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Clinical paper

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 h 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], $p = .039$). This did not persist over 24 h. 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 RQ < 0.7 had 17% survival versus 64% with initial RQ > 0.7 ($p = .131$). VCO_2 was not associated with survival.

Conclusions: There was a significant association between VO_2 and mortality in the first 12 h after ROSC, but not over 24 h. 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.

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.

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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_2O, median (IQR)	39.9 (39.6, 49.8)	39.8 (39.4, 49.9)	40.2 (39.9, 49.6)	0.386
PEEP, cm H2O, 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
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

Legend: IQR: Interquartile range; FiO_2: 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.

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 ≤ 36 °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 cm H_20 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 #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