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Declarations:

Ethics approval and consent to participate: This study was approved by the local Institutional Review Board. All legally authorized surrogates provided verbal consent prior to enrollment in the study.

Abstract

Introduction: Mitochondrial dysfunction leading to impairment of oxygen extraction, referred to as cytopathic hypoxia, contributes to morbidity in sepsis. Oxygen consumption (VO_2) may be a useful measure of the severity of cytopathic hypoxia. We monitored VO_2 and carbon dioxide production (VCO_2) in septic patients and investigated the association with hospital survival.

Methods: We retrospectively identified adult (≥ 18 years) septic patients from a larger prospective observational cohort of critically ill patients on mechanical ventilation. A gas-exchange monitor recorded continuous VO_2 and VCO_2 for up to 48 hours. We then tested the association of median VO_2, VCO_2, respiratory quotient (RQ) and the VO_2:lactate ratio with survival.

Results: A total of 46 septic patients were included in the analysis, of whom 28 (61%) survived. Overall median VO_2 was not associated with survival (3.72 mL/kg/min [IQR: 3.39, 4.92] in survivors and 3.42 mL/kg/min [IQR: 2.97, 5.26] in non-survivors, p=0.12). The overall median VCO_2 and RQ were also not associated with survival. Adjusting for age and the presence of shock did not change these results. The VO_2:lactate ratio was associated with survival (adjusted OR 2.17 [95% CI 1.12, 4.22] per unit increase in ratio, p= 0.03). The percent change in median

VCO_2 was 11.6% [IQR: -8.2, 28.7] in survivors compared to -8.3% [IQR: -18.0, 4.7] in non-survivors (p=0.03). The percent changes in median VO_2 and RQ were not different between groups.

Conclusion: The VO_2:lactate ratio was significantly higher in survivors, while there was no association between median VO_2 alone and survival. There was a significant difference in change in VCO_2 over time between survivors and non-survivors.

Key words: Sepsis, Critical Illness, Oxygen Consumption, Energy Metabolism, Cell Respiration

Introduction
Sepsis is a common cause of hospital admission in the United States (1) and is the leading cause of death in non-cardiac intensive care units. (2,3) Septic shock is characterized by evidence of end-organ damage and elevation in lactate. Historically, the main explanation given for this derangement was inadequate oxygen delivery due to tissue hypoperfusion. In recent years, however, there is growing evidence that cytopathic hypoxia (impaired oxygen extraction from mitochondrial injury) contributes to hyperlactatemia and organ dysfunction in sepsis. (4–7) Oxygen consumption (VO_2), which is determined by both oxygen delivery and oxygen extraction, may be a useful measure of the degree of impairment in oxygen extraction, and low VO_2 has been associated with mortality in septic shock and after cardiac arrest. (8–10)

This area of research has been limited by the difficulty of measuring VO_2 reliably and accurately in the critically ill. (11,12) In earlier studies, VO_2 was either calculated, which required placement of a pulmonary artery catheter, or measured by indirect calorimetry, using large and somewhat cumbersome equipment that is not available in many intensive care units. (13–15) Newer technology allows for direct, non-invasive, and continuous measurement of VO_2 and carbon dioxide production (VCO_2) in patients who are mechanically ventilated.(16,17) Our

group has used this technology previously to evaluate whether VO_2 is associated with survival after cardiac arrest. (10) The same study also explored the ratio between VO_2 and lactate as a possible more sensitive marker of the adequacy of VO_2 for a specific patient at a specific moment and found a stronger association with mortality using this ratio than using VO_2 alone. Oxygen demand can vary by patient due to temperature, levels of sedation, disease state and other factors. (17,18) A lower VO_2 may not therefore always be pathologic or indicative of harm. The VO_2:lactate ratio accounts for this, but has previously only been tested in a small post-arrest cohort. (10)

In the present study, we monitored VO_2 and VCO_2 continuously for up to 48 hours in a cohort of septic patients to investigate whether VO_2 and the ratio of VO_2 to lactate were associated with hospital survival in patients with sepsis. We hypothesized that a higher median VO_2 and VO_2:lactate ratio and an increase in VO_2 over time would be associated with hospital survival. We secondarily assessed the association between VCO_2 and the respiratory quotient (RQ) with hospital survival. Some of the results of this study have been previously reported in the form of an abstract.(19)

Methods

Design and setting

This was an observational study conducted at Beth Israel Deaconess Medical Center, an urban tertiary care center in Boston, Massachusetts, USA, from January 2016 through March 2019. In this study, we retrospectively identified septic patients who were part of an ongoing prospective observational cohort of oxygen metabolism in critically ill adult patients receiving mechanical

ventilation. This study was approved by the local Institutional Review Board. All legally

authorized surrogates provided verbal consent prior to enrollment in the study.

Study population and outcomes

We included adult patients (age $\geq$ 18 years) admitted to the medical or surgical intensive care

unit with a diagnosis of sepsis who required mechanical ventilation and had stable ventilator

settings for at least three hours prior to enrollment. Patients were excluded if they had: 1) factors

known to alter VO_2 such as air-leak (e.g. chest tube) or agitation, 2) positive end-expiratory

pressure (PEEP) >12 cm H_2O, due to the potential risk of a brief disconnection from the

ventilator, 3) fraction of inspired oxygen (FiO$_2$) >60% due to the monitor being validated for

FiO$_2$ of 60% or less, and/or 4) anticipated extubation within 24 hours of the enrollment. Patients

with less than 12 hours of data were excluded prior to analysis.

The primary outcome was hospital survival. Sepsis was defined as a suspected or

confirmed bacterial infection with evidence of a systemic inflammatory response for which the

patient was receiving antibiotics at the time of enrollment. Septic shock was defined as meeting

these same criteria with the addition of shock, defined as requiring vasopressor support

(norepinephrine, epinephrine, vasopressin, and/or phenylephrine) for at least 30 minutes. The

diagnosis of sepsis was based on medical chart review.

VO$_2$ and VCO$_2$ measurement

Continuous VO_2 and VCO$_2$ measurements were obtained with the CARESCAPE^{TM} B650

Monitor with Respiratory Module E-sCOVX (GE Healthcare, Helsinki, Finland). 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.

(15) The CARESCAPE monitor connects in-line with the patient's ventilator tubing and has a

built-in module for measuring spirometry and gas exchange. (Figure 1) Via gas sampling ports

and a flow sensor connected in-line with the ventilator tubing, the gas exchange module

measures the flow and volume of exhaled gas and the difference in O_2 and CO_2 content between

inhalation and exhalation using a pneumotachograph and a rapid paramagnetic analyzer. The

monitor provides continuous readings with each patient breath. The GE S/5 Collect software

records and saves all values averaged over a chosen interval which, for this study, was every

minute.

Data collection

The CARESCAPE 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 abstracted clinical data on each

patient from the electronic medical record, which was saved in an internal database. These data

included demographics, past medical history, ventilator settings, lactates, usage of

neuromuscular blocking (NMB) agents, vasopressors, and/or sedatives, and hospital survival.

Statistical analysis

We used descriptive statistics to present baseline characteristics. Continuous variables were

summarized using mean ± standard deviation (SD) or median and interquartile range (IQR), with

differences between groups tested using Student's *t*-test or Wilcoxon rank-sum test, depending

on the normality of the data. Categorical variables were summarized by frequencies and

percentages with differences between groups tested using Chi-square or Fisher's exact test, as applicable.

Prior to analysis, metabolic data was cleaned using an algorithm designed by our research team in R version 3.51 (R Foundation for Statistical Computing, Vienna, Austria). This automated algorithm excluded VO_2 and VCO_2 data if one or more of the following criteria was met: 1) all values recorded in the 10 minutes following a change in FiO_2 of $\geq$10%, 2) all values recorded while FiO_2 was >60%, 3) all values deviating $\geq$20% from the preceding value and more than two standard deviations away from the mean of the next 5 values, 4) all values more than two standard deviations away from the mean of the corresponding 60-minute interval, and 5) all values out of physiologic range unless these were persistent for more than 30 minutes, as these measurements were considered artifacts. Values considered out of physiologic range, based on the existing literature (8,20), were VO_2 <100mL/min or >1000mL/min and VCO_2 <70mL/min or >800mL/min. We allowed these values if they persisted for at least 30 minutes and if they were not excluded per the algorithm for other reasons, as critically ill patients can sometimes have values well outside of standard normal range, due to medication use such as sedatives and neuromuscular blockade and/or alterations in metabolic function. For one patient, we manually excluded values of VCO_2 that were severely out of physiologic range (>2000ml/kg/min) as these were attributed to monitor error. Concurrent values of VO_2 and RQ for that patient were also dropped as only time points with valid measures of all 3 parameters were included. See Figure 2 for examples of algorithm performance. RQ was defined as VCO_2 divided by VO_2. RQ values were calculated where both VCO_2 and VO_2 measurements were available within the same minute. After data cleaning, all VO_2 and VCO_2 data were adjusted for patient weight in kilograms (mL/kg/min).

We calculated the overall median VO_2 and VCO_2 for the study population based on the individual median of all time points. We also computed patient medians during the first and last five hours of data collection. We planned to categorize the relative change in median VO_2, VCO_2, and RQ from the first five hours to the last five hours of data collection into three trend groups (increasing, decreasing, or constant), with a change threshold of 20%. Calculation of the VO_2:lactate ratio was based on the first lactate drawn after enrollment and the VO_2 within the same minute. Two logistic regression models were used to assess the relationships between overall median VO_2 and VO_2:lactate ratio to survival, adjusting for age (continuous covariate) and septic shock status (binary covariate). Due to the pilot nature of this study, no formal power analysis was performed.

All tests were two-sided and the nominal level of statistical significance (α) was 5%. Analyses were performed using R version 3.51 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 48 septic patients were enrolled. Two were excluded, one due to withdrawal from the study and one due to monitor dysfunction resulting in no usable metabolic data (Figure 3). We included 46 patients in the analysis, of whom 28 (61%) survived and 33 (72%) were in septic shock at the time of enrollment. Baseline characteristics in survivors and non-survivors are presented in Table 1. Time from intubation to enrollment (start of metabolic data collection) ranged from 3 hours to 47 hours, with a median of 9 hours [IQR: 8, 12].

Oxygen consumption (VO_2)

In unadjusted analysis, there was no association between overall median VO_2 and survival (3.72 mL/kg/min [IQR: 3.39, 4.92] in survivors and 3.42 mL/kg/min [IQR: 2.97, 5.26] in non-survivors, p=0.12). This remained unchanged when adjusted for age and presence of shock (adjusted odds ratio [aOR] for survival 1.46 per 1mL/kg/min increase in median VO_2 [95% CI: 0.88, 2.42], p = 0.14).

VO_2:lactate ratio

At least one lactate measurement was available for 38 of 46 (83%) patients, of which 33 (87%) were drawn within 24 hours of study start. Using a Wilcoxon ranked sum test, there was no significant difference in lactate between survivors and nonsurvivors (p=0.26). A higher initial VO_2:lactate ratio was associated with survival (median 3.28 [IQR: 2.05, 3.62] in survivors and 1.41 [IQR: 0.85, 2.39] in non-survivors, p=0.03). (Figure 4) The relationship remained statistically significant when adjusted for age and presence of shock (aOR 2.17 [95% CI: 1.12, 4.22] per unit increase in ratio, p= 0.03). The area under the Receiver Operating Curve (AUROC) was 0.76 [95% CI: 0.59, 0.93] for the VO_2:lactate ratio, compared to 0.62 [95% CI: 0.43, 0.82] for VO_2 alone and 0.65 [95% CI: 0.46, 0.85] for lactate alone. The difference between the AUROC for VO_2:lactate and lactate alone (p = 0.17) or VO_2 alone (p = 0.19) was not statistically significant.

RQ and VCO_2

There was no relationship between RQ or VCO_2 and hospital survival. The overall median VCO_2 in survivors was 2.77 mL/kg/min [IQR: 2.38, 3.38] compared to 2.43 mL/kg/min [IQR: 2.14,

3.38] in non-survivors (p=0.19). The overall median RQ in survivors was 0.69 [IQR: 0.68, 0.72] compared to an RQ of 0.69 [IQR: 0.66, 0.73] in non-survivors, p=0.78.

Trends over time

We were unable to run the planned analysis comparing directions of change within 48 hours due to the small sample size in some of the trend groups. We therefore performed a post-hoc analysis comparing the percent change in VO_2, VCO_2, and RQ from the first five hours to the last five hours in survivors and non-survivors. There was a significant difference in percent change in median VCO_2 (11.6% [IQR: -8.2, 28.7] in survivors and -8.3% [IQR: -18.0, 4.7] in non-survivors, p=0.03). Median VCO_2 over time in survivors and non-survivors is presented in Figure 5. The percent change in median VO_2 (-3.0% [IQR: -11.0, 17.7] in survivors and -3.1% [IQR: -15.7, 4.4] in non-survivors, p = 0.27) and RQ (2.3% [IQR: -2.4, 8.0] in survivors versus 1.58% [IQR: -5.3, 6.6] in non-survivors, p = 0.46) was not significantly different between groups.

Discussion

In this study, we investigated the relationship between VO_2, the VO_2:lactate ratio and survival in septic adults, secondarily assessing whether VCO_2 and RQ were associated with survival. We found that the VO_2:lactate ratio was significantly higher in survivors, while there was no association between median VO_2 alone and survival. We also found a significant difference in change in VCO_2 over time between survivors and non-survivors but did not find any difference in change over time in VO_2 or RQ.

The understanding of the role of oxygen delivery and metabolism in critical illness continues to evolve. Early studies found that increasing oxygen delivery by augmenting cardiac output and the oxygen carrying capacity of the blood increased VO_2 and was beneficial in terms of shorter length of stay in the intensive care unit and better survival. (9,21,22) Subsequent studies, however, found that only some patients were able to increase VO_2 in response to increased delivery, and those who were unable to increase VO_2 had higher hospital mortality. (7,20) A study by Hayes et al compared the oxygen delivery and consumption pattern of 78 sepsis survivors and non-survivors receiving dobutamine to target supratherapeutic levels of oxygen delivery (DO_2). They demonstrated that non-survivors, despite increases in DO_2, were unable to increase VO_2, and had higher lactates and higher mortality. (7) This was one of several studies (4,6,23–25) that led to the current prevailing hypothesis that oxygen extraction is of critical importance in the prognosis of septic shock. The importance of oxygen extraction was also demonstrated in a recent study by Gattinoni et al. (5) Those investigators plotted the relationship between central venous saturation ($ScvO_2$) and lactate, finding that lactate and mortality are high in patients with both very low and very high $ScvO_2$. They concluded that the high-lactate, high $ScvO_2$ pattern in sepsis, caused by impaired oxygen extraction, is a major driver of mortality. Findings like these support the importance of cytopathic hypoxia and highlight the potential harms of focusing solely on hypoperfusion when designing interventions for septic shock. (20) There is currently no proven intervention to improve oxygen extraction, but a reliable method to monitor this parameter could be prognostically useful and provide a potential target for intervention.

VO_2 is determined by delivery and extraction, both of which can be significantly altered in sepsis: The oxygen "supply" may vary somewhat due to alterations in cardiac output or

arterial oxygen content (delivery) and/or decreases in extraction ability due to mitochondrial

dysfunction. The oxygen "demand" may also vary depending on a patient's native metabolic rate

as well as external factors such as sedation, neuromuscular blockade, temperature or disease

state. Thus, a low VO_2 may not always be indicative of harm, as long as the level is adequate to

meet a patient's needs. The adequacy of a given number for VO_2 may be best interpreted in

conjunction with lactate or some other marker of tissue oxygenation. We propose using the

VO_2:lactate ratio to provide a more precise metabolic picture and to differentiate between a

patient whose VO_2 is appropriately low (low VO_2 and low lactate) and one whose VO_2 is

inappropriately low and likely to be harmful (low VO_2 and high lactate). Our group recently

published a small study in post-cardiac arrest patients demonstrating that higher VO_2:lactate ratio

was associated with survival, similar to our findings in the present study. (10) The lack of a

significant relationship between VO_2 and survival in the current cohort, combined with the

positive association of the VO_2:lactate ratio with survival, suggests that perhaps VO_2 is not a

sufficient predictor of survival in sepsis when used as an individual variable but is useful when

combined with a measure of its adequacy for that specific patient. The VO_2:lactate ratio also

appeared to have a stronger association with survival than lactate alone, although this difference

did not achieve statistical significance.

The significance of the difference in change in VCO_2 over time between survivors and

nonsurvivors is unclear. One hypothesis, which has been suggested in post-cardiac arrest patients

and may be similar in sepsis, is that non-survivors may have more severe mitochondrial injury

and thus be more dependent on extramitochondrial respiration, which does not lead to the same

CO_2 production per unit of oxygen consumed. (26, 10) Especially in light of the lack of a

concurrent difference over time in VO_2 and RQ however, the isolated finding in VCO_2 should be validated in a larger cohort before conclusions can be drawn.

Our study has several limitations. First, the diagnosis of sepsis was determined retrospectively based on review of medical charts. The timeline of sepsis is very important in that there may be different stages of metabolic dysfunction at different time points (27), which we were not able to account for. This was an observational study, and therefore we did not have control of when or if the clinical team drew a lactate. This may affect our VO_2:lactate ratio, since the association of this variable with outcome may also depend on at what time point it is calculated. In addition, 18 of the 46 patients (39%) received at least one dose of intravenous thiamine during the study period, and limited data suggests thiamine may have an effect on VO_2. (28,29) Some recent papers have questioned the use of the respiratory module E-sCOVX, stating that the measurements are overestimated. (16,17) However, the overestimation was found to be approximately 10%. As we were more interested in relative differences in VO_2 than absolute values, this small overestimation, if present, likely would not change our conclusions. VO_2 measurements in critically ill patients are also frequently affected by artifact from things such as changes in FiO_2 or medications. We have tested our algorithm to reduce inclusion of artifactual values in multiple patients and it appears to perform well (Figure 2), but this risk cannot yet be eliminated completely. Finally, our sample size was small, and our study was therefore not adequately powered to detect small differences in metabolic parameters between groups. Finally, due to the small sample size these findings should be considered preliminary and validated in future studies in larger cohorts and at other institutions. Despite these limitations, this study contributes to a better understanding of the potential of oxygen consumption as a prognostic value in critically ill patients with sepsis measured by an easy-to-use bedside monitor.

Conclusions

In conclusion, we found that the ratio of VO_2:lactate was associated with survival in a small cohort of septic, mechanically ventilated patients, while median VO_2 alone was not associated with survival. Whether the VO_2:lactate ratio could be a useful treatment target or prognostic tool warrants further investigation.

References

1. Walkey AJ, Lagu T, Lindenauer PK. Trends in sepsis and infection sources in the United States: A population-based study. *Ann Am Thorac Soc* 12(2):216–20, 2015.

2. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K, EPIC II Group of Inveastigators. International Study of the Prevalence and Outcomes of Infection in Intensive Care Units. *JAMA* 302(21):2323–9, 2009.

3. Angus DC, Linde-Zwirble TW, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the Unisted State: Analysis of incidence, outcome and associated costs of care. *Crit Care Med* 29(7):1303–10, 2001.

4. Fink M. Cytopathic hypoxia in sepsis. *Acta Anaesthesiol Scand Suppl* 110:87–95, 1997.

5. Gattinoni L, Vasques F, Camporota L, Meessen J, Romitti F, Pasticci I, Duscio E, Vassalli F, Forni LG, Payen D, et al. Understanding Lactatemia in Human Sepsis. Potential Impact for Early Management. *Am J Respir Crit Care Med* 200(5):582–9, 2019.

6. Fink MP. Bench-to-bedside review: Cytopathic hypoxia. *Crit Care* 6(6):491–9, 2002.

7. Hayes MA, Timmins AC, Yau EHS, Palazzo M, Watson D, Hinds CJ. Oxygen transport patterns in patients with sepsis syndrome or septic shock: Influence of treatment and relationship to outcome. *Crit Care Med* 25(6):926–36, 1997.

8. Rivers EP, Rady MY, Martin GB, Fenn NM, Smithline HA, Alexander ME, Nowak RM. Venous hyperoxia after cardiac arrest; Characterization of a defect in systemic oxygen utilization. *Chest* 102(6):1787–93, 1992.

9. Shoemaker WC. Relation of oxygen transport patterns to the pathophysiology and therapy of shock states. *Intensive Care Med* 13(4):230–43, 1987.

10. Uber A, Grossestreuer AV, Ross CE, Patel PV, Trehan A, Donnino MW, Berg KM. Preliminary observations in systemic oxygen consumption during targeted temperature management after cardiac arrest. *Resuscitation* 127(March):89–94, 2018.

11. Bihari D, Smithies M, Gimsom A, Tinker J. The effects of vasodilation with Prostacyclin on oxygen delivery and uptake in critically ill patients. *N Engl J Med* 317(7):397–403, 1987.

12. Berg KM, Donnino MW, Callaway C. Looking for CO2: Exploring the novel finding of low respiratory quotient after cardiac arrest. *J Am Heart Assoc* 7(13):1–3, 2018.

13. Friedman G, De Backer D, Shahla M, Vincent JL. Oxygen supply dependency can characterize septic shock. *Intensive Care Med* 24(2):118–23, 1998.

14. Goonasekera CDA, Carcillo JA, Deep A. Oxygen delivery and oxygen consumption in pediatric fluid refractory septic shock during the first 42 h of therapy and their relationship to 28-day outcome. *Front Pediatr* 23; 6:314, 2018.

15. McLellan S, Walsh T, Burdess A, Lee A. Comparison between the Datex-Ohmeda M-COVX metabolic monitor and the Deltatrac II in mechanically ventilated patients. *Intensive Care Med* 28(7):870–6, 2002.

16. Stapel SN, Weijs PJM, Girbes ARJ, Oudemans-van Straaten HM. Indirect calorimetry in critically ill mechanically ventilated patients: Comparison of E-sCOVX with the deltatrac. *Clin Nutr* 38(5):2155-2160, 2018.

17. Sundström Rehal M, Fiskaare E, Tjäder I, Norberg Å, 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 20:54, 2016.

18. Manthous CA, Hall JB, Olson D, Singh M, Chatila W, Pohlman A, Kushner R, Schmidt GA, Wood LD. Effect of cooling on oxygen consumption in febrile critically ill patients. Am J Respir Crit Care Med 151(1):10–4, 1995.

19. Hoeyer-Nielsen AK, Holmberg MJ, Grossestreuer A V, Lee D, Yankama T, Donnino MW, Berg KM. Association Between Oxygen Consumption and Survival in Patients With Sepsis; Society of Academic Emergency Medicine Abstracts. *Acad Emerg Med* 26(S1), 2019.

20. Hayes MA, Timmins AC, Yau EHS, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 24:8–24, 1994.

21. Tuchschmidt J, Fried J, Astiz M, Rackow E. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. *Chest* 102(1):216–20, 1992.

22. Denis Edwards J, Ceri S. Brown G, Nightingale P, M. Slater R, Brain Faragher E. Use of survivors cardiorespiratory values as therapeutic goals in septic shock. *Crit Care Med* 17(11):1098–103, 1989.

23. Astiz M , Rackow EC , Weil MH SW. Early impairment of oxidative metabolism and energy production in severe sepsis. *Circ Shock* 26(3);311–20, 1988.

24. MacLean LD, Mulligan WG, McLean AP, Duff JH. Patterns of septic shock in man--a detailed study of 56 patients. *Ann Surg* 166(4):543–62, 1967.

25. TC V. No Sepsis-induced alterations in pyruvate dehydrogenase complex activity in rat skeletal muscle: effects on plasma lactate. *Shock* 6(2); 89–94, 1996.

26. Shinozaki K, Becker LB, Saeki K, Kim J, Yin T, Da T, Lampe JW. Dissociated Oxygen Consumption and Carbon Dioxide Production in the Post-Cardiac Arrest Rat: A Novel

Metabolic Phenotype. *J Am Heart Assoc* 7(13), 2018.

27. Kreymann G, Grosser S, Buggisch P, Gottschall C, Matthaei S, Greten H. Oxygen consumption and resting metabolic rate in sepsis, sepsis syndrome, and septic shock. *Crit Care Med* 21(7); 1012–9, 1993.

28. Berg KM, Gautam S, Salciccioli JD, Giberson T, Saindon B, Donnino MW. Intravenous thiamine is associated with increased oxygen consumption in critically ill patients with preserved cardiac index. *Ann Am Thorac Soc* 11(10):1597–601, 2014.

29. Bautista-Hernández VM, López-Ascencio R, Del Toro-Equihua M, Vásquez C. Effect of thiamine pyrophosphate on levels of serum lactate, maximum oxygen consumption and heart rate in athletes performing aerobic activity. *J Int Med Res* 36(6);1220–6, 2008.

Figure Legends

Figure 1: Representation of the d-lite (translucent yellow tubing) with gas sampling line, which attaches in-line to the ventilator tubing between the endotracheal tube and the Y-connector, for gas sampling for metabolic measurements.
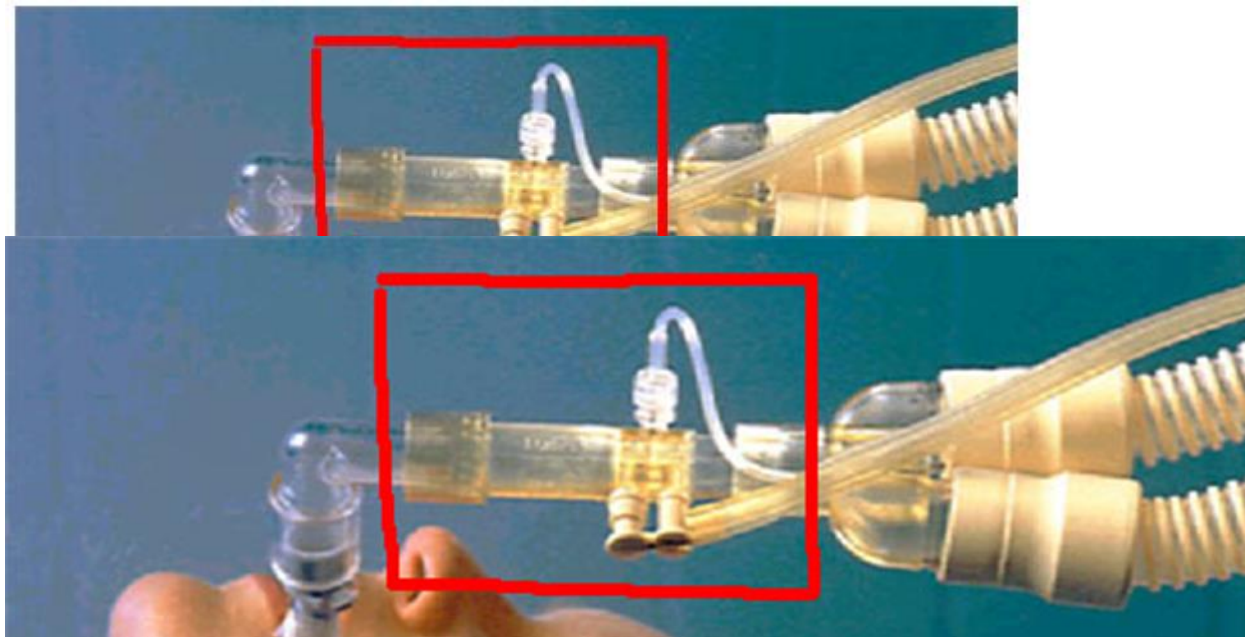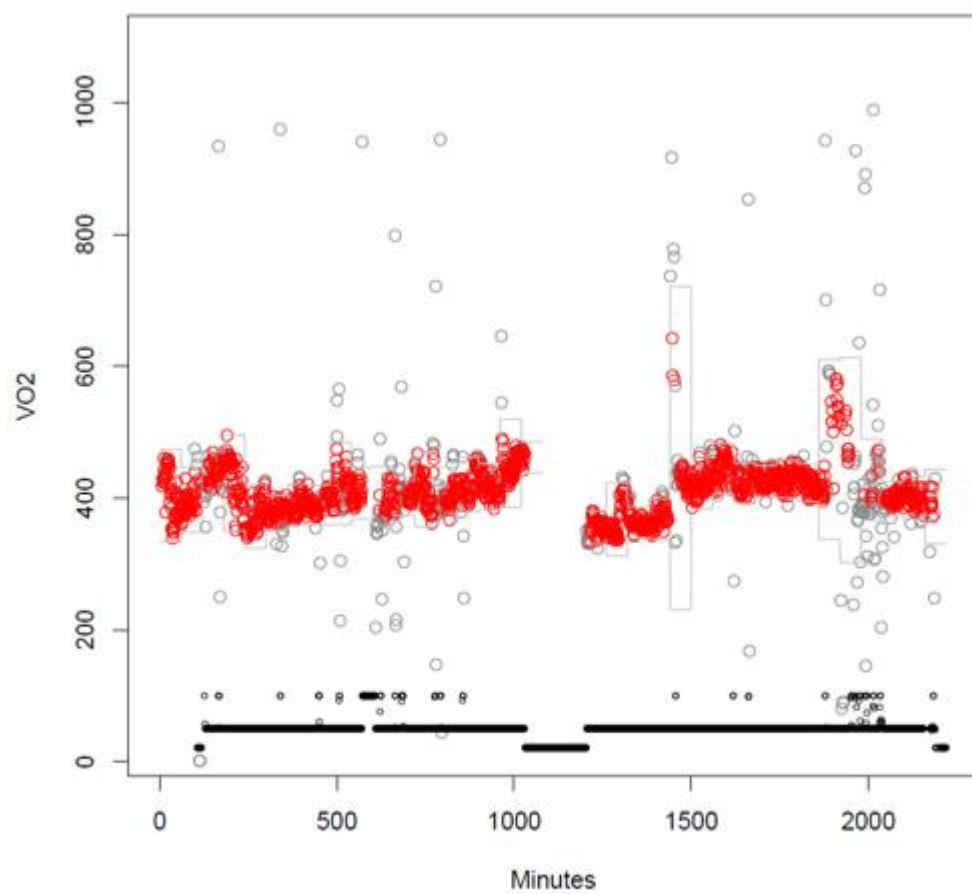
Figure 2a

Figure 3. A flow diagram to illustrate the selection process of septic patients. We consented 168 patients for a larger prospective observational study from which we retrospectively identified 48 septic patients. Two of these were excluded and 46 were included in the analysis.
*Consented not enrolled includes patients of which their legally authorized representative consented, but the patient was not enrolled due to either alternations of ventilator settings or change in goals of care prior to enrollment, [†]Sepsis was defined as a suspected or confirmed bacterial infection with evidence of a systemic inflammatory response, for which a patient was receiving antibiotics during time period of enrollment, [‡] No measurements were saved
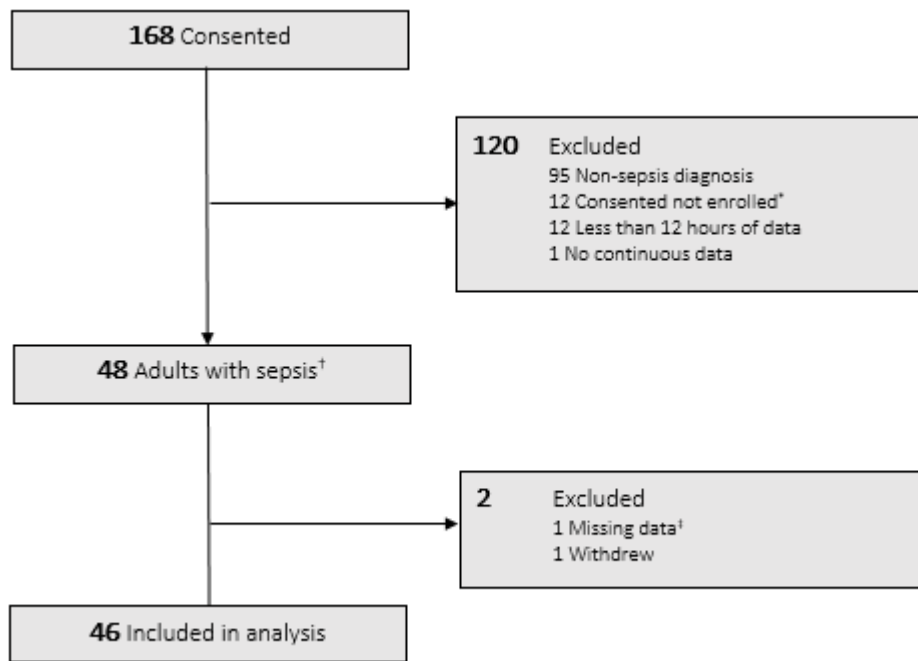
Figure 4: A box plot to illustrate the median initial VO_2:lactate ratio in survivors versus non-survivors. The middle bar in the box represents the median. The lower and upper bar represent the 25th percentile and the 75th percentile, respectively.
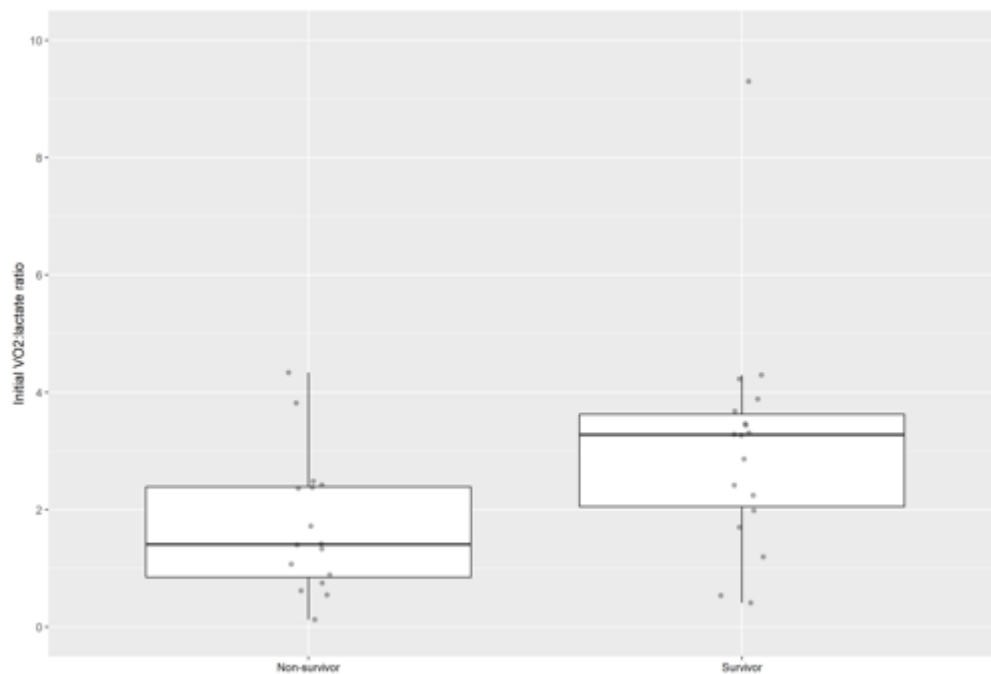
Figure 5: Median of all individual median VCO_2 values by hour in survivors (beige triangles) and non-survivors (blue dots). Lines and bars indicate interquartile range.
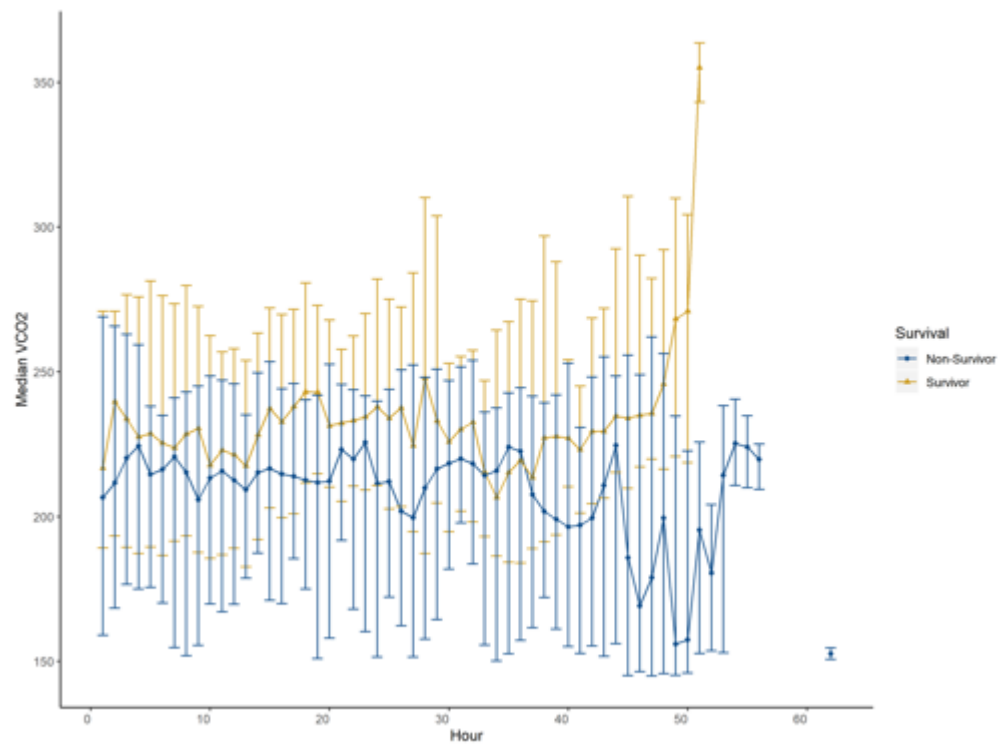
Table 1. Baseline characteristics stratified by survival status

	All (n= 46)	Survivors (n= 28)	Non-survivors (n= 18)
Age (years), mean ± SD	64 ± 14	62 ± 14	69 ± 13
Female, n (%)	24 (52)	16 (57)	8 (44)
Race, n (%)			
1. **Black**	4 (9)	3 (11)	1 (6)
2. **White**	37 (80)	22 (79)	15 (83)
3. **Other**	5 (11)	3 (11)	2 (11)
Past medical history, n (%)			
1. **CAD**	9 (20)	6 (22)	3 (17)
2. **Cancer**	10 (22)	3 (11)	7 (39)
3. **CHF**	4 (9)	3 (11)	1 (6)
4. **COPD**	12 (27)	7 (26)	5 (28)
5. **Diabetes**	18 (40)	11 (41)	7 (39)
6. **Hypertension**	24 (53)	12 (44)	12 (67)
7. **Liver disease**	6 (13)	2 (7)	4 (22)
8. **Renal disease**	7 (16)	2 (7)	5 (28)
9. **Stroke**	7 (16)	3 (11)	4 (22)
ICU settings			
Ventilator settings, median (IQR)			
1. **PEEP, cm H$_2$O**	5 (5, 8)	8 (5, 9)	5 (5, 6)
2. **FiO$_2$, %**	40 (40, 50)	40 (40, 50)	40 (40, 50)
Medication at enrollment, n (%)			
1. **Vasopressor[*]**	33 (72)	18 (64)	15 (83)
2. **Sedation[†]**	45 (98)	28 (100)	17 (94)
3. **Paralytics[‡]**	2 (4)	2 (7)	0 (0)
Medication during enrollment, n (%)			
1. **Vasopressor[*]**	39 (85)	23 (82)	16 (89)
2. **Sedation[†]**	46 (100)	28 (100)	18 (100)
3. **Continuous paralytics[‡]**	6 (13)	5 (18)	1 (6)
Lactate			
1. **Initial lactate, mmol/L, median (IQR)**	1.9 (1.4, 3.0)	1.8 (1.2, 2.7)	2.1 (1.6, 4.8)
2. **Initial lactate ≥ 2 mmol/L, n (%)**	19 (48)	10 (42)	9 (56)
Location of infection, n (%)			
1. **Pulmonary**	29 (63)	20 (71)	9 (50)
2. **Urinary tract**	11 (24)	6 (21)	5 (28)
3. **Brain/meninges**	3 (7)	1 (4)	2 (11)
4. **Bloodstream**	10 (22)	8 (29)	2 (11)
5. **Soft tissue**	3 (7)	1 (4)	2 (11)
6. **Intraabdominal**	8 (17)	6 (21)	2 (11)
7. **Other[§]**	4 (9)	3 (11)	1 (6)

Table 1: SD: standard deviation, CAD: Coronary artery disease, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, IQR: interquartile range, PEEP: Positive end-expiratory pressure, FiO$_2$: Fraction of inspired oxygen, [*]Vasopressors included norepinephrine, vasopressin, phenylephrine, and epinephrine, [†]Sedation included fentanyl, midazolam, propofol, and dexmedetomidine, [‡]Paralytics included vecuronium, rocuronium, cisatracurium, [§] Other locations included one in the endometrium and three were unknown at the time of study period