Published in final edited form as:

Resuscitation. 2018 June ; 127: 89–94. doi:10.1016/j.resuscitation.2018.04.001.

Preliminary observations in systemic oxygen consumption during targeted temperature management after cardiac arrest

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Abstract

Aim—Limited data suggests low oxygen consumption (VO_2), driven by mitochondrial injury, is associated with mortality after cardiac arrest. Due to the challenges of measurement in the critically ill, post-arrest metabolism remains poorly characterized. We monitored VO_2 , carbon dioxide production (VCO_2) and the respiratory quotient (RQ) in post-arrest patients and explored associations with outcome.

Methods—Using a gas exchange monitor, we measured continuous VO_2 and VCO_2 in post-arrest patients treated with targeted temperature management. We used area under the curve and medians over time to evaluate the association between VO_2 , VCO_2 , RQ and the VO_2 :lactate ratio with survival.

Results—In 17 patients, VO_2 in the first 12 hours after return of spontaneous circulation (ROSC) was associated with survival (median in survivors 3.35 mL/kg/min [2.98,3.88] vs. non-survivors 2.61 mL/kg/min [2.21,2.94], $p=0.039$). This did not persist over 24 hours. The VO_2 :lactate ratio was associated with survival (median in survivors 1.4 [IQR: 1.1,1.7] vs. non-survivors 0.8 [IQR: 0.6,1.2] $p<0.001$). Median RQ was 0.66 (IQR 0.63,0.70) and 71% of RQ measurements were <0.7 . Patients with initial $\text{RQ}<0.7$ had 17% survival versus 64% with initial $\text{RQ}>0.7$ ($p=0.131$). VCO_2 was not associated with survival.

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Conflicts of Interest

The remaining authors have no disclosures.

Conclusions—There was a significant association between VO_2 and mortality in the first 12 hours after ROSC, but not over 24 hours. Lower VO_2 : lactate ratio was associated with mortality. A large percentage of patients had RQs below physiologic norms. Further research is needed to explore whether these parameters could have true prognostic value or be a potential treatment target.

Keywords

Heart arrest; Cardiopulmonary resuscitation; Energy metabolism; Cell respiration; Oxygen consumption

Introduction

The difficulty of prognostication after cardiac arrest stems in part from our limited understanding of the physiology underlying cardiac arrest and the post-arrest syndrome, which likely varies considerably even between patients with seemingly similar arrest characteristics. Ischemia-reperfusion injury is thought to damage the mitochondria, leading to alterations in cellular metabolism.¹ Whether physiologic derangements are consistent across patients however, and thus whether our treatments are aimed at the correct targets, remains unclear.

Oxygen consumption (VO_2) is determined by oxygen delivery (DO_2)—the product of cardiac output and the oxygen content in arterial blood—and oxygen extraction. Lower VO_2 is associated with increased mortality in sepsis, and a single small study in post-arrest patients found a similar relationship.² This association was initially thought to be related to inadequate DO_2 ;^{3,4} it is now understood that impairment in oxygen extraction due to alteration in mitochondrial function is a major factor in both sepsis and the post-arrest state, but the variability in this phenomenon from patient to patient is poorly understood.^{5–8}

Prior studies of oxygen metabolism in the critically ill have mostly utilized pulmonary artery catheters and the Fick calculation,² and are limited by mathematic coupling between cardiac output and VO_2 . Indirect calorimetry has also been used for many years, traditionally with large and somewhat cumbersome metabolic carts.^{4,9,10} Newer technology, in the form of a CARESCAPE™ B650 anesthesia monitor with a gas exchange module connecting directly to the ventilator circuit, has made measurement of VO_2 , carbon dioxide production (VCO_2) and the respiratory quotient (RQ) more feasible in the ICU setting. However, this technology has limitations, and reports of clinical experience with it are limited, especially in the post-arrest population.

We conducted a single-center observational study of trends in gas metabolism in post-cardiac arrest patients. We hypothesized that there would be abnormalities in metabolism after cardiac arrest, and that lower VO_2 , VCO_2 , and RQ would be associated with lactate as well as clinical outcome.

Materials and Methods

The study was approved by the Institutional Review Board at Beth Israel Deaconess Medical Center. Legally authorized surrogates of all patients provided verbal informed consent prior to patient enrollment.

Design, Setting, and Population

This study was conducted at an urban tertiary care center in Boston, Massachusetts, USA from January 2016 through July 2017. Included patients were part of an ongoing prospective observational study of metabolism in adult, critically-ill patients receiving invasive mechanical ventilation. To minimize variation in temperature and sedation, (both of which can alter VO_2), we included only patients receiving TTM following in-hospital or out-of-hospital cardiac arrest, with temperature $\geq 36^\circ\text{C}$ at the time of data collection. Patients were excluded if they (1) exhibited factors known to alter VO_2 measurement such as agitation or known air leak; (2) had a positive end-expiratory pressure (PEEP) $>12\text{cm H}_2\text{O}$ as connecting the monitor requires a brief disconnection from the ventilator circuit; (3) required fraction of inspired oxygen (FiO_2) greater than 60%, given the requirements of the monitoring technology (described below) or (4) were co-enrolled in an ongoing randomized, blinded trial of Ubiquinol after cardiac arrest ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02934555) #NCT02934555), due to the theoretical effect of Ubiquinol on VO_2 .

VO_2 Technology

Continuous VO_2 and VCO_2 measurements were obtained with the CARESCAPE™ Monitor B650 with CARESCAPE Respiratory Module E-sCOVX (GE Healthcare, Helsinki, Finland). Values were recorded and saved once per minute using the accompanying GE Healthcare S/5Collect software. RQ values were calculated by dividing VCO_2 by VO_2 . We included all values when measurements appeared to represent steady state (not changing by more than approximately 10% over several minutes).

The CARESCAPE monitor connects in-line with the patient's ventilator tubing and has a built-in module for measuring spirometry and gas exchange. Via gas sampling ports and a flow sensor connected in-line with the ventilator tubing, the gas exchange module measures the flow of exhaled gas and the difference in oxygen and carbon dioxide content between inhalation and exhalation using a pneumotachograph and a rapid paramagnetic analyzer. The monitor provides continuous readings with each patient breath. The S/5 Collect software records all values averaged over the chosen interval, which for this study was every minute. This monitor has been approved for the measurement of VO_2 and VCO_2 in critically ill, mechanically ventilated patients and has been validated against indirect calorimetry using the metabolic cart.^{11,12}

Data Collection

Patients were enrolled as soon after ROSC as possible once verbal consent was obtained. The monitor was connected to the patient's ventilator tubing and set to record data for up to 48 hours. In addition to respiratory parameters, we retrospectively abstracted clinical data on each patient from the electronic medical record. These data included demographics, past

medical history, arrest information, height, body weight, temperature, use of TTM, ventilator settings, lactates, use of neuromuscular blocking (NMB) agents, vasopressors and sedatives, hospital mortality, and neurologic outcomes.

Outcomes

Our primary objective was to characterize trends in VO_2 , VCO_2 , RQ, and the VO_2 : lactate ratio in the 24 hours after ROSC for patients undergoing TTM, and to explore whether any of these parameters were associated with hospital survival. The VO_2 : lactate ratio was chosen in addition to the standard measures of indirect calorimetry as a possible indicator of the relative balance between oxygen supply and demand. For this outcome, all lactates drawn for a patient during the study period were paired with the VO_2 measurement closest to that time point to create the ratio, so each patient could potentially have more than one VO_2 : lactate ratio.

Statistical Analyses

Baseline characteristics were delineated using descriptive statistics. Categorical data are presented as counts with relative frequencies, and continuous data as medians with interquartile range (IQR) due to the non-normal distribution of the data.

Before analysis, VO_2 and VCO_2 values were normalized for body weight by dividing the total mL/min by weight in kilograms. Also prior to analysis and while still blinded to patient outcomes, VO_2 data was cleaned in two steps. First, as VO_2 measurements are known to be disrupted for several minutes after a change in FiO_2 or PEEP, values were reviewed manually after an FiO_2 or PEEP change and were removed until a return to steady state was noted. Second, graphs were made of all remaining data points for each patient and extreme outliers (defined as outliers in reference to the patient's other values around that time point) were removed after visual inspection by two members of the author team who were blinded to subject outcome. All VCO_2 values concurrent with removed VO_2 values were removed as well.

We characterized VO_2 , VCO_2 and RQ in the entire cohort using median and IQR due to nonparametric distribution. To examine the univariate relationship between VO_2 , VCO_2 , and RQ and hospital survival we looked at median values over time and the area under the curve (AUC). Using the AUC as well as medians allowed us to use all data points and adjust for the number of minutes of data available, which varied between patients. We used Wilcoxon rank-sum tests to compare patient-level distributions between survivors and non-survivors. For dichotomized values, we used Fisher's exact test due to our small sample size. To control for clustering at the level of the patient when using serial measurements and assessing the difference in these values over time, we used a mixed effects logistic model with the patient as a random intercept. We controlled for NMB use in multivariate regression because NMB can lower VO_2 by decreasing muscle activity. Due to the small sample size, we were unable to adjust for other factors. All analyses were two-sided with a significance level of $p < 0.05$. Statistical analyses were conducted using STATA, version 14 (College Station, TX, StataCorp LP, USA).

Results

Of 78 patients enrolled to date in the larger ongoing study, 23 were post-cardiac arrest and had data collected during TTM. Six of these were removed due to co-enrollment in the Ubiquinol study, leaving 17 patients for analysis. Baseline characteristics are summarized in Table 1. Non-survivors had longer downtime and a lower percentage of initially shockable rhythms. Other baseline characteristics were similar between groups. Non-survivors appeared to spend more time on vasopressors and less on neuromuscular blockade, although these differences were non-significant. There was no significant difference in mean body temperatures or sedation doses between survivors and non-survivors. Length of time from ROSC to the beginning of metabolic data collection ranged from 5.0–18.7 hours, with a median time of 9.9 hours (IQR: 7.5, 11.4).

Looking at all time points in all patients, median VO_2 was 3.0 mL/kg/min (IQR 2.5, 3.7). In unadjusted analysis of the 24 hours after ROSC, there was no association between the area under the curve (AUC) of VO_2 (adjusted for the amount of time the patient contributed data) or median VO_2 over time and survival. This relationship did not change after adjustment for neuromuscular blockade use. In a post-hoc analysis of the first 12 hours after ROSC, VO_2 was associated with survival (median VO_2 in survivors 3.35 mL/kg/min [2.98, 3.88] vs. non-survivors 2.61 mL/kg/min [2.21, 2.94], $p=0.039$, and VO_2 AUC in survivors 3.39 mL/kg/min [3.03, 4.38] vs. non-survivors: 2.61 mL/kg/min [2.27, 2.87], $p=0.028$, Fig.1). There was no cut-off value for VO_2 that differentiated survivors and non-survivors. The VO_2 :lactate ratio was higher over time in survivors (median: 1.4 [IQR: 1.1, 1.7] vs. 0.8 [IQR: 0.6, 1.2], $p<0.001$).

Median VCO_2 in all patients at all time points was 2.16 mL/kg/min (IQR 1.71, 2.67). There was no association between VCO_2 and survival, although survivors appear to trend higher in the initial hours after ROSC (Fig. 2). Median RQ for the entire cohort was 0.66 (IQR 0.63–0.70) and 71.7% of all values were below 0.7. Patients whose first measured RQ was <0.7 had a survival rate of 17% (1/6), compared to 64% (7/11) in patients whose initial RQ was ≥ 0.7 ($p=0.131$). There was no significant difference in RQ over 12 or 24 hours (Fig. 3). All of the above analyses were also conducted with the 6 patients from our ongoing blinded Ubiquinol study included (for a total of 23 patients). Results were similar in direction but did not attain statistical significance.

Discussion

In this single-center prospective observational study, we characterized patterns in VO_2 , VCO_2 , and RQ in the post-cardiac arrest period in patients being treated with TTM. Although we did not find any associations with survival when looking at the 24 hours after ROSC, in a post-hoc analysis higher VO_2 in the first 12 hours after ROSC was associated with survival. Higher VO_2 : lactate ratio over time was also associated with survival. There was an early difference in VCO_2 and RQ, but no significant association with survival over any time interval.

Ischemia-reperfusion injury is a significant component of the post-cardiac arrest syndrome. This injury is characterized by a pro-inflammatory state with high levels of circulating cytokines and oxygen-derived free radicals,¹³ which have been shown to mediate mitochondrial damage.^{1,14,15} As the mitochondrion is responsible for the utilization of oxygen for cell respiration, quantification of VO_2 may afford insight into a patient's physiology and mitochondrial status, which by extension may aid in post-arrest prognostication or potentially guide future treatments.

Only one prior study by Rivers et al. explicitly examined the association of VO_2 with survival after cardiac arrest.² They defined "venous hyperoxia" as a state in which central venous oxygen saturation remains elevated despite low-to-normal cardiac output, suggesting a cellular inability to utilize oxygen. Similar to our study, they found that lower VO_2 was associated with worse outcome in the first 12 hours after ROSC. Rivers et al. however also found that if patients were unable to increase their VO_2 beyond a certain threshold value in response to attempts to increase DO_2 , mortality reached 100%. In contrast, we found a wide range of VO_2 values in patients of all outcomes; in fact, the lowest steady state value we recorded was in a patient who survived. Potential explanations for this discrepancy include differences in VO_2 data collection methods and the significant differences in patient populations (e.g., out-of-hospital arrest compared to mixed population, differences in intra-arrest adrenaline doses, and the prior study being done before TTM was commonly used).

The relationship between VO_2 , TTM and cell damage is complex as both mitochondrial injury and the cooling that aims to mitigate this injury will lower the consumption of oxygen. At a given temperature however, different levels of VO_2 may indicate varying degrees of mitochondrial dysfunction. A patient with preserved mitochondrial function who is well-sedated and being cooled may have a low VO_2 and also a low lactate, reflecting the relatively low cellular oxygen demand. In contrast, a patient with similar treatments but with severe mitochondrial injury may have a low VO_2 but a high lactate. We explored this VO_2 :lactate ratio concept and found that patients with a higher ratio had lower mortality, which is consistent with the above stated theory. We hypothesize that this ratio could be a more sensitive indicator of mitochondrial injury severity as compared to VO_2 alone.

Our finding that more than 70% of RQ values were less than 0.7 (lower limit of normal physiology) is something that has not been reported previously, except in states of ketosis¹⁶ Interestingly, a low initial RQ appeared to be associated with higher mortality, although this was not significant. During normal metabolism in a healthy cell, >95% of oxygen uptake from the blood is potentiated toward mitochondrial respiration, although some studies have found higher relative levels of non-mitochondrial respiration in the presence of infection or sepsis.^{17,18} Given that the immediate post-arrest period is characterized by a pro-inflammatory state with generation of oxygen-derived free radicals and other reactive oxygen species, it is plausible that low post-arrest RQ values are driven by a higher utilization of oxygen toward non-metabolic processes in order to generate reactive-oxygen species and oxygen-derived free radicals. Alternatively, our findings may reflect a high prevalence of ketosis, perhaps due to a critically ill population not receiving adequate nutrition. Further exploration with consideration given to a larger study with earlier post-ROSC RQ values could aid in understanding the physiologic underpinnings of this finding.

Our study has several limitations. While our methodology for measuring VO_2 represents recent advances in this technology, concerns persist regarding measurement precision. The percentage change in inspiratory and expiratory oxygen concentrations are small, and thus small errors in gas concentration measurement can lead to significant errors in VO_2 values. There are multiple monitor-level and patient-level factors that may produce artifact in the data, including patient-ventilator dysynchrony, changes in patient medications or changes in the humidity, pressure and temperature of air in the ventilator circuit. While we carefully reviewed PEEP and FiO_2 settings to remove any artefactual data as much as possible and only used steady state measurements, the possibility for error remains. Also, our finding of a difference in VO_2 in the first 12 hours after ROSC was a post-hoc analysis, done after noting an early difference when looking at trends over 24 hours. Each subject was enrolled as close to ROSC as possible; however, due to logistical issues there was often a substantial lag time from ROSC to enrollment, which led to an inability to capture data within the first five hours after ROSC. In light of these limitations, our results should be seen as preliminary and hypothesis generating only. Future work to validate these measures as markers of mitochondrial status with any prognostic value should focus on gathering data on a larger number of patients and as soon after ROSC as possible.

Conclusions

We report an association between the novel endpoint of the VO_2 :lactate ratio and hospital survival in post-cardiac arrest patients being treated with TTM. We also report an association between lower VO_2 in the first 12 hours after ROSC and lower hospital survival, although this did not persist over 24 hours. Additionally, we found a large percentage of RQ values that were lower than expected. Further work is needed to explore whether VO_2 or the VO_2 :lactate ratio could be useful as prognostic indicators or possible treatment targets.

Acknowledgments

Sources of Funding

This was an investigator-initiated study funded in part by a grant from General Electric. Study design, data analysis and manuscript preparation were done by the investigator team, independent of the funding source. Amy Uber is a Sarnoff Fellow supported by the Sarnoff Cardiovascular Research Foundation. Dr. Donnino is supported by the American Heart Association (14GRNT20002) and the National Institute of Health (1K24HL127101). Dr. Berg is supported by the National Institute of Health (K23HL128814).

The authors would like to acknowledge Francesca Montillo, M.M. for her work in preparing this manuscript and Jocelyn Portmann B.S., Varun Konanki B.S., Sarah Ganley B.S. for their work in data collection.

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Figure 1.
Median VO_2 over the first 24 hours (a) and first 12 hours (b) post ROSC by survivors (black) and non-survivors (grey)

Figure 2.
Median VCO_2 over the first 24 hours (a) and first 12 hours (b) post ROSC by survivors (black) and non-survivors (grey)

Figure 3.
Median RQ over the first 24 hours (a) and first 12 hours (b) post ROSC by survivors (black) and non-survivors (grey)

Table 1

Sample Characteristics. Categorical variables are presented as count (frequency) and continuous variables as median (quartiles)

Subject Characteristic	All N=17	Survivors N=8	Non-survivors N=9	p-value
Age (years), median (IQR)	70 (59, 81)	71 (59.5, 83.5)	70 (53, 78)	0.413
Female, %	7 (41.2)	5 (62.5)	2 (22.2)	0.153
Race, %				
White	7 (38.9)	3 (37.5)	4 (44.4)	0.582
Black	6 (33.3)	4 (50.0)	2 (22.2)	
Other	4 (27.8)	1 (12.5)	3 (33.3)	
Past medical history, %				
CAD	7 (41.2)	4 (50.0)	3 (33.3)	0.637
Cancer	6 (35.3)	3 (37.5)	3 (33.3)	>0.999
CHF	4 (23.5)	2 (25.0)	2 (22.2)	>0.999
COPD	4 (23.5)	1 (12.5)	3 (33.3)	0.576
Diabetes	5 (29.4)	3 (37.5)	2 (22.2)	0.620
Hypertension	14 (82.4)	6 (75.0)	8 (88.9)	0.576
Liver disease	0 (0)	0 (0)	0 (0)	n/a
Renal disease	3 (17.7)	2 (25.0)	1 (11.1)	0.576
Stroke	3 (17.7)	2 (25.0)	1 (11.1)	0.576
Prior cardiac arrest	0 (0)	0 (0)	0 (0)	n/a
FiO ₂ , cm H ₂ O, median (IQR)	39.9 (39.6, 49.8)	39.8 (39.4, 49.9)	40.2 (39.9, 49.6)	0.386
PEEP, cm H ₂ O, median (IQR)	6.3 (5.1, 9.6)	5.3 (5.1, 9.0)	8.3 (5.6, 9.6)	0.500
Lactate, mmol/L, median (IQR)	2.7 (2.1, 4.2)	2.4 (1.9, 3.5)	3.4 (2.5, 4.4)	0.004
Any lactate >2 mmol/L, %	17 (100)	8 (100)	9 (100)	n/a
Any vasopressor use, Yes/No, (%)	15 (88.2)	7 (87.5)	8 (88.9)	0.929
Proportion of time on vasopressor, median (IQR)	0.66 (0.20,1.0)	0.20 (0.12,0.83)	1.0 (0.61,1.0)	0.122
Any sedation use (Yes/No), %	17 (100)	8 (100)	9 (100)	n/a
Proportion of time on sedation, median (IQR)	1.0 (1.0,1.0)	1.0 (1.0,1.0)	1.0 (1.0,1.0)	
Propofol hourly dose in patients receiving Propofol, median (IQR)	49.4 (38.1, 66.8)	49.4 (6.7, 66.8)	51.5 (40.0, 71.0)	0.724
% on at any time, n(%)	7 (41.2)	3 (37.5)	4 (44.4)	>0.999
Fentanyl hourly dose in patients receiving Fentanyl, median (IQR)	91.2 (66.4, 126.9)	97.7 (80.4, 159.9)	84.2 (53.9, 150.1)	0.600
% on at any time, n(%)	16 (94.1)	8 (100)	8 (88.9)	>0.999
Midazolam hourly dose in patients receiving Midazolam, median (IQR)	2.0 (1.2, 3.1)	1.6 (1.2, 4.0)	2.0 (1.8, 2.3)	0.688
% on at any time, n(%)	12 (70.6)	6 (75.0)	6 (66.7)	>0.999

Subject Characteristic	All N=17	Survivors N=8	Non-survivors N=9	p-value
Any NMB use (Y/N), %	10 (58.8)	6 (75.0)	4 (44.4)	0.201
Proportion of time on NMB, median (IQR)	0.76 (0.00,0.84)	0.80 (0.05,0.92)	0.00 (0.00,0.76)	0.270
Arrest features:				
OHCA %	15 (88.2)	6 (75.0)	9 (100)	0.206
Downtime, mins, median (IQR)	15 (10, 25)	10 (10, 15)	25 (20, 35)	0.020
Initial rhythm shockable %	9 (52.9)	6 (75.0)	3 (33.3)	0.153
Body Temperature, Celsius, median (IQR)	35.0 (34.1, 35.4)	34.8 (34.0, 35.1)	35.4 (34.8, 35.7)	0.102

IQR: Interquartile range; FiO2: Fraction of inspired oxygen; CAD: Coronary artery disease; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; PEEP: positive end expiratory pressure; NMB: neuromuscular blocking agent