

2018-05-23

# Oxygen Consumption in Sepsis

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UNIVERSITY OF SAN DIEGO  
Hahn School of Nursing and Health Science  
DOCTOR OF PHILOSOPHY IN NURSING

Oxygen Consumption in Sepsis

by

Julie Graham

A dissertation presented to the  
FACULTY OF THE HAHN SCHOOL OF NURSING AND HEALTH SCIENCE  
UNIVERSITY OF SAN DIEGO

In partial fulfillment of the  
requirements for the degree  
DOCTOR OF PHILOSOPHY IN NURSING

May 2018

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UNIVERSITY OF SAN DIEGO

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Oxygen Consumption in Sepsis

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Committee Member

## Abstract

**Background:** Sepsis is a life-threatening condition that can lead to septic shock and death. With over 300,000 annual cases (AHRQ, 2011) costing a staggering \$1.5 billion (Health Care Utilization Project Brief #185), the importance of sepsis is becoming clear. However, some basic biological mechanisms are poorly understood.

**Study Purpose:** This study investigated the relationships between select demographics, resting energy expenditure (REE), serum lactate, SOFA score mortality index, oxygen consumption [by way of measuring net oxygen consumed, (VO<sub>2</sub>) and net carbon dioxide produced (VCO<sub>2</sub>)], and sepsis.

**Specific Aims:** Aims were to describe 1) patient demographics, serum lactate, SOFA score mortality index, sepsis diagnosis, and O<sub>2</sub> consumption; 2) the difference in oxygen consumption in ICU patients with and without a diagnosis of sepsis; 3a) the relationships between gender, age, REE, height, weight, lactate and VO<sub>2</sub>; 3b) the relationships between gender, age, REE, height, weight, lactate and VCO<sub>2</sub>; and 4) the relationships between age, gender, height, weight, VO<sub>2</sub>, VCO<sub>2</sub>, lactate, SOFA, REE, and sepsis

**Methods:** Data for this quantitative descriptive feasibility study were accessed from two hospital databases.

**Results:** For the total cases ( $N = 21$ ) mean age was 71.2 years ( $\pm 14.1$ ) and mostly female (71.4%). There was a difference in oxygen consumption between the two groups of cases (sepsis and non-sepsis) [VO<sub>2</sub> ( $t 3.919, p < 0.001$ ); VCO<sub>2</sub> ( $t 3.238, p < 0.007$ )].

Strong relationships were found between VO<sub>2</sub> and REE ( $r = .540, p = 0.011$ ), and sepsis ( $\eta = .670, p = 0.001$ ); between VCO<sub>2</sub> and weight ( $r = .619, p = 0.003$ ), REE ( $r = .669, p = 0.001$ ) and sepsis ( $\eta = .608, p = 0.003$ ); and between sepsis and VO<sub>2</sub> ( $\eta = .670, p =$

0.001), VC02

( $\eta = 608$ ,  $p = 0.003$ ), and lactate ( $\eta = 621$ ,  $p = 0.003$ ).

**Implications:** Nurses are at the forefront of monitoring patients with sepsis. While this study utilized a small sample size, significant relationships were found among a number of important clinical variables. Further research is needed utilizing larger samples to test predictive models for sepsis so that nurses can intervene to prevent the deterioration of these patients.

*keywords:* mitochondrial dysfunction; sepsis; sepsis definition; cytopathic hypoxia; downregulation; nicotinamide adenine dinucleotide; electron transport chain

**Copyright**

## Dedication

I would like to dedicate this dissertation to all my preceptors and nursing mentors. Somehow, I have been so fortunate to learn from the very best. To ICU nurses all over the world, who have endured the moral distress of futility, I will keep working for you and hope that maybe one day, you will also feel that you can contribute to the state of the science, because our patients need us to be their voice and their champion. To my immediate and extended family, the Grahams and the Chapadoses, thank you for your love and support. May you all enjoy this with me. To the loves of my life, all of my dogs. May you continue to remind the world that only love and kindness matter.

And to Dr Mitchell Fink. When I found your work, I found a light. A quantum mechanical model of thermodynamics in sepsis, written in the stars. I hope to one day know your story, but for the time being I will be working on the sequel.

Oh, the hours we've spent inside the Coliseum,  
Dodging lions, and wastin' time.  
Oh, those mighty kings of the jungle, I could hardly stand to see 'em,  
Yes, it sure has been a long, hard climb.

... Someday, everything is gonna be smooth like a rhapsody,  
When I paint my masterpiece.

-Bob Dylan

## **Acknowledgments**

My hero and Dissertation Chair, Dr Ann Mayo, RN, DNSc, FAAN, thank you for years of unrelenting guidance, patience, and encouragement. Your commitment to your students is awe inspiring. You are a model of dedication to the future of nursing science and research.

I would also like to thank Dr. Kathleen Stacy and Dr. Ruth Bush as my dissertation committee members. Thank you for indulging me the opportunity to learn the intricacies of your expertise in critical care publication, and statistical analysis, respectively.

Thank you to Carol Scimone for your professional expertise in editing, and your dedication to the success of PhD graduates. You turn stressful final weeks into a joy, and we are all so grateful for you.

Finally, I would like to acknowledge the Treymed company of Wisconsin and their engineers for their generous support in offering me not only access to their Metaphor<sup>TM</sup> metabolic monitoring device, but also for years of technical support and encouragement. I could never have accomplished this without you.



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## **CHAPTER ONE**

### **INTRODUCTION**

#### **Overview of the Problem**

In the United States sepsis results in 146,000-381,000 deaths) and costs \$23.7 billion dollars per year (Torio & Moore, 2016). Over the years, advancements have been made to decrease deaths and cost. Evidence-based standard assessments and treatments have been ‘bundled’ together by The Centers for Medicaid and Medicare Services (CMS) to help hospitals improve mortality and morbidity as well as the costs of sepsis. The current criteria used by clinicians as part of their clinical decision-making for sepsis identification are well documented in the literature to be overly sensitive and under-specific (Singer et al., 2016). This leads to an over-identification of affected individuals, subjecting them to the risks of unnecessary treatment.

Sepsis remains a significant critical issue for hospitals due to the potential for high mortality rates. At a critical point in the progress of sepsis, patients are unable to adequately saturate bodily tissues with oxygen. Oxygen consumption, if utilized as a clinical indicator, may provide evidence that sepsis is present and even becoming a serious issue. While new technologies allow for oxygen consumption to be measured for the purposes of determining the needs of the critically ill patient, it is unknown if having such a measure would contribute to the quality of clinical decision-making, nursing care, and the associated outcomes of that care. As nurses are held accountable for nurse sensitive indicators outlined by CMS, any condition that is monitored by CMS impacts accountability for professional practice. Additionally, awareness of gaps in nursing practice is the necessary platform needed to design studies that have the potential to

improve practice and patient outcomes. Therefore, research on oxygen consumption as it may or may not be related to sepsis is warranted.

This chapter will provide a definition of sepsis and address incidence, risk factors, current recommended treatments (CMS bundle), and ongoing challenges for managing sepsis in the critically ill patient. Additionally, the study problem statement, purpose, specific aims, conceptual framework and methods will be provided to introduce the reader to the study. This chapter will conclude with a discussion on the potential significance of the study.

## **Background**

### **Sepsis**

Until 2016, sepsis was merely understood to be a systemic response to infection. More recently, sepsis is better understood to be a complex *syndrome* of a dysregulated host response to any numerous types of infections (Singer et al. 2016). The underlying pathology of sepsis and causation remains uncertain. However, an inflammatory response to illness is one of several hypotheses (Urden, Stacy, & Lough, 2014, p904).

In 2001, a study was published by Dr. Emmanuel Rivers recommending Early Goal Directed Therapy (EGDT) for sepsis. Early Goal Directed Therapy is guided by fluid resuscitation and oxygen delivery targeting goals of maintaining blood pressure and serum oxygenation (Rivers et al., 2001). Early Goal Directed Therapy was endorsed by The Society for Critical Care Medicine (SCCM) partnering with the Surviving Sepsis Campaign (SSC) to develop inclusion criteria for identification of an inflammatory response syndrome and to establish criteria to guide EGDT for sepsis treatment (Levy et al, 2003).

Per the SSC, sepsis criteria include two or more of the indicators of the Systemic Inflammatory Response Syndrome (SIRS) in the presence of confirmed or suspected infection. The SIRS criteria include:

Temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$

Heart Rate  $>90\text{bpm}$

Respiratory Rate  $>20/\text{min}$

White Blood Cell Count  $>12,000/\text{ml}$  or  $<4,000/\text{ml}$  or  $>10\%$  immature bands

Therefore, infection in the presence of the SIRS response was then known as *sepsis* (Bone et al., 1992).

### **Sepsis Costs**

Costs of sepsis include loss of life as well as treatment expenditures. Despite recommendations for goal directed therapy, mortality remains 25%-30% and 40%-50% when patients present with shock (Cohen, 2015).

Patients hospitalized for sepsis often need the highest level of care. Over half (51%) of sepsis cases require admission to the Intensive Care Unit (ICU) (Angus & Van der Poll, 2013). Patients have multi-system involvement needing close monitoring for early signs of decline, and often need the support of mechanical ventilation (Angus & Van der Poll, 2013). This level of care is the most expensive care in the hospital, averaging \$45,000 per case (Pfundner, 2011).

### **Risk Factors for Sepsis**

There is mixed evidence in the literature about what actually qualifies as a risk factor for sepsis. According to the Sepsis Alliance, age (very young and very old), immunosuppression, and comorbidity tend to make patients be at increased risk for



sepsis. Additional patients at risk are those with burns, indwelling/invasive medical devices (e.g., dental and orthopedic prosthesis) or equipment (e.g., Foley catheters, central lines) (Sepsis Alliance, 2018.). However, there is no published evidence of *causal* relationships between these risk factors and sepsis.

In a sepsis case review of the National Hospital Discharge Survey (NHDS) dataset it was determined that 33% of cases had respiratory infections and 32% of cases had genitourinary infections (Esper et al., 2006). Males more often had a respiratory condition versus females ( $p<0.01$ ) and females more often had a genitourinary condition versus males ( $p<0.01$ ).

In another study, respiratory infections were present in 35% of the sepsis cases followed by genitourinary infection at 25% (Novosad et al., 2016). Per the Centers for Disease Control and Prevention (CDC), respiratory infection and genitourinary infection are two of the most common infections present when patients are admitted to hospital, suggesting an association with sepsis; however, no causal relationships have been determined by reviewing the literature (Hall, 2011).

A large majority (48%-59%) of cases were reported to have gram positive bacteria. However, cases of sepsis have also been known to be associated with all forms of pathogenic microorganisms (Novosad et al., 2016). This analysis also included the type of comorbid conditions associated with race; persons of non-White races with sepsis having more comorbid conditions such as diabetes, human immunodeficiency virus (HIV), chronic renal failure, and alcohol abuse. Persons of the White race with sepsis cases had more diagnoses of cancer and chronic obstructive pulmonary disease (COPD).

Actual causative factors may be numerous involving many mediating and moderating contributors requiring sophisticated research methods that have yet to be utilized in such vulnerable populations of patients. However, designing studies such as randomized clinical trials to prospectively test actual causative factors would be unethical in human subjects' research.

### **Incidence of Sepsis and Comorbidities**

The incidence of sepsis has risen dramatically since the early 1990s when the SCCM first began to describe the syndrome. The incidence has been difficult to determine for at least two decades.

Without a gold standard for sepsis identification, diagnosis has been provider-dependent. For this reason, sepsis cases are difficult to track and incidence is difficult to determine. Estimates of cases are derived from multiple sources, such as claims, death certificates, and International Classification of Diseases (ICD) codes.

One 2006 retrospective analysis of distribution of sepsis cases was conducted using the National Hospital Discharge Survey (NHDS) dataset (Esper et al., 2006). Data captured in the dataset included demographic data, diagnostic codes (ICD) for sepsis, and procedural codes. The 25-year long dataset captured 12,505,082 cases of sepsis.

### **The Effect of Sepsis upon Organ Systems**

Any number of organ systems can be affected by sepsis. Particularly vulnerable systems include the following: respiratory, cardiovascular, central nervous, digestive, and genitourinary.

**Respiratory system.** In sepsis, involvement of the respiratory system pertains to ventilation occurring in the lungs and cellular respiration occurring within the

mitochondria of the cell. Manifestations of sepsis with respiratory system involvement include shortness of breath and may require supplemental oxygen to maintain partial pressure of dissolved oxygen in the arterial circulation ( $PaO_2$ ). Shortness of breath may progress to respiratory failure due to acute respiratory distress syndrome (ARDS), as evidenced by bilateral infiltrates and  $PaO_2$  over  $FiO_2$  (fraction of inspired oxygen) or ( $P/f$ ) *ratio*, of  $<300$  (requires arterial blood gas for evaluation). Acute respiratory distress syndrome can be triggered in sepsis by endovascular injury from cytokine release during the inflammatory process. Respiratory failure requires mechanical ventilation, guided by ongoing evaluation of arterial blood gas targeted at improving  $PaO_2$ . Steroids are not shown to be of benefit when sepsis compromises the respiratory system and should be avoided due to the risk of immune suppression (Confalonieri, Salton, & Fabiano, 2017).

**Cardiovascular system.** In sepsis, involvement of the cardiovascular system pertains to the heart and systemic circulation. Manifestations of cardiovascular involvement can include left ventricular strain and elevated troponin in the absence of any sign or symptom of acute coronary vascular blockage. Damage at the cellular level is believed to be the result of hypoperfusion (inadequate delivery of oxygen to the tissues), resulting in decreased functional capacity of the myocardial tissue. In some instances, inotropic drugs such as Dobutamine can help with cardiac output. Cardiovascular system involvement is generally evaluated by measurement of mean arterial pressure (MAP). A  $MAP < 70\text{mmHg}$  is the threshold for consideration of shock (Levy, 2003). Shock can be triggered in sepsis by capillary leak from low serum albumin from nutritional malabsorption and other causes. Management of cardiovascular compromise can include IV administration of albumin and nutritional support (Bossier et al., 2017).

**Central nervous system.** In sepsis, involvement of the nervous system pertains to cerebral function due to hypoperfusion, sepsis related encephalopathy or toxic encephalopathy from sedating medications. Manifestations of nervous system involvement could be an altered level of consciousness (assessed by Glasgow Coma Scale) and delirium (assessed by the Confusion Assessment Method [CAM]) or CAM-ICU. Delirium, also known as acute confusion, is a sudden change in alertness from baseline with or a waxing and waning in alertness. Management for delirium in a patient that has sepsis would depend on severity and might include treatment of underlying infection, removal of Foley catheter, discontinuation of benzodiazepine medications, or reduction in any use of restraints ([icudelirium.org](http://icudelirium.org)).

**Digestive system.** In sepsis, digestive system involvement pertains to the liver and the digestive tract. Manifestations of liver involvement can include acute elevation of liver enzymes, known as “shock liver.” The digestive system can be affected in sepsis by decreased ability to absorb nutrients, as well as increased risk of gastric bleeding and perforation (believed to be a result of hypoperfusion). Management is aimed at fluid resuscitation to ensure adequate perfusion of tissues with fluids and nutrients (Gazmuri et al., 2017).

**Genitourinary system.** In sepsis, genitourinary system involvement pertains to the kidneys with acute kidney injury (AKI) resulting from pre-renal azotemia or hypoperfusion of the kidney. Manifestations include an increase in elevated serum creatinine (in the absence of pre-existing renal disease) and diminishing urine output. A delicate balance of fluid resuscitation, in addition to the administration of loop diuretics to draw fluid into the distal tubules, can help to reverse AKI. Caution must be used as

there is risk of fluid volume overload with fluid resuscitation versus fluid volume depletion with the use of loop diuretics (Bellomo et al., 2017).

### **Clinical Indicators of Sepsis**

Increasing attention is being paid to at-risk patients for a variety of high cost, high mortality conditions and syndromes. Sepsis is one of the “of concern” syndromes causing healthcare organizations to implement surveillance systems. For patients in critical care settings, a variety of indicators include vital signs, urinary output, and hemodynamic pressures. Two critically important indicators include serum lactate and the Sequential Organ Failure Assessment (SOFA) score.

**Serum lactate.** Lactate is an important consideration in the critically ill patient with sepsis. Along with other signs of vital organ damage, an elevated serum lactate is one of the cardinal signs of tissue damage in a patient with sepsis. Therefore, an elevated serum lactate is often used by clinicians when determining a differential diagnosis of sepsis (Ganesh, Sharma Varghese, & Pillai, 2016).

Lactate is a by-product of anaerobic metabolism. In sepsis, cells are thought to resort to anaerobic metabolism due to hypoperfusion of tissues, resulting in disrupted oxygen delivery to the tissues. Oxygen is metabolized within the cell by powerhouse organelles called the mitochondria. A four-step process along the electron transport chain within the mitochondria reduces oxygen to Adenosine Tri Phosphate (ATP) or usable energy. When cells are deprived of oxygen, they convert to anaerobic metabolism, breaking down protein into much smaller yields of ATP, releasing lactic acid or lactate into the serum. As serum lactate is an acid, this process acidifies the blood, lowering the pH, and contributing to a state of metabolic acidosis.

**SOFA score.** The SOFA score has been validated as a predictor of patient acuity and mortality risk (Raith et al., 2017). In sepsis, it is used as a proxy identifier for sepsis, as it can predict mortality risk. For example, a patient with a SOFA score of 7-9 has a mortality risk matching that of sepsis; and in the presence of infection, matching mortality risk to presence of infection is the most specific way to identify severe sepsis and sepsis shock given the state of the science (Raith et al., 2017). As the score increases, mortality risk increases. For example, score of 0 represents risk of mortality of <10% and an extreme score of 24 would represent 100% mortality. As there is no gold standard diagnostic test or indicator for sepsis, the SOFA score is used in clinical decision-making to determine if a patient has sepsis when there is a suspected infection. SOFA scores have been recently tested for specificity over SIRS and qSOFA (modified SOFA with only three criteria), demonstrating improved specificity for prediction of mortality over SIRS ( $p < 0.001$ ) and qSOFA ( $p < 0.001$ ) with validity of Area Under Receiver Operating Curve (AUROC) 0.753, 99% CI (0.750-0.757). Reliability statistics are not reported.

### **Sepsis Treatment and Management**

In 2001, management of sepsis gained world attention. The algorithmic, goal-directed recommendations from a randomized control trial were accepted as the gold standard for treatment by the SCCM and the SCC was born (Rivers et al., 2001). The recommendations were *protocolized* management aimed at targeted therapy for fluid resuscitation, blood pressure support, and oxygen delivery. Years later, the Rivers et al. study would be criticized for its lack of generalizability, as it was done at a single

medical center. An additional criticism was that the study's outcomes were not compared to outcomes associated with usual/reasonable care (Cho, 2005).

In 2014, a large scale 31-center randomized trial challenging the protocolized care was published in the New England Journal of Medicine (Angus et al., 2014). As a result, the SSC then adopted *goal directed care*, giving providers the freedom to use their best clinical judgment in managing sepsis, provided they were guided by evidence-based targets for mean arterial blood pressure, serum lactate, and time to antibiotics. Recent studies now recommend delivery of antibiotics within one hour of identification of sepsis because it is associated with improved survival (Wallgren, Antonsson, Castren, & Kurland, 2016).

### **Septic Shock**

When the initial sepsis is not managed early in its course, septic shock may be the next critical stage. In septic shock, the patient's circulatory system can no longer be maintained and treatment involves managing the mean arterial pressure (MAP) using vasopressors to maintain a value  $>65$ mmhg. Patients who reach this level of clinical deterioration meet the criteria for a diagnosis of *septic shock* (Lee & An, 2016). The insult to the circulatory system is the result of poor vascular tone or of capillary leakage from decreased absorption of albumin. This cascade results in hypoperfusion. Hypoperfusion is the cornerstone of shock, requiring resuscitation that is directed to restore of functionality of the tissue (Marik, 2010). As part of the resuscitation efforts, current guidelines recommend that patients who are unable to maintain a mean arterial pressure of 65-70mmhg require vasopressors to maintain blood pressure to support tissue perfusion (Dellinger et al., 2013).

## **Sepsis and the Patient in the ICU**

Patients with sepsis who are admitted to the ICU have multisystem problems requiring intensive nursing surveillance and supportive care as well as management from an interdisciplinary team. When sepsis involves organ dysfunction and multiple systems are affected, the patient has progressed to severe sepsis (Angus & Van der Poll, 2013). These patients need organ support for any system involved. Patients need intubation and ventilation for respiratory failure, dialysis for renal failure, screening for and mitigation of delirium, IV bolus fluid resuscitation to address overall failure of other systems (hepatic, gastrointestinal, integumentary) due to hypoperfusion and inotropic infusions for cardiac failure (Angus & Van der Poll, 2013).

When patients are unable to maintain a mean arterial pressure despite fluid volume resuscitation of 30ml/kg of a crystalloid such as normal saline, sepsis has evolved to septic shock and patients require IV vasopressor support (Dellinger et al., 2013). In addition to antibiotic therapy, sepsis patients in the ICU require prophylaxis because they are vulnerable to secondary infection. Additional intensive treatment is frequently needed for thrombosis (deep vein, pulmonary, cerebral), gastrointestinal bleeding, neuromuscular deconditioning and pressure ulcers. Prophylaxis includes tube feeding, anticoagulation therapy and peptic ulcer prophylaxis, physical therapy, and interventions aimed at preventing skin breakdown (e.g., frequent turns, prophylactic dressings, off-loading of pressure areas and bony prominences, perineal care) (Dellinger et al., 2013; Pather & Hines, 2016).



## **Oxygen Consumption in the ICU Patient with Sepsis**

Oxygen consumption in the ICU patient with sepsis is a novel concept that has not been adopted clinically. As mentioned in the introduction, oxygen consumption in sepsis has not been sufficiently studied in vivo (Kreymann et al., 1993). Oxygen consumption as measured for other purposes includes evaluation of metabolic need and cardiac output.

### **Indirect Calorimetry**

Oxygen consumption is the clinical measure of aerobic respiration (Kreymann et al., 1993). Oxygen consumption can be measured clinically by way of indirect calorimetry. Indirect calorimetry measures the percentage of oxygen inspired versus the percentage of carbon dioxide that is expired. This value is then entered in to an equation to determine energy expenditure (Marson, 2004). Traditionally, these measures have been captured in hospitalized patients to determine metabolic demand for prescribing tube feeding (Urden et al., 2014).

### **Cardiac Output (Fick Principle)**

In a steady state, oxygen coming in from the lungs should equal oxygen in the pulmonary vein ( $vO_2$ ), which should also equal oxygen *consumed* ( $V_{O_2}$ ) during normal (aerobic) cellular respiration. Measured levels of arterial  $O_2$  ( $aO_2$ ) and mixed venous  $O_2$  can be inputted into the following equation to determine cardiac output:  $CO = V_{O_2} (aO_2 - vO_2)$ . These measurements are obtained by way of a Swanz-Ganz pulmonary arterial catheter (Rhoades & Bell, 2009).

### **Oxygen Consumption – Lactate Connection**

Serum lactate accumulates during hypoperfusion of tissues. Fluid resuscitation and adequate delivery of oxygen should encourage normal aerobic metabolism and the

elimination of lactate from the serum. However, in sepsis, lactate remains despite fluid resuscitation and often continues to rise (Lee & An, 2016). It is for this reason that elevated serum lactate serves as a differentiator for septic shock over other forms of shock.

Referring to the physiological model of the Electron Transport Chain (see Theoretical Underpinnings below), when cells cannot consume oxygen to produce ATP, protein is used, resulting in the accumulation of the byproduct of anaerobic respiration, lactic acid. Therefore, elevated serum lactate serves as a *distal* proxy measure of impaired oxygen consumption.

Serum lactate should be considered every time a patient triggers an alert for sepsis. Serum lactate should be re-evaluated within 6 hours of initiation of any treatment provided for sepsis (Levy et al, 2003). However, it should be reinforced that serum lactate, while considered a differentiator in sepsis, is a distal proxy measure for impaired oxygen consumption.

### **Problem Statement**

Any type of shock has the potential to result in hypoperfusion. However, somehow, elevated serum lactate, despite adequate fluid volume resuscitation and oxygen delivery, cannot be overcome and therefore, remains a differentiator for all forms of sepsis.

Why then, despite availability of oxygen in the resuscitated septic patient, do cells continue to contribute lactate from anaerobic respiration into the serum? Could it be a dysregulation in the cells' ability to metabolize or *consume* oxygen in the case of sepsis?

There is no gold standard for a diagnosis of sepsis. The determination of sepsis is a *clinical* decision left to the discretion of the interdisciplinary clinical team members, including ICU nurse clinicians. Therefore, more evidence, especially evidence that could serve as a potential specific biomarker for sepsis to ICU nurses, is needed to assist these clinicians. Evidence of cellular dysregulation in the form of oxygen consumption data may yield a much-needed added specific and sensitive indicator for sepsis.

### **Study Purpose and Aims**

The purpose of this study was to investigate the relationships between select available demographics, resting energy expenditure (REE), serum lactate, SOFA score mortality index, oxygen consumption (by way of measuring  $V_{O_2}$  and  $V_{CO_2}$ ), and sepsis.

### **Specific Aims**

This study had four specific aims:

Aim #1: Describe patient demographics, serum lactate, SOFA score mortality index, sepsis diagnosis, and  $O_2$  consumption.

Aim #2: Describe the difference in oxygen consumption in ICU patients with and without a diagnosis of sepsis.

Aim #3a: Describe the relationships between gender, age, REE, height, weight, lactate, and  $VO_2$ .

Aim #3b: Describe the relationships between gender, age, REE, height, weight, lactate, and  $VCO_2$ .

Aim #4: Describe the relationships between age, gender, height, weight,  $VO_2$ ,  $VCO_2$ , lactate, SOFA, REE, and sepsis

## **Theoretical Underpinnings**

The conceptual framework for the study is derived from theories in the field of quantum mechanics in the context of normal human cell physiology (Huether and McCance, 2015; Van Ness, 1969). Quantum mechanics explains a thermodynamic system, a system where energy can change states within a system. The electron transport chain is an in vivo model of a thermodynamic system.

### **Quantum Mechanical Model: Second Law of Thermodynamics**

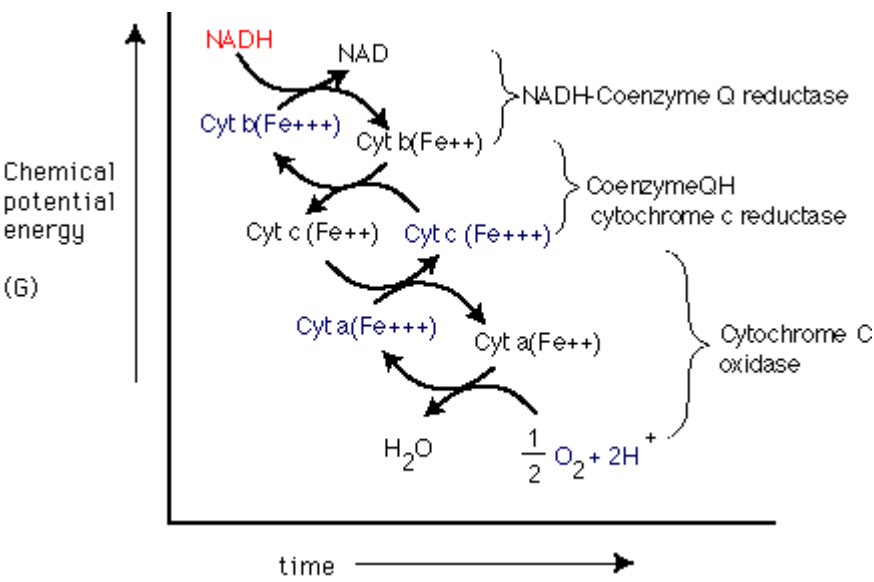
From the discipline of physics, the quantum mechanical model is applying mathematical principles to subatomic particles to explain energy and momentum (Ismael, 2015). Within the quantum mechanical model, the second law of thermodynamics is described. The second law of thermodynamics concerns transfer of energy within a system, for example, an engine (Van Ness, 1969, p52). In an engine, heat is applied to a fuel source, creating a force that drives movement forward. Mitochondria, within the cell, are another example of a thermodynamic system. Energy is not lost within the boundary of the mitochondria, it is only converted to useable energy in the form of ATP.

### **Normal Human Cell Physiology: The Electron Transport Chain**

Normal aerobic cellular metabolism, needed to sustain life, yields energy in the form of ATP from reduction of oxygen along the electron transport chain within the mitochondria (Rhoades & Bell, 2009, p320). Reduction of oxygen occurs along four points within the electron transport chain, with diminishing energy potential over time toward inertia, or in this case, natural death of the cell. The model of the electron transport chain is thermodynamics in vivo (Laisk & Walker, 1989), where fuel (oxygen)

is converted to energy to drive cellular processes. Figure 1 demonstrates the down regulation of energy potential over time, in normal human aerobic cellular metabolism.

Figure 1. The Electron Transport Chain



The overall purpose of many pharmaceuticals is to interfere with damaged processes along the electronic transport chain caused by genetic mutations, diseases and injuries.

**Study Research Conceptual Framework**

The study research conceptual framework demonstrates the relationship between the independent variables and having a clinical diagnosis of sepsis.

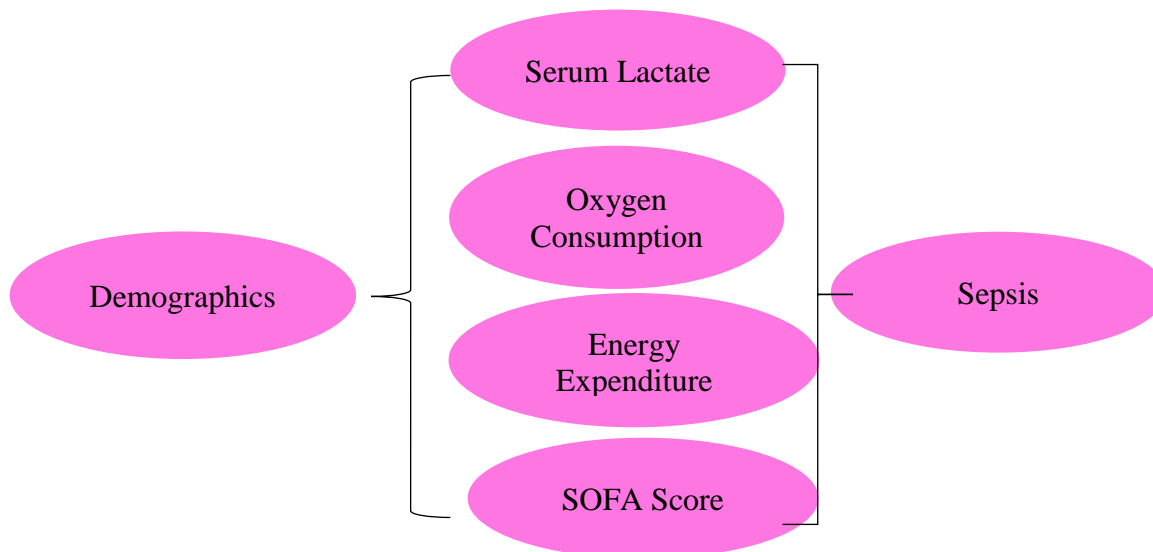


Figure 2. Conceptual Framework

### Serum Lactate and Sepsis

Measurement of serum lactate, as a marker for hypoperfusion in sepsis, has been driving sepsis identification since Emmanuel Rivers first recommended Early Goal Directed Therapy (EGDT) in 2001 (Rivers et al., 2001). Per the International Sepsis Definition Conference of 2001, serum lactate of  $>3.0$  mmol/L is indicative of hypoperfusion in sepsis (Levy et al, 2003). Since the launch of EGDT, the sepsis management apparatus had hinged on the notion that elevated serum lactate in sepsis is due to hypoperfusion, or impaired delivery of oxygen (Rivers et al., 2001).

Around the same time that EGDT was published, an alternative hypothesis was recommended by Dr. Mitchell Fink; that elevated serum lactate, as well as elevated venous oxygen, was in fact, due to mitochondrial dysfunction rather than impaired delivery of oxygen (Fink, 2001). Fink coined the term *cytopathic hypoxia* to describe the notion of mitochondrial dysfunction in sepsis. Fink forewarned implicitly that ignoring

cytopathic hypoxia, and only subscribing to hypoperfusion as an explanation for elevated lactate, was a dangerous path to take. However, his recommendation never gained any traction, and EGDT remained the gold standard for sepsis care (Dellinger et al., 2012).

Dr. Fink was part of the University of Pittsburgh team who published in 2014 that EGDT had no benefit over usual care (Angus et al., 2014). Unfortunately, Dr Fink died in 2015 and was unable to investigate oxygen cytopathic hypoxia as it might be related to sepsis.

### **Oxygen Consumption and Sepsis**

As mentioned above, elevated serum lactate can represent impaired *delivery* of oxygen. However, it can also represent impaired intracellular *consumption* of oxygen. As a result of a shift to anaerobic metabolism, elevated serum lactate can occur due to unavailability of oxygen or due to the inability to convert available oxygen into useful energy. A study published in 1993 demonstrated clinically significant ( $p < 0.001$ ) differences in oxygen consumption were observed between mechanically ventilated patients with sepsis, sepsis syndrome, septic shock, and healthy adults (Kreymann et al., 1993). In this study, oxygen consumption was compromised in the sepsis syndrome and in septic shock patients compared to the healthy adults (metabolic norms) ( $p < 0.001$ ). Study weaknesses included 1) no validity or reliability statistics reported for the instruments; 2) the monitor used was simply described as a “pragmatic oxygen sensor and infrared CO<sub>2</sub> sensor”; and 3) definitions and stratifications of sepsis have changed since 1993, making it extremely difficult to apply this evidence today. Because there is limited research investigating the relationship between oxygen consumption and sepsis, it is important to add to this limited body of knowledge.

### **Energy Expenditure and Sepsis**

Energy expenditure (REE), or resting metabolic rate, is calculated from oxygen consumption ( $V_{O2}$ ) and carbon dioxide production ( $V_{CO2}$ ) in aerobic respiration. The Weir equation is used to determine metabolic need. This is called indirect calorimetry and is usually calculated to determine the rate of tube feeding required for the critically ill (Urden et al., 2014). The Weir equation is as follows:  $EE\ kcal/day = 3.941 \times V_{O2}(L/min) + 1.11 \times V_{CO2}(L/min) \times 1440$  (Stapel et al., 2015).

Since calculation of REE is dependent on measures of oxygen consumption, a difference in oxygen consumption will therefore influence a difference in REE. Thus, if a significant difference in oxygen consumption exists in a patient with sepsis compared to a patient without sepsis, a significant difference in REE would exist in that patient with sepsis compared to a patient without sepsis. Thus, REE may be an important variable in determining the odds of a patient having sepsis.

### **SOFA Score and Sepsis**

In 2002, a manuscript was published comparing the Acute Physiology and Chronic Health Evaluation (APACHE II) score against the Multiple Organ Dysfunction Score (MODS) and the Sequential Organ Failure Assessment (SOFA) score for prediction of mortality in critical illness (Bota, Melot, Ferreira, Ba, & Vincent, 2002).

No significant difference in the performance of the measures in predicting sepsis was found for patients who did not present with shock compared to patients who did present with shock. For patients who did present with shock, SOFA was found to be most predictive of mortality over APACHE II and MODS. The AUROC for the SOFA of



0.750 was significantly different compared to MODS of 0.694 (between means difference  $p < 0.01$ ). The AUROC for APACHE II was not reported.

When the new definition of sepsis was published in 2016, the consensus recommendation for improved sepsis identification was to use the SOFA score to identify patients at risk for sepsis (Singer et al., 2016). Investigators conducting a retrospective analysis using the University of Pittsburgh dataset for patients with *suspected infection* determined that the AUROC for SOFA in predicting mortality was 0.74 compared to the SIRS of 0.64, within a between means difference of  $p < 0.001$ . This group stated that the traditional focus on inflammation and the SIRS response was “misleading” and lacked specificity for sepsis. SOFA was recommended for improved specificity, specifically in ICU patients.

Most recently, findings from a large-scale study (184,875 patients at 182 ICUs across New Zealand and Australia) substantiated the use of the SOFA score to predict mortality in patients with suspected infection who are admitted to the ICU (Raith et al., 2017). This study was also a retrospective database analysis. The AUROC for SOFA at 0.753 was significantly different when compared to the SIRS AUROC (0.589) with a between means difference of  $p < 0.001$ .

Without a gold standard to identify sepsis, clinicians remain dependent on the SOFA mortality index scores for identification of patients at risk for sepsis. A patient with a SOFA score of 8 (20%) to 12 (50%) has a mortality index matching that of a diagnosis of sepsis (Raith et al., 2017). Pertaining to the examples above, SOFA has been repeatedly demonstrated to have superior specificity for predicting mortality over the

APACHE II and MODS. Based on this evidence it will be important to measure the relationship between the SOFA score and sepsis.

### **Summary**

This chapter has introduced the condition of sepsis with background pertaining to the pathophysiology and history of sepsis management. A case for the study has been presented. Chapter 2 will offer a systematic review of the literature to investigate what is currently known about oxygen consumption in sepsis.

## CHAPTER TWO

### Systematic Review

In the 25 years since the original “SEP-1” definition of sepsis in 1992, many patients have died, many lives have been significantly altered, and many resources have been spent while the mortality from sepsis continues to rise. The cost to patients and families in terms of loss and disability are immeasurable. In addition, there is an environmental cost to consider. The downstream effects of decades of empiric, broad spectrum antibiotic use include increasing rates of bacterial resistance and alterations to the human microbiome. Costs to healthcare resources are also considerable. Under the Value Based Purchasing plan, the Centers for Medicare & Medicaid Services (CMS) have enlisted the Hospital Engagement Networks to assist with monitoring of patient safety indicators. The Agency for Healthcare Research & Quality (AHRQ) reports on healthcare delivery costs captured by the Healthcare Cost and Utilization Project (HCUP). Their 2014 report, (HCUP brief #185), described the average cost of treating sepsis in hospital in 2011 as \$45,500 per case, with a total number of cases at 304,367. That is a cost of \$1.5 billion annually on sepsis care (Barrett, Smith, Elixhauser, Honigman, & Pines, 2014).

In October of 2015, CMS launched a campaign to optimize the current state of sepsis care in the United States. As the entity entrusted to monitor quality and ensure patient safety with a goal of reducing mortality, CMS will eventually mandate hospitals to report the incidence of sepsis, as well as measures for sepsis management. Mandatory reporting would apply to all individuals who rule in for sepsis based on inclusion criteria

endorsed by the Surviving Sepsis Campaign; patients must have two or more of the following signs in the presence of confirmed or suspected infection:

Temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$

Heart Rate  $>90\text{bpm}$

Respiratory Rate  $>20/\text{min}$

White Blood Cell Count  $>12,000/\text{ml}$  or  $<4,000/\text{ml}$  or  $>10\%$  immature bands

Reporting was expected to be mandatory by fiscal year 2018, however that target date has been delayed and remains to be determined. Many hospitals are finding these inclusion criteria, based on the Systemic Inflammatory Response Syndrome (SIRS) model, overly sensitive in identifying patients (Graham, Krall, Presente, Saucier, & Butler, 2016). As the SIRS model is an adaptive model, these criteria can be present in adaptive states, such as multiple forms of stress, anxiety, pain, or milder illness.

In February 2016, a new definition of sepsis, “SEP-3,” was introduced. This new definition described sepsis for the first time as a “dysregulated” host response to infection (Singer et al., 2016). The nature of the dysregulated response is yet to be declared. Understanding the dysregulated nature of sepsis offers an opportunity to yield criteria for identification that have increased specificity for sepsis over SIRS.

### **Mitochondrial Dysfunction in Sepsis**

Mitochondrial dysfunction in sepsis has been tested in the laboratory setting; however, its role in sepsis is still unclear. The discovery of a clear relationship between mitochondrial dysfunction and sepsis could potentially provide new information to inform the new definition of sepsis as a dysregulated response. For the purposes of this paper, mitochondrial dysfunction is operationalized as dysregulation of oxygen

consumption along the electron transport chain. Mitochondrial dysfunction has been studied in human cells at the level of laboratory science and is now being tested in animal studies. No clinical evidence exists in the literature to demonstrate what mitochondrial dysfunction in sepsis would look like as a clinical, in vivo manifestation of the disease. The purpose of this paper is to examine the existing scientific evidence regarding the relationship between mitochondrial dysfunction and sepsis.

### **Entropy and Aerobic Respiration**

Mitochondria are intracellular organelles responsible for aerobic metabolism or the production of energy in the form of adenosine triphosphate (ATP). The mitochondria are a thermodynamic system and thus subjected to the second law of thermodynamics. The second law of thermodynamics states that the irreversible natural degradation of matter occurs over time. This concept is referred to as entropy (Van Ness, 1969). Mitochondria are exquisitely designed to create useable energy within the boundary of its system. Energy is not lost in the process, but it is transformed within the system. The mitochondrial system is considered an open system, as it can exchange matter and energy across its boundaries. Thus, mitochondria are subject to entropy (disorder and dysfunction over time) as the system proceeds through its lifespan toward an irreversible, natural death.

### **Sepsis Management**

Although strides have been made since sepsis was first defined in 1992 as the SIRS response to infection, sepsis remains a leading cause of death with a mortality rate of 30% (Bone et al., 1992; Vincent, Martin, & Levy, 2016). Goals of sepsis management include aggressive fluid resuscitation, adequate oxygenation, and early empiric antibiotic

therapy (Seymour & Rosengart, 2015). Treatment recommendations have not changed significantly since 2001 when the Surviving Sepsis Campaign (SSC) championed Early Goal Directed Therapy (Rivers et al., 2001). These recommendations were tested by a National Institute of Health (NIH) funded study which challenged the recommendations and published no difference in outcomes when measured against usual care (Angus et al., 2014). However, one could argue that “usual care” has regressed to mean targets that the SSC has championed and endorsed.

### **Cytopathic Hypoxia and the Electron Transport Chain**

The electron transport chain within the mitochondria creates useable energy for the organism in the form of ATP in normal, aerobic cellular respiration. The process of ATP synthesis consists of four complexes. Each complex represents an area for necessary sequential enzymatic *cytochrome oxidase* activity. Potential for disruption of these normal enzymatic processes occurs when nitric oxide (NO) reacts with ROS creating peroxynitrite (ONOO<sup>-</sup>), leading to further downregulation of normal mitochondrial respiration. This disruption leads to conversion to anaerobic respiration, resulting in accumulation of excess serum lactate in the septic host.

The phenomenon of mitochondrial dysfunction in sepsis was first coined by Dr. Mitchell Fink in 2002, as a process he named “cytopathic hypoxia” (Fink, 2002). Fink’s description of cytopathic hypoxia is a process in which enzymatic reactions along the electron transport chain are disrupted in the presence of nitrous oxide (NO). NO is a substrate produced when cells are exposed in vitro to lipopolysaccharide endotoxin (LPS), a laboratory proxy for bacterial infection. This early process is a *reversible* (capable of recovery). If further disruption of normal respiration occurs, NO devolves

into ONOO<sup>-</sup> yields when NO combines with the reactive oxygen species (ROS), superoxide (O<sub>2</sub><sup>-</sup>). Once ONOO<sup>-</sup> production occurs, disruption is *irreversible* (incapable of recovery). As O<sub>2</sub><sup>-</sup> is generated by NO disruption of enzymatic processes along the electron transport chain, it is only a matter of time before ONOO<sup>-</sup> is produced and mitochondrial dysfunction becomes irreversible (entropic), resulting in cell death.

### **Materials and Methods**

Healthcare literature databases were searched for the review using key terms to elicit relevant literature on mitochondrial dysfunction in sepsis. Articles retrieved were evaluated for inclusion/exclusion (see Study Selection below). A subsequent search was done using terminology derived from themes in the retrieved articles.

#### **Key Terms**

The initial search was conducted using the terms sepsis, mitochondrial dysfunction, and cytopathic hypoxia. The initial review of the literature identified nicotinamide adenine dinucleotide (NAD) as a consistent theme in cytopathic hypoxia. As NAD is also a key term in Fink's conceptualization of cytopathic hypoxia, it was added to the mix of terms for a subsequent search.

#### **Data Sources**

Articles were retrieved from databases PubMed and CINAHL (Cumulative Index of Nursing and Allied Health Literature). The selection process is demonstrated in Table 1.

Table 1.

*Selection of Articles for Review*

Database/Search Engine	Terms Used	Number of Articles Retrieved	Included/Excluded
CINAHL	Sepsis Mitochondrial dysfunction	25	8/17
CINAHL	Sepsis Cytopathic hypoxia	2 *Both were captured by previous search*	1/1
PubMed	Sepsis Mitochondrial dysfunction	576	<i>Deferred</i> , add Cytopathic hypoxia, add nicotinamide, add adenine dinucleotide
PubMed	Sepsis Cytopathic hypoxia	31	6/25
PubMed	Sepsis Mitochondrial dysfunction Cytopathic hypoxia	19 ( <i>of original 576</i> )	4/15
PubMed	Sepsis Mitochondrial dysfunction, Nicotinamide adenine dinucleotide	22 ( <i>of original 576</i> )	4/18

**Study Selection**

Studies of human subjects or human cells, after 2001, full text, available in English from peer reviewed journals, original experimental, quasi experimental, or cohort studies only. Studies examining the relationship between mitochondrial dysfunction in sepsis, using a combination of keywords to serve as search terms (sepsis + mitochondrial dysfunction, sepsis + cytopathic hypoxia, sepsis + mitochondrial dysfunction +



cytopathic hypoxia, sepsis + mitochondrial dysfunction + NAD). After deselecting for duplicates, animal studies, non-English text, editorials, reviews of the literature, and those predating 2001, of the 99 articles retrieved, only 10 were selected to meet criteria for study selection.

### **Data Extraction and Risk of Bias Assessment**

Searches were done solely by the author to eliminate risks to inter-rater reliability. Some variability in instrumentation exists between the studies included in the analysis and where consistent instrumentation may have been used in more than one study, measurements were independent of each other.

Techniques for culture and inoculation of cells of subjects demonstrate consistency as cells were either from individuals with a diagnosis of sepsis, or cells inoculated with lipopolysaccharide (LPS) gram-negative endotoxin.

### **Description of Included Studies**

Characteristics of the included studies are listed in Table 2. All studies were conducted on human cells. Four studies used cells from human patients infected with sepsis or septic shock (platelets, peripheral blood mononuclear cells, skeletal muscle cells, plasma). Six studies were conducted on commercially available human cells (endothelial cells, hepatoma cells, human dermal fibroblasts, renal tube epithelial cells, umbilical vein endothelial cells, colon carcinoma cells). Six studies were laboratory experimental, two were prospective observational, one cohort, one quasi-experimental. Of the laboratory studies, four used a lipopolysaccharide endotoxin as a proxy for sepsis, one used *cytomix* (a commercially available mixture of cytokines), and one used serum from sepsis patients to inoculate commercially available cells. Three studies included

pharmacologic intervention to investigate reversibility of mitochondrial dysfunction in sepsis.

Table 2.

*Articles Included in Review*

Study	Country	Setting	Study Design	Study Population	Instrumentation	Findings
Protti et al. (2015).	Italy	Hospital	Prospective, observational, case control study	Platelets isolated from patients with septic shock, cardiogenic shock, and controls	Lumi-aggregometry Spectro-photometry	Depressed responsiveness of platelets and respiratory chain activity cases (r sq. 0.36, 0.38, 0.43 for the 3 respective complexes measured
Japiassu et al. (2011).	Brazil	Hospital	Cohort Study	Peripheral blood mononuclear cells, isolated from 20 patients with septic shock, 18 uncomplicated post op hips as control	High resolution respirometry	Mitochondrial activity significantly impaired compared to control, with an increasing prevalence in organ failure (r=0.46, p<0.005). Pharmacologic activation of PGC1a and NFE2L2 pathways protected loss of mitochondrial membrane potential and activity (p<0.0002, p<0.00009 and p<0.5 and p<0.0001) respectively
McCreath et al. (2016).	UK	Laboratory	Experimental	Commercially available Human endothelial cells, control & treatment	Fluorimetry, spectrophotometry	Mitochondrial oxygen consumption altered by 16-22% (p<0.05), enzymatic markers (ci Ciii) altered by 32% and 42% (p<0.05).
Garrabou et al. (2012).	Spain	Hospital	Quasi-experimental	19 patients with a diagnosis of sepsis, 20 matched controls from post op hip surgery.	Western blot assay, polarography, spectrophotometry, flow cytometry, Luminex assay	Mitochondrial oxygen consumption altered by 16-22% (p<0.05), enzymatic markers (ci Ciii) altered by 32% and 42% (p<0.05).

Jeger et al. (2015).	Switzerland	Laboratory	Experimental	commercially available hepatoma cells (HepG2) and primary hepatocytes. 2 groups: intervention & matched control	High resolution respirometry	sepsis severity correlated with depressed mitochondrial activity (r squared 0.715) Decrease in respiration (p<0.006 & 0.007) for HepG2 at 24h respiration observed to decrease at 8h (p<0.016). Mitochondrial membrane potential and ATP content decreased in compared to control (p<0.0001)
Trentadue, R. et al. (2012).	Italy	Laboratory	Experimental	commercially available Normal Human Dermal Fibroblasts (NHDF-neo).	Oxygen polarography, Milliplex Map assay	Depressed respiration vs. control (p<0.0001), depressed mitochondrial enzymatic activity (p<0.001 & p<0.01). H2O2 generation increased (p<0.0001) over control.
Quoilin, C. et al. (2014).	Belgium, France	Laboratory	Experimental	commercially available human renal tube epithelial cells (HK-2)	Multiple commercial assays, laboratory reduction procedures, fluorometry, Flow cytometry	NO increased (p<0.0001) NOX-4 increased (p<0.008), cytochrome c was elevated at 6h & 24h (p<0.05, p<0.08). complex 4 activity dropped off in the LPS group (p<0.0001). ATP levels dropped 30% at 6h & 24h (p<0.004, p<0.0007)
Lorente, L., et al. (2011)	Spain	Hospital ICUs	Prospective, multi center, observational	96 septic patients from 6 intensive care units (ICU) in Spain	Spectrophotometry, calorimetry	Higher levels of cytochrome c was associated with long term

						survival at 6 months (p<0.006). cytochrome c activity and predicted survival (p<0.04, p<0.02). The ROC for survival at 6 months was 62% (CI 95%, 0.51-0.74). For cytochrome c activity was 67% (CI 95%, 0.56-0.76, p<0.003).
Apostolova et al. (2011).	Spain	Laboratory	Experimental	Human umbilical vein endothelial cells (HUVEC), treatment and control	Fluorimetry, Electrode (capturing P02 pressure drop), spectrophotometry, Western Blot Assay	NO and ONOO- increased more in the 02 21% group (p<0.05). coincubation with antioxidant reduced NO and ONOO- by 75%.
Khan, A.U., et al. (2002).	USA	Laboratory	Experimental	Commercially available human colon carcinoma line cultured Caco-2 cells.	Multiple commercial assays and laboratory reduction procedures, fiber optic 02 sensor, and polarography.	Oxygen consumption decreased (p<0.05), with a subsequent increase in lactate production (p<0.037) over control

### Common Instrumentation Used

Instruments used for measurement of substrates include spectrophotometry (three studies), high resolution respirometry (three studies), polarography (three studies), fluorimetry (three studies), Western blot assay (two studies), flow cytometry (two studies). Additionally, multiple other assays were used to identify substrates along the electron transport chain, mitochondrial membrane potential, and the presence of ATP.

## **Analysis**

Studies were evaluated to identify themes for analysis. Many differing instruments were used in the studies, and a high degree of variability exists between the substrates measured within the 10 studies included in the review. This illustrates a gap in the current literature for consistency in measurement.

Table 3 demonstrates the most frequently used instruments identified in the review, grouped against the most frequently observed substrates. Elements of mitochondrial function including electron transport chain activity, ATP yield, and mitochondrial membrane potential were measured as common themes within the studies reviewed. Fluorimetry, Polarography, & Spectrophotometry yielded the most frequent observations. Table 2 demonstrates p values of substrates measured (see Findings, Table 2). Of the substrates observed along the electron transport chain, 19 significant p-values were identified for substrates of respiratory chain activity measured by spectrophotometry. The substrates measured included cytochrome c oxidase, NADH-dehydrogenase, ATP hydrolase, & hydrogen peroxide. The matrix demonstrated the most frequent distribution of significant findings in respiratory chain activity.

Table 3.

*Grouped p values (p<0.05) of substrates measured*

	Mitochondrial Membrane Potential	ATP Synthesis	FOS	Respiratory Chain Activity	O <sub>2</sub> consumption
Spectrophotometry			p<0.0001, p<0.005	p<0.05, p<0.001, p<0.01, p<0.006, p<0.001, p<0.001, p<0.001, p<0.002, p<0.001, 0.001, 0.01, p<0.05, p<0.05, p<0.002, p<0.005, p<0.01, p<0.04, p<0.006, p<0.03	
High Resolution Respirometry		p<0.01		p<0.005, p<0.004	
Polarography					p<0.005, p<0.001, p<0.05, p<0.05, p<0.05
Fluorimetry	p<0.0001, p<0.005, p<0.05			p<0.002	

## Results

These p-values were then entered in to Statistical Package for the Social Sciences (SPSS) software for descriptive modeling. P-values for respiratory chain activity of cells cultured in either sepsis serum of LPS endotoxin versus control were not normally distributed, rejecting the null hypothesis and therefore, offering evidence of mitochondrial dysfunction in sepsis consistently among the test cases.

## Discussion

*Time is Toxin.* The articles reviewed in this investigation map out a complex picture of mitochondrial disruption in the presence of sepsis, especially in the context of a gram negative LPS endotoxin. The disruption is dynamic, stimulating the production of reactive nitrogen species (RNS) in the form of nitric oxide (NO), causing eventual, irreversible disruption of multiple complexes along the electron transport chain by inhibiting cytochrome oxidase, resulting in decreased ATP synthesis. However, an earlier study conducted by Borutaite and Brown (1996) demonstrated that irreversibility

(eventual production of ONOO-) only occurs when high levels of NO are generated, and reversibility is possible if the process is interrupted before NO rises above a sub-molecular threshold. Current therapies aimed at fluid resuscitation and oxygen delivery have not demonstrated to have any capacity to halt or reverse this process. As the cascade is triggered by the infecting sepsis-causing agent, the bleak analogy of an accelerated process of entropy in the presence of an LPS endotoxin underscores the urgency of early antibiotic intervention, that is, if there is any hope of reversibility of inhibition of cytochrome oxidase.

Time is toxin, and time to antibiotics, should be given the same urgency as “time is muscle” or “time is brain,” the colloquialisms used to encourage fibrinolytic therapy for an acute stroke, or percutaneous intervention for acute myocardial infarction. A study by Wallgren et al. (2016) investigated mortality associated with antibiotic delay in 61 patients presenting to the Emergency Department with overt sepsis versus covert sepsis. Their findings demonstrated mortality risk associated with time delay to antibiotics. Delays beyond the first hour dropped survival to 20%. The 2016 SSC consensus guidelines recommended administration of antibiotic therapy within one hour after identification of sepsis or septic shock (Rhodes et al., 2017). This was given a “strong recommendation, moderate quality of evidence” under the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, suggesting that the highest quality of evidence existed to correlate antibiotics within one hour to survival.

### **Conclusion**

The articles included in the review demonstrated consistent, statistically significant differences when investigating mitochondrial function in sepsis. The evidence

however remains weak as there is no consistent thread of instrumentation and measured substrate within the base of evidence. As the pooled results for spectrophotometry suggests rejecting the null hypothesis, further investigation is warranted. As the current state of this evidence is limited to laboratory investigation, it remains to be tested in vivo to determine clinical significance for mitochondrial dysfunction as a manifestation of disease in sepsis. In the meantime, our best weapon against sepsis is to protect host cells with *timely* administration of antibiotics, as *time is toxin*.



## **CHAPTER THREE**

### **Study Methods**

#### **Study Design**

This investigation was a retrospective database descriptive study and utilized a hospital evidence-based practice (EBP) project database and an electronic health record (EHR) database. The primary dataset was previously developed for the purpose of collecting metabolic data under an evidenced-based practice model. The original clinical data had been collected comprehensively at discrete patient encounters, once per patient during their stay, for the purpose of determining metabolic need and tube feeding formula/rate.

#### **Potential Significance of Proposed Study**

Improving on the specificity and sensitivity for sepsis identification can only improve each hospital's CMS bundle compliance, appropriateness of care, allocation of resources, and result in the best possible patient outcomes. The addition of oxygen consumption and possibly other independent variables identified in this study may inform a growing list of more appropriate criteria used for clinical decision-making in the identification of sepsis among ICU patients. Addressing this gap has the potential to shift the course of sepsis management for the first time in 25 years.

#### **Statement of Purpose**

The purpose of this study was to investigate the relationships between select available demographics, resting energy expenditure (REE), serum lactate, SOFA score mortality index, oxygen consumption (by way of measuring  $V_{O_2}$  and  $V_{CO_2}$ ), and sepsis. The cases for this study were identified via a metabolic dataset that had been developed for a tube feeding EBP project.

## **Study Aims**

This study had four specific aims:

Aim #1: Describe patient demographics, serum lactate, SOFA score mortality index, sepsis diagnosis, and O<sub>2</sub> consumption.

Aim #2: Describe the difference in oxygen consumption in ICU patients with and without a diagnosis of sepsis.

Aim #3a: Describe the relationships between gender, age, REE, height, weight, lactate, and VO<sub>2</sub>.

Aim #3b: Describe the relationships between gender, age, REE, height, weight, lactate and VCO<sub>2</sub>.

Aim #4: Describe the relationships between age, gender, height, weight, VO<sub>2</sub>, VCO<sub>2</sub>, lactate, SOFA, REE, and sepsis.

## **Setting**

Cases included were from a 12-bed medical ICU within a small community hospital (<150 beds) in Southern California. The population served by this community hospital includes many community members from multiple local skilled nursing facilities that are within close proximity to the hospital. Many patients admitted to this ICU are elderly and frail and are admitted for exacerbations of chronic illness, influenza, healthcare associated conditions (pneumonia, urinary tract infection), and sepsis. Per City-Data.com (2018), the ethnic groups within this community are White 63.3%, Hispanic 18.3%, Asian 11.6%, Black 1.4%, and American Indian 0.5%. The community is somewhat affluent with a median income of \$105,241, and average home cost of \$617,911.

## **Sample**

Patients admitted from June to December 2017 were selected as cases. All case data were extracted from an EBP project database.

**Inclusion criteria:** All patients included in the original EBP project were included as cases in this research study. Specifically, these were patients in the ICU intubated for mechanical ventilation who were anticipated to require tube feeding.

**Exclusion criteria:** Only cases in the original EBP project were included in this research study; there were no exclusion criteria for this research study. However, it should be highlighted that ICU patients who were ventilated but not identified as requiring tube feeding (e.g., NPO status, comfort care) would not have been in the original EBP database; therefore, they were not included in this research study.

## **Study Variable Operational Definitions and Measures**

**Demographics.** Age, weight, and gender were abstracted from the EHR. Age and weight were included because they each can have an effect upon metabolic demand. Two options for gender were available: male or female.

**Serum Lactate.** Serum lactate values are typically used by physicians to determine a differential diagnosis of sepsis. Serum lactate guides fluid volume resuscitation and repeat lactate values are used to inform the provider of patient's responsiveness to treatment. Serum lactate is also considered a current differentiator for septic shock over other types of shock. Serum lactate values were abstracted from the EHR as a continuous numeric value.

**Sepsis versus Non-Sepsis.** There is no gold standard for the diagnosis of sepsis. At the hospital site used for this study, diagnosis of sepsis was made clinically at the

discretion of the physicians. Sepsis diagnosis data were abstracted from the EHR and options included yes or no.

**SOFA Score.** The Sepsis-related Organ Failure Assessment (SOFA) is a mortality index score (range 0-24) and is a calculated number based on six clinical criteria (Glasgow Coma Scale, Platelets, Mean Arterial Pressure, Serum Creatinine, total bilirubin, and Partial Pressure of Arterial Oxygen over Fraction of Inspired Oxygen or P/F ratio). Patient specific values for these criteria are assigned a final score based on the criteria. The SOFA score has gained acceptance as the most specific metric for sepsis.

The SOFA Index score was calculated by the investigator per standardized instructions that are based on abstraction of the six clinical criteria from the medical record and plotted against the “calculator” or value index table (Table 4). A higher score is interpreted as an increased risk of mortality.

Table 4.

*SOFA score mortality risk index criteria*

Variables	SOFA score				
	0	1	2	3	4
Respiratory PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg	> 400	≤ 400	≤ 300	≤ 200*	≤ 100*
Coagulation platelets × 10 <sup>3</sup> /μl <sup>†</sup>	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Liver bilirubin, mg/dl <sup>†</sup>	< 1.2	1.2 ~ 1.9	2.0 ~ 5.9	6.0 ~ 11.9	> 12.0
Cardiovascular hypotension	No hypotension	MAP <sup>  </sup> < 70 mmHg	Dop <sup>‡</sup> ≤ 5 or Dob <sup>**</sup> (any dose) <sup>†</sup>	Dop > 5, Epi <sup>††</sup> ≤ 0.1, or Norepi <sup>††</sup> ≤ 0.1 <sup>†</sup>	Dop > 15, Epi > 0.1, or Norepi > 0.1 <sup>†</sup>
Central nervous system GCS <sup>§§</sup> scale	15	13 ~ 14	10 ~ 12	6 ~ 9	< 6
Renal creatinine, mg/dl or urine output, ml/dl <sup>§</sup>	< 1.2	1.2 ~ 1.9	2.0 ~ 3.4	3.4 ~ 4.9 or < 500	> 5.0 or < 200

**Oxygen Consumption.** Oxygen consumption is the conversion of inspired oxygen (O<sub>2</sub>) to Adenine Tri-Phosphate, or ATP, where carbon dioxide is a by-product of this reaction. For the EBP project, oxygen consumption was measured using the

Metaphor™ metabolic monitor by attaching it to the ventilator circuit to evaluate metabolic demand and was used clinically for the purpose of determining tube feeding requirements. Oxygen consumption was calculated by analysis of gases on inspiration against the net gains/losses of gases on expiration. Oxygen consumption data in the form of VO<sub>2</sub> and VCO<sub>2</sub> (measures discussed below) were abstracted from an evidence-based practice project database.

Table 5.

*Study Variables*

<b>Variable</b>	<b>Operational Definition</b>	<b>Instrumentation/Data Sources</b>	<b>Measures</b>
<b>Demographics</b>	Age, Gender, Weight	EHR	Age in years, Gender (M/F), Weight in kg
<b>Lactate</b>	Serum lactate (lactate dehydrogenase protein in blood)	Electronic Health Record (EHR)	Laboratory value for serum lactate in mmol/L
<b>O<sub>2</sub> Consumption</b>	Net pp O <sub>2</sub> inspired & net pp CO <sub>2</sub> expired	Metabolic Monitor	VO <sub>2</sub> & VCO <sub>2</sub> values in mmHg
<b>REE</b>	Resting energy expenditure	Calculated using EHR data & Weir Equation	Weir Equation: Metabolic rate (kcal per day) = 1.44 (3.94 VO <sub>2</sub> + 1.11 VCO <sub>2</sub> )
<b>SOFA Severity Score</b>	Mortality index (0-24) based on 6 criteria	Calculated using EHR data & SOFA Score Calculator	SOFA Score Calculator: Calculated based on 6 criteria (assessment and lab data) at admission and 48 hours
<b>Sepsis Diagnosis</b>	Clinical diagnosis of sepsis as determined by MD	EHR	Sepsis (yes/no)

## **Instrumentation**

While no instrumentation was expressly used to collect data for this study, instruments were used previously in the clinical setting to obtain the original patient assessment data for the EBP project.

**Metabolic Monitor.** The metabolic monitor used for the earlier EBP project was a Metaphor™ unit developed by TreyMed (Milwaukee, WI). The device is non-invasive and attaches to the ventilator circuit in a similar way that standard end tidal CO<sub>2</sub> monitoring devices attach to ventilators. The Metaphor™ unit is easily attached and removed from a ventilator. No published data exists on reliability for the Metaphor™.

Oxygen consumption is the gold standard for determination of metabolic need in the critically ill patient and globally represented as a Respiratory Quotient (RQ).  $RQ = \text{VCO}_2 \text{ eliminated} / \text{VO}_2 \text{ consumed}$ . Raw scores can range from 1.0-0.7. Raw scores are acceptable for reporting, provided the measurement device has passed internal calibration testing. Mean scores are calculated by summing scores and dividing by number of cases.

For the purposes of this study the two portions of global oxygen consumption are utilized separately: VO<sub>2</sub> (oxygen consumption) and VCO<sub>2</sub> (carbon dioxide production). Each is reported as a range: 0.1 to 1,000ml/min e Accuracy: 2 ml/min plus 7%.

**Weir Equation.** The Weir equation is the gold standard equation for determining resting energy expenditure (REE). The calculation of Metabolic rate (kcal per day) =  $1.44 (3.94 \text{ VO}_2 + 1.11 \text{ VCO}_2)$  guides recommendations for metabolic requirements for nutritional support (tube feeding) in ventilated patients.

Table 6.

*Instrumentation*

<b>Instrument</b>	<b>Description</b>	<b>Validity</b>	<b>Reliability</b>
Metaphor* Metabolic Monitor	FDA 510(k) pre-market cleared device. Device captures many components r/t oxygenation and metabolism. This device will capture O <sub>2</sub> consumption and EE.	VO <sub>2</sub> Oxygen consumption VCO <sub>2</sub> Carbon dioxide production Range: 0.1 to 1000ml/min Accuracy: 2 ml/min plus 7%	No published data
Lab Analysis of Serum Lactate	“Siemens Vista” Laboratory Platform for in-vitro diagnostics	Serum lactate correlation coefficient for Siemens Vista 0.998, R 122	Mean precision repeatability of Siemens Vista for serum lactate 0.03(2.3)
SOFA Score Calculator	The SOFA score, is the gold-standard predictive sepsis mortality index endorsed by the Society of Critical Care Medicine	Improved specificity for prediction of mortality over SIRS (p<0.001) and qSOFA (p<0.001) AUROC 0.753, 99% CI(0.750-0.757)	Cronbach’s alpha for SIRS and qSOFA (α=0.57), for qSOFA and SOFA (α=0.28) and SIRS compared to SOFA (α=0.06)
Weir Equation (1949)	Gold Standard equation for determining resting energy expenditure (REE) and metabolic need; Metabolic rate (kcal per day) = 1.44 (3.94 VO <sub>2</sub> + 1.11 VCO <sub>2</sub> ).	No published data	CI 95%

**Sample Size Calculation**

G-Power sample size calculation yields a desired sample size of 602 using an alpha of .05 and a beta of .20.

**Protection of Human Subjects**

This study was conducted with oversight from two Institutional Review Boards (IRBs). As data were collected from two hospital databases, no human contact was made.

### **Data Acquisition Plan**

After obtaining IRB study oversight, data were extracted from EBP project database for metabolic measurements and the ERH. Data were then deidentified and entered into an Excel spreadsheet and finally entered into SPSS version 23 for statistical analysis.

### **Data Analysis Plan**

To address Aim #1, means and standard deviations were used to describe age, weight, oxygen consumption, and serum lactate and frequencies were conducted for gender, SOFA, and sepsis diagnosis. To address Aim #2, an independent  $t$  test was used to compare the difference in oxygen consumption in ICU patients with and without a diagnosis of sepsis. Aims 3a, 3b, and 4 were addressed using Pearson  $r$  correlations and Etas. To obtain  $p$  values for the Eta statistics, ANOVAs were utilized.

### **Summary**

This study examined oxygen consumption in cases with and without a diagnosis of sepsis. Other variables such as lactate, demographics, and SOFA score were analyzed to understand their relationship to oxygen consumption in sepsis.



## CHAPTER FOUR

### Results

The purpose of this study was to investigate the relationships between select available demographics, resting energy expenditure (REE), serum lactate, SOFA score mortality index, oxygen consumption (by way of measuring  $V_{O2}$  and  $V_{CO2}$ ), and sepsis. The cases for this study were identified via an ICU ventilated patients tube feeding EBP project metabolic database.

This chapter will present the results the study including case characteristics. Results will be presented in order of the identified aims of the study. Of the 21 cases, none had missing data.

#### **Study Aim #1**

Describe patient demographics, serum lactate, SOFA score mortality index, sepsis diagnosis, and  $O_2$  consumption.

To address aim #1, means, standard deviations and distributions for continuous data were conducted. For categorical data, percentages were calculated.

Study sample size was 21 cases. Mean age was 71.2 years ( $SD$  14.1), height 64.4 inches ( $SD$  3.7), and weight 171.3 pounds ( $SD$  51.1). The majority of the sample was female ( $n=15$ , 71.4%). Clinical data included a mean SOFA score of 5.2 ( $SD$  2.2), mean lactate of 2.8 mmol/L ( $SD$  2.5), and mean Resting Energy Expenditure (REE) of 1,823.4 kcal/day ( $SD$  685.6). Sepsis diagnosis for the entire sample was 52.4% ( $n = 11$ ).

Next, to further characterize the sample, the descriptive data was compared by sepsis groups (sepsis versus non-sepsis) (see Table 7 for specifics). There were no significant differences between the two groups in terms of demographics (age, gender,

height, and weight) or SOFA scores. Serum lactate was significantly different between the two groups with the sepsis diagnosis group having higher serum lactate levels ( $t = 3.456$ ,  $p < 0.004$ ). VO<sub>2</sub> and VCO<sub>2</sub> will be discussed in Aim #2 results.

Table 7.

*Case Characteristics by Sepsis Diagnosis*

	All (N= 21)	Sepsis (n=11)	Non-Sepsis (n=10)	Significance (p value)
Age in years, mean (SD)	71.2 (14.1)	73.8 (11.1)	68.4 (17.0)	.393
Female, no. (%)	15 (71.4)	7 (63.6)	8 (80.0)	.997
Height in inches, mean (SD)	64.4 (3.7)	63.0 (3.6)	65.9 (3.8)	.068
Weight in lbs, mean (SD)	171.3 (51.1)	161.7 (53.3)	181.8 (49.0)	.381
SOFA	5.2 (2.2)	4.3 (1.9)	6.0 (2.1)	.070
VO <sub>2</sub> in mmHg, mean (SD)	37.8 (11.2)	30.9 (8.3)	45.5 (8.8)	<b>.001</b>
VCO <sub>2</sub> in mmHg, mean (SD)	34.3 (6.6)	30.5 (3.4)	38.4 (7.0)	<b>.007</b>
Lactate in mmol/L, mean (SD)	2.8 (2.5)	4.2 (2.8)	1.2 (0.3)	<b>.004</b>
REE in kcal/day, mean (SD)	1823.4 (685.6)	1582.9 (475.1)	2087.9 (803.3)	.092

**Study Aim #2:**

Describe the difference in oxygen consumption in ICU patients with and without a diagnosis of sepsis.

To address aim #2, an independent  $t$ -test was used to compare the two groups.

There was a statistically significant difference in oxygen consumption between the two groups of cases (sepsis and non-sepsis) for VO<sub>2</sub> ( $t = 3.919$ ,  $p < 0.001$ ) and for VCO<sub>2</sub> ( $t = 3.238$ ,  $p < 0.007$ ). The VO<sub>2</sub> and the VCO<sub>2</sub> were higher in the non-sepsis group. The  $t$ -test results are presented in Table 7.

**Study Aim #3a**

Describe the relationships between gender, age, REE, height, weight, serum lactate, and VO<sub>2</sub>.

To address study aim # 3a, a Pearson's  $r$  Correlation was conducted for the continuous level variables and Eta for the categorical level variables. (See Table 8).

There were strong positive relationships between V02 and sepsis ( $\eta = .670$ ,  $p < .001$ ) and REE ( $r = .540$ ,  $p < .011$ ), respectively.

Table 8.

*Bivariate Correlations with V02*

<b>Variables</b>	<b>Association with V02</b>	<b>Significance (p values)</b>
Age	$r = .018$	.939
Gender	$\eta = .092$	.692
Height	$r = .369$	.100
Weight	$r = .332$	.142
REE	$r = .540$	<b>.011*</b>
Lactate	$r = -.329$	.145
Sepsis	$\eta = .670$	<b>.001*</b>

**Study Aim #3b**

Describe the relationships between gender, age, REE, height, weight, lactate, and VCO<sub>2</sub>.

To address study aim #3b, a Pearson  $r$  Correlation was conducted for the continuous level variables and an Eta was conducted for the categorical level variables (See Table 9).

There were strong relationships between VCO<sub>2</sub> and sepsis ( $\eta = .608$ ,  $p < .003$ ), REE ( $r = .669$ ,  $p < .001$ ), and weight ( $r = .619$ ,  $p < .003$ ), respectively.

Table 9.

*Bivariate Correlations with VC02*

<b>Variable</b>	<b>Association with VC02</b>	<b>Significance (p values)</b>
Age	$r = -.275$	.229
Gender	$\eta = .108$	.642
Height	$r = .299$	.188
Weight	$r = .619$	<b>.003*</b>
REE	$r = .669$	<b>.001*</b>
Lactate	$r = -.258$	.258
Sepsis	$\eta = .608$	<b>.003*</b>

**Study Aim #4**

Describe the relationships between age, gender, height, weight, VO<sub>2</sub>, VC0<sub>2</sub>, lactate, SOFA, REE, and sepsis.

To address aim #4a, chi square and Eta statistics were used to determine the relationships between the independent variables and the dependent variable (sepsis). There were strong relationships between sepsis and gender ( $\eta = 0.687$ ,  $p = 0.407$ ), V0<sub>2</sub> ( $\eta = 0.670$ ,  $p = 0.001$ ), VC0<sub>2</sub> ( $\eta = 0.608$ ,  $p = 0.003$ ), and lactate ( $\eta = 0.621$ ,  $p = 0.003$ ) (see Table 10).

Table 10.

*Bivariate Analysis with Sepsis as the Dependent Variable*

<b>Independent Variables</b>	<b>Sepsis (yes/no)</b>	<b>Significance (p value)</b>
Gender	<b>0.687<sup>1</sup></b>	0.407
Age	0.197 <sup>2</sup>	0.393
Height	0.406	0.068
Weight	0.202	0.381
V02	<b>0.670</b>	0.001
VC02	<b>0.608</b>	0.003
Lactate	<b>0.621</b>	0.003
SOFA	0.403	0.070
REE	0.377	0.092

Note: <sup>1</sup> Chi square, <sup>2</sup> Eta

### **Study Limitations**

This study had a smaller than required G power sample size of 602. The sample was dependent on the number of patients in an available EBP project database.

Additional study limitations are discussed in chapters four and five.

### **Summary**

This study examined oxygen consumption in critically patients using hospital data bases as the source of data. Differences were discovered between those with and without a diagnosis. Strong relationships were found between important clinical variables and measures of oxygen consumption and sepsis.

## CHAPTER FIVE

### Discussion of Findings

The purpose of this study was to investigate the relationships between select available demographics, resting energy expenditure (REE), serum lactate, SOFA score mortality index, oxygen consumption (by way of measuring  $V_{O_2}$  and  $V_{CO_2}$ ), and sepsis. The cases for this study were identified via a metabolic dataset that had been developed for a tube feeding EBP project.

This chapter will present a summary of the findings, limitations, and strengths of this study. Implications for nursing practice will also be presented.

This study had four specific aims. Each were to describe 1) patient demographics, serum lactate, SOFA score mortality index, sepsis diagnosis, and  $O_2$  consumption; 2) the difference in oxygen consumption in ICU patients with and without a diagnosis of sepsis; 3a) the relationships between gender, age, REE, height, weight, lactate, and  $VO_2$ ; 3b) the relationships between gender, age, REE, height, weight, lactate, and  $VCO_2$ ; the relationships between age, gender, height, weight,  $VO_2$ ,  $VCO_2$ , lactate, SOFA, REE, and sepsis.

### Summary of Study Findings

#### Case Demographic Characteristics

The study cases had a mean age of 71.2 (*SD* 14.1) years with more females ( $n = 15$ , 71.4%) compared to males. Mean height 64.4 inches (*SD* 3.7), and weight 171.3 pounds (*SD* 51.1). The mean age and gender split are reflective of the surrounding community (retirement villages and skilled nursing facilities). There were no significant

differences in age or gender between cases in this sample with a diagnosis of sepsis compared to those without.

### **Case Clinical Characteristics**

Clinical variables for this study included measures of oxygen consumption ( $V_{O_2}$ ,  $VC_{O_2}$ ), resting energy expenditure (REE), serum lactate, mortality index (SOFA score), and sepsis. Sepsis diagnosis for the entire sample was 52.4% ( $n = 11$ ). Specific results for  $V_{O_2}$ ,  $CO_2$ , and REE clinical variables are available in chapter four. Of interest here is the mean scores for  $V_{O_2}$ ,  $CO_2$ , and REE for those cases with a diagnosis of sepsis were significantly lower when compared to those without. Clinically, this possibly could be interpreted as meaning that despite available oxygen and adequate tissue perfusion, normal metabolism is altered in sepsis, perhaps reflecting mitochondrial injury. However, there are no known cutoff scores and/or ranges or standards established for evaluating oxygen consumption ( $V_{O_2}$ ,  $VC_{O_2}$ ) or REE in sepsis. This information among patients with sepsis in an ICU represents a novel study finding and warrants further research.

The mean serum lactate level for cases with a diagnosis of sepsis was higher (mean 4.2mmol/L; *SD* 2.8) and significantly different from those without a diagnosis of sepsis (mean 1.2mmol/L; *SD* 0.3). Using the 2016 Clinical Practice Guideline from the Surviving Sepsis Campaign (SSC) a patient would be considered ruled in as suspicious for sepsis for any value greater than 2mmol/L. The mean score for cases in this study with a diagnosis of sepsis attained that threshold, therefore it was important that cases were examined by sepsis diagnosis versus no sepsis diagnosis.

The SOFA score is used to predict mortality among ICU patients. The mean SOFA score for the entire sample was 5.2 with no significant difference between cases

with a diagnosis of sepsis compared to those without. A SOFA score of 5.2 reflects a low mortality index of approximately 15% (Raith et al., 2017). This is lower overall than the mortality risks associated with sepsis-induced septic shock, which are between 25% and 50% (Cohen, 2015). Therefore, for the total cases in this study were at low risk for death. The mean SOFA score for the sepsis group was 4.3(*SD* 1.9), and for the non-sepsis patients 6.0 (*SD* 2.1). The difference is not significant ( $p=0.070$ ), however, it is an interesting finding as a higher score is generally expected to be associated with a diagnosis of sepsis.

### **Sepsis and Oxygen Consumption**

For this study, two measures of oxygen consumption were examined separately, VO<sub>2</sub> and VCO<sub>2</sub>. For VO<sub>2</sub>. As stated previously, there have been no prior studies to offer clinical findings for oxygen consumption in sepsis, making these clinical findings unique in the field of sepsis.

Strong positive relationships between V02 and sepsis ( $\eta = .670, p<.001$ ) and REE ( $r = .540, p<.011$ ), respectively, were identified, and strong relationships between VC02 and sepsis ( $\eta = .608, p<.003$ ), REE ( $r = .669, p<.001$ ), and weight ( $r = .619, p<.003$ ) respectively. Strong relationships were also identified between sepsis and gender ( $\eta = 0.687, p = 0.407$ ), V02 ( $\eta = 0.670, p = 0.001$ ), VC02 ( $\eta = 0.608, p = 0.003$ ), and lactate ( $\eta = 0.621, p = 0.003$ ).

More research is needed examining these potentially important study findings.

### **Limitations of the Study**

Study limitations are common when using a secondary dataset for analysis. A sample of 21 cases were utilized for this study that were obtained from an EBP project.



The data for this study were extracted from the EBP project database and EHRs. Therefore, the data had not been collected for the purpose of prospectively investigating the difference in oxygen consumption between sepsis versus non-sepsis patients. This limited the amount of cases as well as the number of variables. Had a prospective study been conducted, additional variables would have included ethnicity, socioeconomic status, mean arterial pressure (MAP), and suspected sources of infection and the timeline for data collection would have been extended to obtain the calculated sample size ( $N = 602$ ).

Additionally, a selection bias may have been present in this study. The data were originally collected to determine the nutritional needs of patients admitted to the ICU who were being considered for tube feedings. Therefore, potential cases where tube feeding was contraindicated (e.g., nutritionally stable, NPO status, comfort care status) were eliminated from this study. It is recommended that inclusion criteria for future studies include a broader range of nutritional status among the ICU patients.

Finally, all reported results for which inferential statistics determined the findings in this study should be viewed with caution due to the small sample size ( $N = 21$ ). This study statistically was underpowered.

### **Study Strengths**

Many studies utilizing clinical data are cost prohibitive to conduct. This study incurred no such costs because the data were already available. While this study was completed with a small sample size, there were considerably large effect sizes demonstrated. Therefore, this investigation has the potential to contribute to the design of future studies. In that sense, it may be considered a feasibility study (Arain, Campbell,

Cooper, & Lancaster, 2010). Finally, this is the first study to examine oxygen consumption in patients with sepsis and therefore, makes a significant first step in understanding important clinical relationships that may eventually lead to predictive models to prevent and manage sepsis in critically ill patients.

### **Study Implications**

Sepsis can be especially difficult to prevent in patients, especially older adults. Sepsis represents a significant management challenge for healthcare professionals, because it often leads to septic shock and death among their patients. Nurses are positioned on the frontline level to prevent and/or to be alert for signs of sepsis. Additionally, they may offer opportunities to slow the decline of sepsis into deadly cases of septic shock when the appropriate types of clinical data are available (Schorr, 2016). As this study pertains to clinical observations of indicators in sepsis, it draws a particular appeal to nursing practice and research. Study implications will be discussed here, including opportunities for nursing practice and nursing research.

### **Nursing Practice**

Nurses have the opportunity to champion themselves as experts in clinical surveillance. Objective clinical measures such as vital signs, lab values, wave form tracings, and pressure readings that are captured daily during clinical monitoring may be utilized as triggers of clinical deterioration, thus providing opportunities to intervene. Surveillance differs from monitoring in that it utilizes data in a systematic way that is goal-directed for the purpose of initiating rapid, appropriate interventions (Giuliano, 2017).

While this study utilized a small sample, it represents the first step that may eventually offer a predictive model for sepsis that employs one or more variables representing oxygen consumption, novel variables. Oxygen consumption currently is easy to measure; it is already being utilized to determine the metabolic needs of ICU patients. Practically, nurses could use falling measures of oxygen consumption to intervene and prevent untoward clinical outcomes such as further deterioration of patients with sepsis.

### **Nursing Research**

A number of subsequent research studies can be recommended to continue this study's line of inquiry. These include further expansion of the study to include more variables that are often included in other sepsis studies (mean arterial pressure, time to first antibiotic, survival to discharge) and other variables that might contribute to a phenotype model (ethnicity, immunologic profiling, and other biomarkers). Alternately, a larger scale prospective study or secondary analysis of existing larger metabolic-type databases may offer the opportunity for improved statistical power and the generation of a meaningful predictive model for sepsis.

There have been no earlier studies identifying measures of oxygen consumption as a significant biomarker for sepsis. Such a specific biomarker for sepsis would be a prudent next step. A larger scale analysis could identify a sensitive intercept where oxygen consumption starts to trend down even prior to the major signs of infection. This could offer for the first time, a biomarker for an early identification of sepsis.

## **Summary**

The purpose of this study was to investigate the relationship between oxygen consumption and sepsis. Secondary databases were accessed for the purpose of conducting the study statistical analysis. Utilizing these secondary databases came with certain limitations. However, the study findings did identify a statistically significant difference in measures of oxygen consumption (VO<sub>2</sub> and VCO<sub>2</sub>) in sepsis cases when compared to non-sepsis cases as well as some important clinical variables that were related to VO<sub>2</sub>, VCO<sub>2</sub> and sepsis.

## **Conclusion**

The mortality risk for sepsis remains high, 25% - 50% (Seymour & Rosengart, 2016). Per the Healthcare Cost and Utilization Project (HCUP) report, the average cost of treating one case of sepsis in the hospital is \$45,500 amounting to \$1.5 billion annually being spent on sepsis care (Barrett et al., 2014).

There is no gold standard for the diagnosis of sepsis. The determination of sepsis is a clinical decision left to the discretion of the interdisciplinary clinical team members, including ICU nurse clinicians and physicians. In 2016, the Third International Consensus definition of sepsis was published (Singer et al., 2016). This definition rejected the 25-year-old notion of the SIRS response and offered that sepsis was a “dysregulated” host response to infection. No operational definition has been offered to explain the dysregulated nature of this host response to infection. Evidence of cellular dysregulation in the form of oxygen consumption may yield a much-needed added specific and sensitive biomarker for sepsis. This study has contributed some of the first tentative, preliminary findings to launch further scaled-up research studies.

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## Appendix

5/7/2018

University of San Diego Mail - Fwd: IRB-2018-392 - Initial: Initial - Exempt



Carol Scimone &lt;cscimone@sandiego.edu&gt;

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### Fwd: IRB-2018-392 - Initial: Initial - Exempt

1 message

**Julie Graham** <jgraham@sandiego.edu>  
 To: Carol Scimone <cscimone@sandiego.edu>

Mon, May 7, 2018 at 4:05 PM

Hi Carol!

I don't think this attached to my last email... The forward below is my IRB letter. I don't think I received a hardcopy but I will check. Do you if this copy can be converted to a word document or pdf? I tried on my end but not having much luck!

Julie =)

----- Forwarded message -----

From: <irb@sandiego.edu>  
 Date: Tue, Mar 27, 2018 at 9:44 AM  
 Subject: IRB-2018-392 - Initial: Initial - Exempt  
 To: amayo@sandiego.edu, jgraham@sandiego.edu



Mar 27, 2018 9:44 AM PDT

Julie Graham  
 Hahn School of Nursing & Health Science

Re: Exempt - Initial - IRB-2018-392, Resting Oxygen Consumption in Sepsis (ROCS)

Dear Julie Graham:

The Institutional Review Board has rendered the decision below for IRB-2018-392, Resting Oxygen Consumption in Sepsis (ROCS).

Decision: Exempt

Selected Category: Category 4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Findings: None

Research Notes:

[https://mail.google.com/mail/u/0/?ui=2&ik=db5489978f&jsver=awrWbfDFcFs.en.&cbl=gmail\\_fe\\_180429.15\\_p3&view=pt&search=inbox&th=1633cdaa012ab78b&siml=](https://mail.google.com/mail/u/0/?ui=2&ik=db5489978f&jsver=awrWbfDFcFs.en.&cbl=gmail_fe_180429.15_p3&view=pt&search=inbox&th=1633cdaa012ab78b&siml=)

5/7/2018

University of San Diego Mail - Fwd: IRB-2018-392 - Initial: Initial - Exempt

## Internal Notes:

*Note: We send IRB correspondence regarding student research to the faculty advisor, who bears the ultimate responsibility for the conduct of the research. We request that the faculty advisor share this correspondence with the student researcher.*

*The next deadline for submitting project proposals to the Provost's Office for full review is N/A. You may submit a project proposal for expedited or exempt review at any time.*

*Sincerely,*

*Dr. Thomas R. Herrinton*  
*Administrator, Institutional Review Board*

*Office of the Vice President and Provost*  
*Hughes Administration Center, Room 214*  
*5998 Alcalá Park, San Diego, CA 92110-2492*  
*Phone (619) 260-4553 • Fax (619) 260-2210 • [www.sandiego.edu](http://www.sandiego.edu)*