective hospital record data for this study. One major challenge in completing this study was the need to organize the multiple data points into a cohesive document for analysis. Each variable for each patients was extracted with a specific time stamp. Often when aligning and combining the data, findings that occurred at similar time intervals were documented in the EHR at different time points. For example, body temperature and device water temperature were often documented one minute apart. To correct this, we had to develop algorithms to correctly match variables to a common time in order to prevent the assumption of missing data during analysis. We chose 15 minute intervals as that is a common documentation interval for assessments in the ICU. If data were documented within the same 15-minute interval, we aligned the data to a common time stamp. Occasionally, there were more than one documented data point from the same category during a 15-minute interval (for example, two device water temperatures). We then averaged the two values to only have one datum from each category for that 15-minute interval. It is possible that one of the documented values was recorded in error, as sometimes, especially the device water temperature, the two recorded values differed by several units. To minimize the risk for error, we did review instances where there was a large discrepancy in the recorded values during a 15-minute interval. Often, it was possible to exclude a value recorded in error when put in context of other related variables.

### *Implications for Practice*

This dissertation has several implications for practice. First, we found that TTM at 36°C offers only small changes in EE compared to normothermia. As much of our assumption regarding how TTM confers benefit was based on cooling to 32-34°C, it may be that TTM at 36°C is not the same intervention as cooling to a more hypothermic temperature. Clinicians could use this information when delivering interventions. For example, nutritional support is often held during

TTM because of reduced gastrointestinal motility seen during hypothermia. As we have demonstrated similar EE during TTM at 36°C compared to other critically ill populations, it is plausible that nutritional support would be better tolerated at 36°C. In addition, drug metabolism and clearance is reduced during hypothermia. It may be that delayed drug metabolism is less of a significant concern at 36°C given similar EE compared to normothermia.

Second, we described the relationship between changes in body temperature and cooling device water temperature. Using this information, a clinician would be able to recognize early indications of excessive heat generation, such as caused by shivering. Early recognition of excessive heat generation could trigger the clinician to more closely monitor the patient and implement appropriate interventions before body temperatures rise above the clinically acceptable temperature limit of 36.5°C.

Lastly, many institutions embrace the concept of the need for tight temperature control during TTM. To achieve tight control, often deep sedation and continuous paralytic infusions are used from the very beginning of TTM to prevent shivering and excessive heat generation. As both sedatives and paralytic use have known negative effects on morbidity, it is important to limit use when possible. Our findings are in alignment with other studies that suggest that the ability to generate heat (such as during shivering) is associated with less severe brain injury and improved survival. It may be that shivering could be managed as it occurs using a step-wise treatment plan, and only institute paralytics when shivering cannot be controlled using other, less-aggressive measures. This may also be the case as our findings demonstrated that the cooling device was able to maintain body temperature within the acceptable temperature range much of the time despite shivering.

### *Future Directions*

As less is known about TTM at 36°C, it is important to include this targeted temperature in future studies of cardiac arrest patients. This is especially evident as many organizations have instituted TTM at 36°C, despite many remaining knowledge gaps. In studies using cooling device water temperature, it would be beneficial to include information obtained directly from the device. This would not only limit the possibility of recording errors, but would also provide much more detailed information regarding the response of the temperature control device to changes in body temperature. Additionally, as reduced metabolism may not be a significant contributing factor to TTM at 36°C, it would be important to investigate other factors that contribute to the protective effect of TTM at this targeted temperature.

# REFERENCES

1. Graham R, McCoy, M. A., Schultz, A. M. STRATEGIES TO IMPROVE CARDIAC ARREST SURVIVAL: A Time to Act. 2015; https://www.nap.edu/read/21723/chapter/1.
2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation.* 2017;135(10):e146-e603.
3. Callaway CW, Donnino MW, Fink EL, et al. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2015;132(18 Suppl 2):S465-482.
4. Nolan JP, Neumar RW, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication: a scientific statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke (Part II). *International emergency nursing.* 2010;18(1):8-28.
5. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical

Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation.* 2008;118(23):2452-2483.

6. Walters EL, Morawski K, Dorotta I, et al. Implementation of a post-cardiac arrest care bundle including therapeutic hypothermia and hemodynamic optimization in comatose patients with return of spontaneous circulation after out-of-hospital cardiac arrest: a feasibility study. *Shock.* 2011;35(4):360-366.
7. Mongardon N, Dumas F, Ricome S, et al. Postcardiac arrest syndrome: from immediate resuscitation to long-term outcome. *Annals of intensive care.* 2011;1(1):45.
8. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med.* 2013;369(23):2197-2206.
9. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. *Critical care medicine.* 2009;37(7 Suppl):S186-202.
10. Nunnally ME, Jaeschke R, Bellingan GJ, et al. Targeted temperature management in critical care: a report and recommendations from five professional societies. *Critical care medicine.* 2011;39(5):1113-1125.
11. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *The New England journal of medicine.* 2002;346(8):557-563.
12. HACA. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002;346(8):549-556.
13. Kochanek PM, Jackson TC. The Brain and Hypothermia-From Aristotle to Targeted Temperature Management. *Critical care medicine.* 2017;45(2):305-310.
14. Frank A, Bonney M, Bonney S, Weitzel L, Koeppen M, Eckle T. Myocardial ischemia reperfusion injury: from basic science to clinical bedside. *Seminars in cardiothoracic and vascular anesthesia.* 2012;16(3):123-132.

15. Idris AH, Roberts LJ, 2nd, Caruso L, et al. Oxidant injury occurs rapidly after cardiac arrest, cardiopulmonary resuscitation, and reperfusion. *Critical care medicine.* 2005;33(9):2043-2048.

16. Polderman K, Nielsen N, Graffagnino C, Wayne M. Therapeutic Hypothermia in Post-Cardiac Arrest. *Therapeutic hypothermia and temperature management.* 2014.

17. Badjatia N, Strongilis E, Prescutti M, et al. Metabolic benefits of surface counter warming during therapeutic temperature modulation. *Critical care medicine.* 2009;37(6):1893-1897.

18. Glover GW, Thomas RM, Vamvakas G, et al. Intravascular versus surface cooling for targeted temperature management after out-of-hospital cardiac arrest - an analysis of the TTM trial data. *Crit Care.* 2016;20(1):381.

19. Tomte O, Draegni T, Mangschau A, Jacobsen D, Auestad B, Sunde K. A comparison of intravascular and surface cooling techniques in comatose cardiac arrest survivors. *Critical care medicine.* 2011;39(3):443-449.

20. Tommasi E, Lazzeri C, Bernardo P, et al. Cooling techniques in mild hypothermia after cardiac arrest. *Journal of cardiovascular medicine (Hagerstown, Md).* 2014.

21. Sonder P, Janssens GN, Beishuizen A, et al. Efficacy of different cooling technologies for therapeutic temperature management: A prospective intervention study. *Resuscitation.* 2018;124:14-20.

22. Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: A focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. *Critical care medicine.* 2007;35(9):2196-2204.

23. Annborn M, Bro-Jeppesen J, Nielsen N, et al. The association of targeted temperature management at 33 and 36 degrees C with outcome in patients with moderate shock on admission after out-of-hospital cardiac arrest: a post hoc analysis of the Target Temperature Management trial. *Intensive care medicine.* 2014;40(9):1210-1219.

24. Bro-Jeppesen J, Annborn M, Hassager C, et al. Hemodynamics and vasopressor support during targeted temperature management at 33 degrees C Versus 36 degrees C after out-of-hospital cardiac arrest: a post hoc study of the target temperature management trial*. *Critical care medicine.* 2015;43(2):318-327.

25. Thomsen JH, Nielsen N, Hassager C, et al. Bradycardia During Targeted Temperature Management: An Early Marker of Lower Mortality and Favorable Neurologic Outcome in Comatose Out-of-Hospital Cardiac Arrest Patients. *Critical care medicine.* 2016;44(2):308-318.

26. Badjatia N, Strongilis E, Gordon E, et al. Metabolic impact of shivering during therapeutic temperature modulation: the Bedside Shivering Assessment Scale. *Stroke; a journal of cerebral circulation.* 2008;39(12):3242-3247.

27. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Critical care medicine.* 2009;37(3):1101-1120.

28. Bay J, Nunn JF, Prys-Roberts C. Factors influencing arterial PO2 during recovery from anaesthesia. *Br J Anaesth.* 1968;40(6):398-407.

29. Frank SM, Fleisher LA, Olson KF, et al. Multivariate determinants of early postoperative oxygen consumption in elderly patients. Effects of shivering, body temperature, and gender. *Anesthesiology.* 1995;83(2):241-249.

30. Kranke P, Eberhart LH, Roewer N, Tramer MR. Pharmacological treatment of postoperative shivering: a quantitative systematic review of randomized controlled trials. *Anesth Analg.* 2002;94(2):453-460, table of contents.

31. Giesbrecht GG, Sessler DI, Mekjavic IB, Schroeder M, Bristow GK. Treatment of mild immersion hypothermia by direct body-to-body contact. *Journal of applied physiology (Bethesda, Md : 1985).* 1994;76(6):2373-2379.

32. Oddo M, Frangos S, Maloney-Wilensky E, Andrew Kofke W, Le Roux PD, Levine JM. Effect of shivering on brain tissue oxygenation during induced normothermia in patients with severe brain injury. *Neurocritical care.* 2010;12(1):10-16.

33. Ralley FE, Wynands JE, Ramsay JG, Carli F, MacSullivan R. The effects of shivering on oxygen consumption and carbon dioxide production in patients rewarming from hypothermic cardiopulmonary bypass. *Can J Anaesth.* 1988;35(4):332-337.

34. Deem S, Lee CM, Curtis JR. Acquired neuromuscular disorders in the intensive care unit. *Am J Respir Crit Care Med.* 2003;168(7):735-739.

35. Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. *Resuscitation.* 2014;85(12):1779-1789.

36. Samaniego EA, Mlynash M, Caulfield AF, Eyngorn I, Wijman CA. Sedation confounds outcome prediction in cardiac arrest survivors treated with hypothermia. *Neurocritical care.* 2011;15(1):113-119.

37. Rossetti AO, Rabinstein AA, Oddo M. Neurological prognostication of outcome in patients in coma after cardiac arrest. *Lancet Neurol.* 2016;15(6):597-609.

38. Jessen C. *Temperature Regulation in Humans and Other Mammals.* Berlin, Germany: Springer-Verlag; 2001.

39. Childs C. Human brain temperature: regulation, measurement and relationship with cerebral trauma: part 1. *Br J Neurosurg.* 2008;22(4):486-496.

40. Nair SU, Lundbye JB. The occurrence of shivering in cardiac arrest survivors undergoing therapeutic hypothermia is associated with a good neurologic outcome. *Resuscitation.* 2013;84(5):626-629.

41. da Rocha EE, Alves VG, da Fonseca RB. Indirect calorimetry: methodology, instruments and clinical application. *Curr Opin Clin Nutr Metab Care.* 2006;9(3):247-256.

42. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr.* 2016;40(2):159-211.
43. Murnin MR, Sonder P, Janssens GN, et al. Determinants of heat generation in patients treated with therapeutic hypothermia following cardiac arrest. *Journal of the American Heart Association.* 2014;3(3):e000580.
44. Psota T, Chen KY. Measuring energy expenditure in clinical populations: rewards and challenges. *Eur J Clin Nutr.* 2013;67(5):436-442.
45. Tatucu-Babet OA, Ridley EJ, Tierney AC. Prevalence of Underprescription or Overprescription of Energy Needs in Critically Ill Mechanically Ventilated Adults as Determined by Indirect Calorimetry: A Systematic Literature Review. *JPEN J Parenter Enteral Nutr.* 2016;40(2):212-225.
46. Rosomoff HL, Holaday DA. Cerebral blood flow and cerebral oxygen consumption during hypothermia. *Am J Physiol.* 1954;179(1):85-88.
47. Holzinger U, Brunner R, Losert H, et al. Resting energy expenditure and substrate oxidation rates correlate to temperature and outcome after cardiac arrest - a prospective observational cohort study. *Crit Care.* 2015;19:128.
48. Oshima T, Furukawa Y, Kobayashi M, Sato Y, Nihei A, Oda S. Fulfilling caloric demands according to indirect calorimetry may be beneficial for post cardiac arrest patients under therapeutic hypothermia. *Resuscitation.* 2015;88:81-85.
49. Guttormsen AB, Pichard C. Determining energy requirements in the ICU. *Curr Opin Clin Nutr Metab Care.* 2014;17(2):171-176.
50. Schlein KM, Coulter SP. Best practices for determining resting energy expenditure in critically ill adults. *Nutr Clin Pract.* 2014;29(1):44-55.

51. Poehlman ET. A review: exercise and its influence on resting energy metabolism in man. *Med Sci Sports Exerc.* 1989;21(5):515-525.

52. Levine JA. Measurement of energy expenditure. *Public Health Nutr.* 2005;8(7a):1123-1132.

53. Genton L, Pichard C. Protein catabolism and requirements in severe illness. *Int J Vitam Nutr Res.* 2011;81(2-3):143-152.

54. Sabatino A, Theilla M, Hellerman M, et al. Energy and Protein in Critically Ill Patients with AKI: A Prospective, Multicenter Observational Study Using Indirect Calorimetry and Protein Catabolic Rate. *Nutrients.* 2017;9(8).

55. Frankenfield DC, Ashcraft CM, Drasher TL, Reid EK, Vender RL. Characteristics of Resting Metabolic Rate in Critically Ill, Mechanically Ventilated Adults With Cystic Fibrosis. *JPEN J Parenter Enteral Nutr.* 2017;41(4):601-606.

56. Lev S, Cohen J, Singer P. Indirect calorimetry measurements in the ventilated critically ill patient: facts and controversies--the heat is on. *Crit Care Clin.* 2010;26(4):e1-9.

57. Kross EK, Sena M, Schmidt K, Stapleton RD. A comparison of predictive equations of energy expenditure and measured energy expenditure in critically ill patients. *J Crit Care.* 2012;27(3):321.e325-312.

58. Walker RN, Heuberger RA. Predictive equations for energy needs for the critically ill. *Respir Care.* 2009;54(4):509-521.

59. Harris JB, JA. *Biometric studies of basal metabolism in man.* Washington, DC: Carnegie Institiute; 1919.

60. Frankenfield D, Hise M, Malone A, Russell M, Gradwell E, Compher C. Prediction of resting metabolic rate in critically ill adult patients: results of a systematic review of the evidence. *J Am Diet Assoc.* 2007;107(9):1552-1561.

61. Cerra FB, Benitez MR, Blackburn GL, et al. Applied nutrition in ICU patients. A consensus statement of the American College of Chest Physicians. *Chest.* 1997;111(3):769-778.

62. Frankenfield DC, Rowe WA, Smith JS, Cooney RN. Validation of several established equations for resting metabolic rate in obese and nonobese people. *J Am Diet Assoc.* 2003;103(9):1152-1159.

63. Frankenfield D. Validation of an equation for resting metabolic rate in older obese, critically ill patients. *JPEN J Parenter Enteral Nutr.* 2011;35(2):264-269.

64. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. *Am J Clin Nutr.* 1990;51(2):241-247.

65. Ireton-Jones C, Jones JD. Improved equations for predicting energy expenditure in patients: the Ireton-Jones Equations. *Nutr Clin Pract.* 2002;17(1):29-31.

66. Ireton-Jones CS, Turner WW, Jr., Liepa GU, Baxter CR. Equations for the estimation of energy expenditures in patients with burns with special reference to ventilatory status. *J Burn Care Rehabil.* 1992;13(3):330-333.

67. Flancbaum L, Choban PS, Sambucco S, Verducci J, Burge JC. Comparison of indirect calorimetry, the Fick method, and prediction equations in estimating the energy requirements of critically ill patients. *Am J Clin Nutr.* 1999;69(3):461-466.

68. Frankenfield DC, Ashcraft CM, Galvan DA. Longitudinal prediction of metabolic rate in critically ill patients. *JPEN J Parenter Enteral Nutr.* 2012;36(6):700-712.

69. Rousing ML, Hahn-Pedersen MH, Andreassen S, Pielmeier U, Preiser JC. Energy expenditure in critically ill patients estimated by population-based equations, indirect calorimetry and CO2-based indirect calorimetry. *Annals of intensive care.* 2016;6(1):16.

70. Boullata J, Williams J, Cottrell F, Hudson L, Compher C. Accurate determination of energy needs in hospitalized patients. *J Am Diet Assoc.* 2007;107(3):393-401.

71. Frankenfield DC, Coleman A, Alam S, Cooney RN. Analysis of estimation methods for resting metabolic rate in critically ill adults. *JPEN J Parenter Enteral Nutr.* 2009;33(1):27-36.

72. Kee AL, Isenring E, Hickman I, Vivanti A. Resting energy expenditure of morbidly obese patients using indirect calorimetry: a systematic review. *Obes Rev.* 2012;13(9):753-765.

73. Drolz A, Wewalka M, Horvatits T, et al. Gender-specific differences in energy metabolism during the initial phase of critical illness. *Eur J Clin Nutr.* 2014;68(6):707-711.

74. Frankenfield D, Roth-Yousey L, Compher C. Comparison of predictive equations for resting metabolic rate in healthy nonobese and obese adults: a systematic review. *J Am Diet Assoc.* 2005;105(5):775-789.

75. Anderegg BA, Worrall C, Barbour E, Simpson KN, Delegge M. Comparison of resting energy expenditure prediction methods with measured resting energy expenditure in obese, hospitalized adults. *JPEN J Parenter Enteral Nutr.* 2009;33(2):168-175.

76. Frankenfield DC, Ashcraft CM. Estimating energy needs in nutrition support patients. *JPEN J Parenter Enteral Nutr.* 2011;35(5):563-570.

77. Critical Illness Evidence-Based Nutrition Practice Guideline. 2012; https://www.andeal.org/topic.cfm?cat=4800.

78. Al-Dorzi HM, Albarrak A, Ferwana M, Murad MH, Arabi YM. Lower versus higher dose of enteral caloric intake in adult critically ill patients: a systematic review and meta-analysis. *Crit Care.* 2016;20(1):358.

79. Soar J, Callaway CW, Aibiki M, et al. Part 4: Advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation.* 2015;95:e71-120.

80. Cheifetz IM, Myers TR. Respiratory therapies in the critical care setting. Should every mechanically ventilated patient be monitored with capnography from intubation to extubation? *Respir Care.* 2007;52(4):423-438; discussion 438-442.

81. Mehta JH, Williams GW, 2nd, Harvey BC, Grewal NK, George EE. The relationship between minute ventilation and end tidal CO2 in intubated and spontaneously breathing patients undergoing procedural sedation. *PLoS One.* 2017;12(6):e0180187.

82. Jabre P, Jacob L, Auger H, et al. Capnography monitoring in nonintubated patients with respiratory distress. *Am J Emerg Med.* 2009;27(9):1056-1059.

83. Singer P. Simple equations for complex physiology: can we use VCO2 for calculating energy expenditure? *Crit Care.* 2016;20:72.

84. Mehta NM, Smallwood CD, Joosten KF, Hulst JM, Tasker RC, Duggan CP. Accuracy of a simplified equation for energy expenditure based on bedside volumetric carbon dioxide elimination measurement--a two-center study. *Clin Nutr.* 2015;34(1):151-155.

85. Stapel SN, de Grooth HJ, Alimohamad H, et al. Ventilator-derived carbon dioxide production to assess energy expenditure in critically ill patients: proof of concept. *Crit Care.* 2015;19:370.

86. Oshima T, Graf S, Heidegger CP, Genton L, Pugin J, Pichard C. Can calculation of energy expenditure based on CO2 measurements replace indirect calorimetry? *Crit Care.* 2017;21(1):13.

87. Liggett SB, St John RE, Lefrak SS. Determination of resting energy expenditure utilizing the thermodilution pulmonary artery catheter. *Chest.* 1987;91(4):562-566.

88. Fung EB. Estimating energy expenditure in critically ill adults and children. *AACN Clin Issues.* 2000;11(4):480-497.

89. Ogawa AM, Shikora SA, Burke LM, Heetderks-Cox JE, Bergren CT, Muskat PC. The thermodilution technique for measuring resting energy expenditure does not agree with

indirect calorimetry for the critically ill patient. *JPEN J Parenter Enteral Nutr.* 1998;22(6):347-351.

90. Brandi LS, Grana M, Mazzanti T, Giunta F, Natali A, Ferrannini E. Energy expenditure and gas exchange measurements in postoperative patients: thermodilution versus indirect calorimetry. *Critical care medicine.* 1992;20(9):1273-1283.

91. Brandi LS, Bertolini R, Santini L. Calculated and measured oxygen consumption in mechanically ventilated surgical patients in the early post-operative period. *Eur J Anaesthesiol.* 1999;16(1):53-61.

92. Walsh BJ, Morley TF. Comparison of three methods of determining oxygen consumption and resting energy expenditure. *J Am Osteopath Assoc.* 1989;89(1):43-46.

93. Soussi S, Vallee F, Roquet F, et al. Measurement of Oxygen Consumption Variations in Critically Ill Burns Patients: Are the Fick Method and Indirect Calorimetry Interchangeable? *Shock.* 2017;48(5):532-538.

94. Rao M, Koenig E, Li S, et al. Direct calorimetry for the measurement of heat release in preterm infants: methods and applications. *J Perinatol.* 1995;15(5):375-381.

95. Haugen HA, Chan LN, Li F. Indirect calorimetry: a practical guide for clinicians. *Nutr Clin Pract.* 2007;22(4):377-388.

96. Gibson D, MacGregor C. A novel solid state non-dispersive infrared CO2 gas sensor compatible with wireless and portable deployment. *Sensors (Basel, Switzerland).* 2013;13(6):7079-7103.

97. Langton J, Hutton, A. Respiratory gas analysis. *Continuing Education in Anaesthesia Critical Care & Pain.* 2009;9(1):19-23.

98. Headley JM. Indirect calorimetry: a trend toward continuous metabolic assessment. *AACN Clin Issues.* 2003;14(2):155-167; quiz 266.

99. Black C, Grocott MP, Singer M. Metabolic monitoring in the intensive care unit: a comparison of the Medgraphics Ultima, Deltatrac II, and Douglas bag collection methods. *Br J Anaesth.* 2015;114(2):261-268.

100. Graf S, Karsegard VL, Viatte V, Maisonneuve N, Pichard C, Genton L. Comparison of three indirect calorimetry devices and three methods of gas collection: a prospective observational study. *Clin Nutr.* 2013;32(6):1067-1072.

101. Rehal MS, Fiskaare E, Tjader I, Norberg A, Rooyackers O, Wernerman J. Measuring energy expenditure in the intensive care unit: a comparison of indirect calorimetry by E-sCOVX and Quark RMR with Deltatrac II in mechanically ventilated critically ill patients. *Crit Care.* 2016;20(1):54.

102. Graf S, Karsegard VL, Viatte V, et al. Evaluation of three indirect calorimetry devices in mechanically ventilated patients: which device compares best with the Deltatrac II((R))? A prospective observational study. *Clin Nutr.* 2015;34(1):60-65.

103. Bruder N, Raynal M, Pellissier D, Courtinat C, Francois G. Influence of body temperature, with or without sedation, on energy expenditure in severe head-injured patients. *Critical care medicine.* 1998;26(3):568-572.

104. Madden LK, Hill M, May TL, et al. The Implementation of Targeted Temperature Management: An Evidence-Based Guideline from the Neurocritical Care Society. *Neurocritical care.* 2017;27(3):468-487.

105. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. *Resuscitation.* 2015;95:202-222.

106. Geocadin RG, Wijdicks E, Armstrong MJ, et al. Practice guideline summary: Reducing brain injury following cardiopulmonary resuscitation: Report of the Guideline

Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology.* 2017;88(22):2141-2149.

107. Badjatia N, Kowalski RG, Schmidt JM, et al. Predictors and clinical implications of shivering during therapeutic normothermia. *Neurocritical care.* 2007;6(3):186-191.

108. Mahmood MA, Zweifler RM. Progress in shivering control. *J Neurol Sci.* 2007;261(1-2):47-54.

109. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol.* 1949;109(1-2):1-9.

110. Olejnik LA, Peters EN, Parrott JS, et al. Abbreviated Steady State Intervals for Measuring Resting Energy Expenditure in Patients on Maintenance Hemodialysis. *JPEN J Parenter Enteral Nutr.* 2017;41(8):1348-1355.

111. Huet O, Dupic L, Batteux F, et al. Postresuscitation syndrome: potential role of hydroxyl radical-induced endothelial cell damage. *Critical care medicine.* 2011;39(7):1712-1720.

112. Mooij C, Beurskens, CJ., Juffermans, NP. Energy expenditure in different patient populations in intensive care: One size does not fit all. *Netherlands Journal of Critical Care.* 2013;17(3):3-8.

113. Uber AJ, Perman SM, Cocchi MN, et al. Increased Heat Generation in Postcardiac Arrest Patients During Targeted Temperature Management Is Associated With Better Outcomes. *Critical care medicine.* 2018.

114. Deye N, Vincent F, Michel P, et al. Changes in cardiac arrest patients' temperature management after the 2013 "TTM" trial: results from an international survey. *Annals of intensive care.* 2016;6(1):4.

115. Bray JE, Stub D, Bloom JE, et al. Changing target temperature from 33 degrees C to 36 degrees C in the ICU management of out-of-hospital cardiac arrest: A before and after study. *Resuscitation.* 2017;113:39-43.

116. Rittenberger JC, Friess S, Polderman KH. Emergency Neurological Life Support: Resuscitation Following Cardiac Arrest. *Neurocritical care.* 2015;23 Suppl 2:S119-128.

117. Elmer J, Polderman KH. Emergency Neurological Life Support: Resuscitation Following Cardiac Arrest. *Neurocritical care.* 2017;27(Suppl 1):134-143.

118. Casamento A, Minson A, Radford S, et al. A comparison of therapeutic hypothermia and strict therapeutic normothermia after cardiac arrest. *Resuscitation.* 2016;106:83-88.

119. Ang KH, Chong, G.C.Y., & Li, Y. PID control system analysis, design, and technology. *IEEE Transactions on Control Systems Technology.* 2005;13(4):559-576.

120. May T, Seder DB, Fraser GL, et al. Association of the Bedside Shivering Assessment Scale and derived EMG power during therapeutic hypothermia in survivors of cardiac arrest. *Resuscitation.* 2011;82(8):1100-1103.

121. Presciutti M, Bader MK, Hepburn M. Shivering Management During Therapeutic Temperature Modulation: Nurses' Perspective. *Critical Care Nurse.* 2012;32(1):33-42.

122. May T, Seder DS., Fraser GF., Hoover CF., Riker RR., McCrum BM. Shivering during targeted temperature management after cardiac arrest: a physiologic description. *Crit Care.* 2014;18(Supp 1):498.

123. Tian J, Kaufman DA, Zarich S, et al. Outcomes of critically ill patients who received cardiopulmonary resuscitation. *Am J Respir Crit Care Med.* 2010;182(4):501-506.

124. Geri G, Fahrenbruch C, Meischke H, et al. Effects of bystander CPR following out-of-hospital cardiac arrest on hospital costs and long-term survival. *Resuscitation.* 2017;115:129-134.

125. Stockl M, Testori C, Sterz F, et al. Continuous versus intermittent neuromuscular blockade in patients during targeted temperature management after resuscitation from cardiac arrest-A randomized, double blinded, double dummy, clinical trial. *Resuscitation.* 2017;120:14-19.

126. Oddo M, Schaller MD, Feihl F, Ribordy V, Liaudet L. From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. *Critical care medicine.* 2006;34(7):1865-1873.