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Physiologic Capacity as a Predictor of Postoperative Complications and Associated Costs in Three Types of Oncological Surgeries

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Abstract

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by

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M.A., Tulsa University, 1985

B.S., Oral Roberts University, 1975

Dissertation Submitted in Fulfillment

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Abstract

An estimated 12 million individuals undergoing non-cardiac surgery in the United States each year will experience postoperative complications. The costs of complications are manifested in the growing healthcare economic burden and patients reduced quality of life, long-term survival, and future economic productivity. This research, launched from a pilot study, is supported by the underlying theory is that physiologic capacity may define the degree of physiologic reserve that determines an individual‟s ability to adapt to perioperative stress, and the requirements for that adaptation may be different for each surgical procedure. The hypothesis of this dissertation study is: *physiologic capacity is a predictor of postoperative complications and associated costs in three types of oncological surgery: Esophagectomy, hepatectomy and radical cystectomy.*

This study produced four major findings: a) risk predictors of postoperative complications *change according to the surgical procedure*; b) predictive risk threshold levels *change according to the surgical procedure;* c) predictive models for each surgical type also *predicted length of stay and hospital costs*, and d) significant *trends identified the type of complication and when complications were most likely to manifest* for each of the three surgical types. These findings compel next step validation to refocusing study design according to surgical types. Implications for social change entail a paradigm shift from subjective to objective phenotypic physiology risk assessment affecting standards, policy, procedure, and decision-making changes in the healthcare and insurance industry and physician/surgeon practice, resulting in better patient outcomes, fewer surgical complications, and increased quality of life.

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Dedication

I dedicate this work to all the surgical patients who were trail blazers as part of this study. Who exercised to exhaustion and underwent surgery not knowing what their outcome would be, so that surgical patients in the not too distant future might have the opportunity to reduce their risk or avoid postoperative complications.

I also dedicate this work to my two puppies, Remy and Rueger, who never once whimpered or complained when we missed the majority of our nightly walks because I was engrossed in reading, writing, or my computer screen. They were relegated to only seeing the backside of me sitting at the computer with too frequent interruptions to throw a ball or give a kiss. Through it all, any tidbit of attention was welcomed with ecstatic tail wagging, sparkling eyes and a hopeful anticipation that I would stop what I was doing and devote attention to them. Sorry guys, I'll make it up to you by playing ball to your heart's content.

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Lastly, to all my friends who endured a weekly update for 3 ½ years on what has been and will continue to be one of my greatest passions. Although this chapter has come to an end, I am far from being finished and more excited than ever about this vital work that will change so many lives.

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Chapter 1: Introduction to the Study

Background of the Study

An estimated 30 million individuals undergo non-cardiac surgery in the United States each year. Up to 10% of these patients will experience a major adverse cardiac event (Potyk & Raudaskoski, 1998, p. 164; Jassal, 2006, p. 1). Patients with postoperative myocardial infarction are estimated to have a 50% or greater reduction in their 2-year survival rate (Mangano, 1998, p. 162). Deveraux et al., (2005, p. 628) reported a 4% incidence of MI in patients undergoing nonoperative surgery. The incidence of major adverse pulmonary events after abdominal surgery ranges from 9% to 40% (Arozulla, Daley, Henderson, & Khuri, 2000, p. 847). A United States Department of Veterans Affairs study reported that the occurrence of postoperative complications independently reduced the 30-day survival rate by 69% in an 8-year study (Khuri, Henderson, DePalma, Mosca, Healey & Kumbhani, 2005, p. 336). The same study reported that 7 of the top 12 predictors of 30-day mortality were postoperative complications. More specifically, postoperative pulmonary complications and wound infection reduced median long-term survival by 87% and 42%, respectively. In addition, Khuri et al. (2005, p. 339) reported that the median cost of an operation in general surgery is estimated to increase approximately 5-fold when major adverse pulmonary events occur.

Current preoperative risk assessment strategies have not kept pace with the technical and therapeutic advances achieved in the clinical practices of anesthesia, surgery, and postoperative care medicine (Finlayson & Birkmeyer, 2001). According to the 2003 Practice Advisory for Preanesthesia evaluation (a report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation), a pre-anesthesia evaluation is considered a basic element of anesthesia care and serves many important functions, including the preoperative assessment and quantification of the patient‟s postoperative risk. Despite the importance of preoperative assessment, at present there is no accepted objective means of quantifying a patient‟s overall risk for postoperative complications. Furthermore, an exhaustive literature search (see chapter 2) regarding investigating a potential association between physiologic capacity as a preoperative risk predictor and overall hospital costs and length of stay resulted in no findings of publications for this association.

Problem Statement

According to Potyk and Raudaskoski (1998, p.164), an estimated 30 million individuals will have non-cardiac surgery in the United States each year. Up to 50% of these individuals will experience some type of postoperative complication and adversely impact the cost of care, quality of life, and survival. Recent research has shown that parameters of physiologic capacity are statistically significant objective predictors of who will and who won‟t have postoperative complications (Hightower et al., 2010). However, a gap in understanding the relationship between the parameters and surgical types has created some conflicts. Therefore, there is a need for research that examines the predictive relationships between surgical types and physiologic capacity parameters for each surgical type in order to determine the likelihood of postoperative complications.

Additionally, there is a need for research to investigate the predictive parameter(s) of surgical types for prediction of hospital costs and length of stay.

Purpose of the Study

The purpose of this quantitative study investigated: (a) the relationship of surgical type and the parameter(s) that are predictors of postoperative complications, (b) the relationship of surgical type on thresholds that differentiate between those who did and did not experience postoperative complications, and (c) the predictive associations between risk parameter(s) and hospital costs and length of stay.

Nature of the Study

Three study aims were applied to a retrospective data analysis of three heterogeneous cancer surgeries, namely esophagectomy, radical cystectomy, and hepatectomy that will test this hypothesis: (a) To determine if each surgical type has the same or different parameter(s) that are predictors of postoperative complications, (b) To determine if each surgical type has the same or different thresholds that differentiate between those who did and did not experienced postoperative complications, and (c) To determine if a correlation exists between risk parameter(s) and associated hospital costs and length of stay. For each surgical procedure, Cardiopulmonary Exercise Test (CPET)-derived parameters were compared between those patients who developed postoperative complications and those who did not. Predictive parameters common to two or more surgeries and predictive parameters unique to each surgery and associated costs have been identified.

Research Questions and Hypotheses

This study sought to answer the following three hypotheses and associated research questions:

Research Question 1: Are different surgical procedures associated with different predictive physiologic capacity parameters?

H1 Null: Different surgical procedures will have no association with different physiologic capacity parameters, as measured by the CPET test.

H1 Alternative Research: Different surgical procedures will have significant association with different physiologic capacity parameters, as measured by the CPET test.

Research Question 2: Are there different threshold ranges that stratify risk for each surgical type?

H2 Null: Threshold levels that stratify risk of each surgical type, as measured/determined by the associative predictive parameter, will demonstrate no significant difference.

H2 Alternative Research: There will be a significant difference in threshold ranges that stratify risk for each surgical type, as measured/determined by the associative predictive parameter.

Research Question 3: Is there a correlation between risk parameters and collateral consequences of hospital costs and length of stay?

H3 Null: No significant correlation exists between risk parameters, as measure/determined by the associative predictive parameter, and collateral consequences as measured by hospital costs and length of stay.

H3 Alternative Research: A significant correlation exists between risk parameters, as measure/determined by the associative predictive parameter, and collateral consequences as measured by hospital costs and length of stay.

Theoretical Base

There are many theories that explain how the human body works. Even focusing more narrowly on theories related to physiologic capacity include several major biological system theories including cardiovascular, respiratory, cellular, and heat dissipation systems. Because all biological systems rely on energy to complete their functions, the choice for this study concentrated on the theory of energy metabolism and two associated theories (oxygen delivery and oxygen utilization theories). The primary role of the cardiorespiratory systems is to supply oxygen to cells for the purpose of releasing energy to organs, muscles, and other biological functions needed to meet the energy demands for life. A series of studies demonstrate that similar to exercise, the postoperative recovery period poses special challenges to physiologic capacity because the energy requirement, and therefore oxygen requirement, is greatly increased (Bland, Shoemaker, & Cobo, 1985; Shoemaker, Boyd & Kim et al., 1971; Shoemaker, Montgomery, Kaplan, et al., 1973; Shoemaker, Appel, & Kram, 1992; and Shoemaker, Appel, & Kram, 1993). Therefore, the foundational theories of energy metabolism, oxygen delivery and utilization play important roles in evaluating the physiologic indicators that may be predictors of postoperative complications.

To evaluate the efficiency of energy metabolism, gas exchange data is captured during cardiopulmonary exercise testing (CPET) which employs purposefully and systematically increasing the energy demand, or intensity level in a controlled environment. The data on physiologic capacity parameters (many related to oxygen consumption and utilization) derived from CPET form crucial insight into a surgical patient‟s ability to meet the energy demands during the stressful postoperative period (Wasserman, 2005, p. 18). While evaluation of a person‟s cardiovascular, respiratory, and cellular systems is not new, the way that it is now measured and evaluated is new. Computers and rapidly responding gas analyzers make it possible now to evaluate and analyze individual parts and the systems as a whole in a quantitative way. This allows physicians and researchers to move beyond testing for organ functionality and disease only. While the knowledge of the pathophysiology of exercise is growing, the application toward identification of predictive parameters of postoperative complications is still new. The goal of this study is to extend the knowledge base in the predictive area.

Definition of Terms

Basic gas exchange terms:

- Aerobic – with oxygen. Work performed at a rate in which oxygen is sufficiently supplied on a bases that meets the demands
- Anaerobic – without oxygen. Work performed at a rate which exceeds the body‟s ability to supply oxygen to meet the demands
- Anaerobic Threshold (AT, L/min., mL/min., or mL/kg/min.) – Oxygen uptake at which sustained supplemental anaerobic production of carbon dioxide, VCO_2, can be detected by gas exchange analysis.
- Potential Energy - stored energy

- Kinetic energy – energy involved in the production of work
- Metabolic energy – physical changes occurring in the body as result of energy expenditure
- Efficiency – a percentage of energy input that appears as useful work
- Oxygen debt – occurs when O_2 is insufficient to meet demands
- Oxygen uptake (VO_2, L/min., mL/min., or mL/kg/min.) - oxygen extracted from inspired gas.
- Carbon dioxide output (VCO_2, L/min., mL/min., or mL/kg/min.) - carbon dioxide exhaled.
- Peak oxygen uptake (P-VO_2, L/min., mL/min., or mL/kg/min.) - highest oxygen uptake achieved during maximal effort (the point at which the patient stops the test).
- Oxidative energy reserve capacity - difference in oxygen consumption at rest and at anaerobic threshold.
- Physiologic energy reserve capacity - difference in oxygen consumption at rest and at peak oxygen uptake.
- Physiologic capacity - a composite of derived physiologic gas exchange parameters measured during CPET (degree of physiologic adaptation in response to the controlled metabolic stress of exercise).

Assumptions

This study explores the identification of predictive parameters of physiologic capacity in three cancer surgical types, associated threshold ranges and relation to collateral hospital costs and length of stay. Two assumptions were made as to the scope of the study and results. The following were the assumptions considered:

1. CPET is an acceptable surrogate for the oxidative and metabolic demands of the postoperative period.
2. Measurements of fitness, as defined by CPET, are more relevant to the association and prediction of postoperative outcomes than other possible predictors such as traditional diagnostic tests or empirical risk assessment methods.

Limitations

Potential limitations of the study include the following. Discussion of each limitation"s potential impact to the proposed study is detailed in Chapter 3 of this manuscript.

1. The study is not randomized.
2. The study is biased in that only patients who were willing to undergo an exercise test were enrolled in the study.
3. The study is biased in that only patients who are scheduled for one of the three surgical types being investigated in this study are enrolled.
4. There was no control as to whether a patient significantly increased or decreased his/her level of activity within the 1-week period between his/her CPET and their scheduled surgery.
5. This study does not evaluate the degree of variability in patients" risk levels.

Delimitations

The study was limited to the 103 cases already gathered that comprised the 3 surgical procedures examined in this study. The study was also limited in that all study participants were patients at University of Texas M. D. Anderson Cancer Center and were being treated for 1 of 3 specific diagnosis‟ (cancer of the esophagus, bladder, or liver). All financial data were limited to the information provided by the business office at M. D. Anderson Cancer Center and were calculated based on the hospital charges.

Significance of the Study

The significance of the study improves confidence in risk stratification for surgeons and patients to better evaluate the relative risk/benefit ratio of consequences unrelated to the surgical prognosis. Ultimately, information gained through this study will justify or not justify a larger study that will create a foundation for preoperative intervention that decreases risk, limits complications, significantly decreases the cost of surgical care, and allows for better use of healthcare resources.

The social significance of an adverse postoperative outcome, unrelated to the surgical prognosis, is that the patient‟s long-term survival, quality of life, and future economic productivity are reduced. The costs associated with the medical management of complications represent a growing economic burden on the United States healthcare system (Khan, Quan, Bugar, Lemaire, Brant & Ghali, 2006, p. 177; 2007 Congressional Budget Office report). Confidence in risk stratification would allow both healthcare providers and patients to better evaluate the relative risk-benefit ratio of the surgical prognosis versus the postoperative consequences of a morbidity unrelated to the surgical prognosis. The methodology used in this study allows for both the evaluation of parameters of physiologic capacity as preoperative predictors of postoperative adverse outcomes and a more complex evaluation to discover if different surgical types are associated with diverse predictive parameters and differing parameter threshold ranges. This study addresses the complexity of this issue by supplying information that other studies have not investigated. Ultimately, the positive social change gained through this study"s information will create a foundation for preoperative intervention that decreases risk, limits complications, significantly decreases the cost of surgical care, and allows for better use of healthcare resources.

Summary and Transition

Khuri et al. (2005, p. 331) cites that upwards to 50% of all non-cardiac surgical patients will experience at least one adverse postoperative event. The extended consequences increase costs to the healthcare system, reduces quality of life and reduces survival rates. Assessing surgical risk unassociated to the disease or surgical prognosis is one of the first steps in mitigating adverse events. Although therapeutic measures have improved the surgical prognosis, measures to improve stratification of risk for outcomes have fallen short of the accurate clinical predictions expected in today"s perioperative environment (Hightower et al., 2010). Only recently has attention turned to objective measures of physiologic capacity as risk predictors. The results of research have been confusing and contradictive. This may be explained by the lack of consistency between population groups and parameters being studied and by the lack of understanding the nature of the relation between physiologic capacity parameters and postoperative outcomes. However, an accepted objective and reliable risk assessment tool has not yet been realized. The results of this study are beneficial in bringing additional understanding to the parameter/outcome relationship, move a critical step forward in identifying the needed objective and reliable risk assessment tool, and provide a basis for extended studies.

Chapter 2 provides a comprehensive review of the theories that undergird the study, literature on risk prediction assessment strategies, and the recent inroads made by Hightower et al. (2010) from which this study extends. The chapter concludes with a discussion of how the literature and proposed study relate to social change. Chapter 3 explores the research methods employed in the study, including the research design, description of the population, dataset, and data analysis.

Chapter 2: Literature Review

Section One: Introduction

Overview of content

The purpose of this chapter is to provide an overview of the theories and research that undergird physiologic capacity as a predictor of postoperative complications. This chapter contains four sections. The first section begins with an overview of the chapter content, an organizational view of the chapter, and closes with the methodology employed in the literature search. The second section presents a description of the theories that undergird the concepts within the proposed study. The third section presents an exhaustive review of past and current literature that has and continues to drive investigation into physiologic capacity parameters as an objective predictive risk assessment tool of postoperative complications. This section also includes research regarding efforts that healthcare providers are utilizing to address and predict collateral consequences (hospital costs and length of stay). The fourth and final section presents a discussion in which research findings and conclusions are compared, contrasted, and discussed for relevance, as well as identification of themes, common and contrasting perspectives, and relationship to the proposed study. The discussion speaks to the intersection of clinical practice with administrative responsibility and their relation to social change.

Organization of Chapter 2

This chapter is organized into four major sections.

1. Introduction to Chapter 2

a) Overview of content

b) Organization of Chapter 2

c) Strategy used in literature search

2. Review of foundational theories

    a) Physiologic theories

        1. Energy metabolism, Oxygen transport, and Oxygen utilization theories

        2. Differentiation between functional capacity theory and physiologic capacity theory

3. Review of literature

    a) A history of risk assessment methods.

    b) Limitations of risk assessments

        1. CPET role in determining risk assessment

    c) On the Forefront

    d) Literature review relative to collateral consequences of postoperative complications: hospital costs and length of stay.

4. Discussion of literature search to relevance of the proposed study and its impact on social change

Strategy used in literature search

The search strategy utilized in this literature review was based on the Boolean system (Whitesitt, 1961). The Boolean system uses keywords and phrases such as *physiologic capacity, surgical costs, postoperative complications, and anaerobic* *capacity.* Literature searches were conducted on seven databases through the EBSCO, MEDLINE, PubMed, Ovid, CINAHL, Academic Search Premier, MDConsult online database search engines as well as ProQuest"s online dissertation and theses search. While the number of studies pertaining to postoperative complications and associated issues number in the tens of thousands, there is a distinctive gap in the amount of scientific studies related to physiologic capacity parameters as predictors of postoperative complications and an absence of studies investigating the potential of physiologic capacity parameters as predictors of hospital costs and length of stay. When available, data on the use of physiologic capacity parameters for prediction were reported.

A review of each article"s abstract was performed first when available, before a full text article was reviewed. For abstracts that included the keywords of this study but were not available online, the articles were obtained through the University of Texas Medical Center Library System or inter-library loan system located in Houston, Texas. Criteria were developed in order to narrow the focus of the review due to the tens of thousands of articles produced during the initial search. Criteria were prioritized with the first being the elimination of studies that were not available in the English language. The second criterion eliminated any articles that were not peer-reviewed and the third criterion eliminated studies that were of lower scientific rigor. Lastly, articles that involved diagnosis of cancer and more specifically, the three cancer surgeries involved in the proposed study (esophagectomy, radical cystectomy, and hepatectomy), were given special attention.

Section Two: Review of Foundational Theories

Physiologic theories

Energy metabolism, oxygen transport, and oxygen utilization theories. The foundational theories and principles that support the dynamics of physiologic capacity are rooted in the key cardiovascular, respiratory, heat dissipation, and cellular systems which drive the oxidation of metabolic substrate thereby producing energy to maintain life and its changing levels of activity (deVries, 1966). The inherent physiologic capacity of an individual to respond to increased functional demands depends on the ability to produce sufficient energy to meet the energy demand at hand. deVries writes that "The essence and the uniqueness of the study of physiology of exercise lie in its concern with physiological mechanisms not during rest but while the organism is stressed by physical activity" (deVries,1966, p. 188). The physical activity that deVries speaks of is not limited to exercise, rather includes any physical stress (including surgical and postsurgical stress) that life presents. The early1920"s work of Hill and Herbst set the general theory of energy metabolism when they demonstrated the existence of three primary energy producing processes, namely adenosine triphosphate-phosphocreatine (ATP-PC), glycolytic, and oxidative processes (Bassett & Howley, 2000). Warphea (2003) explains that the three systems were originally thought to be "…interconnected to such a degree that no one system provided the entire source of energy (ATP) to working muscles at any one time, regardless of the activity, duration or intensity" (Warphea, 2003, p.1). The work by exercise physiologists such as McArdle, Katch, Katch (1986) fine tuned the theory and held that during *anaerobic* activity (high intensity exercise producing significantly elevated energy demand, lasting a few seconds to a few minutes) the majority of energy is supplied by the ATP-PC and glycolytic systems. In contrast, the oxidative system is the major producer for *aerobic* energy demands (rest and low intensity activity of long duration whose energy demands are largely met by aerobic metabolism). Although rest and low intensity activity draw mainly from the oxidative processes and high intensity for short duration draw mainly from ATP-PC and glycolytic substrates, it is important to remember that no matter what the intensity level of the energy demand is, utilization is not limited to only one energy substrate at a time, rather the contribution of each system changes to meet the energy demand.

deVries (1986) explains that because all biological metabolic processes utilize oxygen and produce the byproduct of carbon dioxide, the study of oxygen uptake kinetics and carbon dioxide output kinetics becomes valuable . Furthermore, deVries maintains that we can ascertain the energy output as directly related to the quantity of these respiratory gasses. Soni, Fawcell, and Halliday (1993) wrote of updated technology that allows for both inspired and expired gases to be captured for a breath-by-breath analysis during activity periods by way of mechanical devices and electronic measuring methods which quantify gas exchange values. Such is the case using the cardiopulmonary exercise test (CPET) and breath-by-breath analysis which the proposed study utilizes.

Wasserman, (2002, ch.1) theorized that in the resting and low exercise intensity state the supply of oxygen (O_2) to the tissues is sufficient so a complete breakdown of glycogen occurs resulting in carbon dioxide (CO_2) and water (H_2O) with no accumulation of lactic acid. This is a picture of work in which the metabolic energy demands are primarily met by aerobic processes. As exercise intensity increases, energy demands are increased and can reach an intensity level where those energy requirements cannot be adequately met by cardiorespiratory processes. At this level, anaerobic mechanisms increasingly meet elevated energy demands resulting in increased lactic acid production, lactic acid accumulation is a condition referred to as *lactic acidosis*. Lactic acid is not the end of the energy producing cycle as McArdle, Katch, Katch (1986, p. 113) explain, "Apparently the major portion of lactic acid is oxidized for energy. Indeed, it is well established that the heart, liver, kidneys, and skeletal muscle use lactic acid in the blood as an energy substrate during both exercise and recovery" (McArdle, Katch, Katch, 1986, p. 113). deVries (1986) clarifies that when the supply of O_2 is insufficient to meet demands, *oxygen debt* occurs, but this is not to be confused with *oxygen deficit.* As energy intensity increases from rest to exercise/activity a lag naturally occurs in which the O_2 supply via aerobic mechanisms lacks adequacy. This creates an oxygen debt. However, the body continues to function during this period drawing on other energy substrates of ATP-PC, glycolytic, the use of O_2 stored in the muscles, and the amount of oxygen in the blood (McArdel, Katch, Katch, 1983). It is important to note that repayment for any anaerobic metabolism beyond the initial lag must be repaid as well as the O_2 deficit. In light intensity where a steady level of O_2 is supplied the O_2 debt may be due entirely to the O_2 deficit at the beginning of the activity. At the end of the activity there must be a recovery period during which the O_2 debt is repaid. According to Wassermann (2002) this is the reason why the heart and the ventilation rates remain elevated after high intensity/demand ceases. Shoemaker, Appel, & Kram (1993, p. 978) and more recently, Hightower et al. (2010, p. 470) assert that this may be the condition in which some post-surgical patients find themselves.

When a steady state of O_2 cannot be adequately supplied, as in an overload situation, the duration of effort (metabolic energy) is limited by the individual‟s ability to sustain an O_2 debt. This defines the oxidative energy reserve capacity. At this level the individual can no longer provide adequate oxygen at a rate to meet the energy demand and glycolysis becomes increasing used to provide energy resulting in a lactate accumulation in the blood. The exercise intensity at which this accumulation can be measured is referred to as the *anaerobic threshold* (AT). Wasserman (2005, p. 57) explains that "…it is not uncommon in workloads where the supply is mainly produced from anaerobic sources, the individual can only sustain the workload for one to two minutes and recovery may take forty-five minutes or even longer" (Wasserman, 2005, p. 57). Hightower et al. (2010, p. 471) asserts that it may be the individuals with low aerobic and hence a greater reliance on anaerobic metabolism that cannot meet the continued demand during the post surgical period that experience complications. Therefore, the role of oxygen is established as a key player in an individual‟s ability to meet energy demands. Additionally, the value of physiologic capacity parameters such as maximal O_2 consumption (Max O_2) and anaerobic threshold (AT) become criterion of interest for how well various physiological mechanisms can meet the increased metabolic needs during increased stress *and* therefore may be of interest in the investigation of parameters that predict who will and will not experience postoperative complications.

While the role oxygen plays in energy metabolism is critical, Saltin and Rowell (1980) contended that the emphasis should be placed on the *supply* of oxygen thereby justifying their Oxygen Delivery Theory which places prominence on the cardiorespiratory system. This theory asserts that the maximal volume of oxygen consumed (VO_2 max) is determined by the ability of the body to *deliver* oxygen to the cellular level where it is used to produce ATP. Oxygen delivery then is the lynch pin in the thread of energy metabolism. Saltin and Rowell suggest that key factors are the cardiovascular system"s ability to increase both blood delivery to the muscle i.e. maximal cardiac output, and perfusion of the muscles. Wasserman (2005) explains that there is a demonstrative intersection between the volume of oxygen and cardiac output. "Oxygen uptake (VO_2) during exercise is related to the product of cardiac output and arterial mixed venous oxygen content difference. The highest VO_2 isopleth, or highest aerobic production of ATP, is obtained by simultaneously and maximally increasing the cardiac output and the arterial-mixed venous oxygen content difference" (Wasserman, 2005, p. 69).

To the contrary, Wilmore and Costill (2005) contend that the critical factor in the thread of energy metabolism is the *utilization* of oxygen at the cellular level i.e. the Oxygen Utilization Theory. This theory maintains that physiologic capacity may be limited by a reduced ability to generate energy aerobically due to a lack of sufficient oxidative enzymes within the cell"s mitochondria. Therefore, it is the body"s ability to utilize the available oxygen that determines physiologic capacity. In fact, Wasserman, Hanson, Sue, Stringer, and Whipp (2005, ch.3) support the notion that oxidative enzymes and the number and size of mitochondria increase with training resulting in improved VO_2 max. This is described and quantified by measurement of the arterial volume of oxygen - (a-VO_2) difference or the difference between arterial and venous blood oxygen concentrations (Wilmore and Costill, 2005, ch.2). It would appear then that dynamics of the cardiovascular and respiratory systems drive both delivery and utilization which also serve as the theoretical basis in the dynamics of energy metabolism.

Principles of Cardiopulmonary Exercise Testing. It has been the work of Dr. Karlman Wasserman that has blazed the trail in understanding and utilizing the cardiopulmonary exercise test (CPET) as the tool of choice for synchronous evaluation of all the components of aerobic energy synthesis. Wasserman (2005, p. 3) states that "Cardiopulmonary exercise testing is one of the most inexpensive ways of diagnosing the pathophysiology of the cardiovascular and ventilatory systems because, in contrast to other diagnostic tests that evaluate one organ system, CPET evaluates each and every organ system essential for exercise, simultaneously" (Wasserman, 2005, p. 3). The CPET then becomes a crucial tool for evaluating the dynamics of energy metabolism. This test allows for capture of gas exchange variables. The plotting and subsequent analysis of these variables gathered breath-by-breath during the test provides indications of inefficient energy synthesis and possible inefficiencies in the entire of the body, including the three associated biological systems (cardiovascular, pulmonary, cellular), in the pre-surgical patient. (See figure 1). For example, Wasserman, (2002, p. 79) explains that the slope of the VO_2 over time provides an index of circulatory response capacity. "It reflects the oxygen cost of carrying out the work and a reduced slope indicates the more the anaerobic metabolism is called on, and the potential severity of circulatory failure" (Wasserman, 2002, p.79). Likewise, the oxygen pulse reflects the capacity of the heart to deliver oxygen per beat (VO_2/HR) (Wasserman, 2002, ch. 6). For these reasons, the analyses of the gas exchange data derived from CPET may provide insights into potential adverse outcomes, and is therefore crucial to preoperatively understanding postoperative risk assessment. The selection and analysis of parameters of physiologic capacity captured via CPET is discussed in greater detail in section 3.

Differentiating between theory of functional capacity and physiologic capacity

The theories of functional and physiologic capacity are often thought of as one and the same. However, there is a marked difference between the two and understanding this difference aids in understanding the theory behind the choice of using parameters of physiologic capacity as predictors of postoperative outcomes for this study. Diagnostic stress tests measure the amount of work a person can perform without signs or symptoms of disease (i.e., functional capacity). This is not the same as measuring physiologic capacity, which is the *metabolic intensity* of the performance. The distinction between functional capacity and physiologic capacity is important. To illustrate, assume three runners run one mile in 4 minutes (abreast). Runner A crosses the finish line and immediately falls over dead of heart failure. Runner B crosses the finish line and takes a slow jogging lap around the track to recover (to replace the oxygen deficit). Runner C crosses the finish line and promptly asks, "When do we go again?" Since all three runners ran the same distance in the same time (i.e., at the same rate), all three demonstrated the ability to achieve the same level of functional capacity. Functional capacity therefore, is the measurement of the work that all three runners achieved. Physiologic capacity, on the other hand is the efficiency of each runner‟s energy production and utilization (i.e., metabolic intensity) while doing that work. With this difference in mind, it could be said that the post-race outcomes were determined by each runner‟s physiologic capacity. Runner A exceeded his body‟s capacity to efficiently supply the oxygen needed to satisfy the oxygen demand and thus suffered organ failure. The capacity of Runner B‟s body to efficiently supply the oxygen needed to satisfy the oxygen demand was adequate, although he did need to recover. The capacity of Runner C‟s body to efficiently supply the oxygen need was far superior to the oxygen demand. Thus, despite having the same functional capacity, the three runners are judged to have three significantly different physiologic capacities. Similarly, surgical patients may be starting their "race" in the postoperative period with vastly different physiologic capacities. Because of the potentially altered energy demand during the postoperative period (Brandi et al., 1988; Miles, 2006), patients may not have the option of "stopping to recover" if the oxygen demand exceeds their capacity to meet their need during the acute recovery phase. CPET, acting as a substitute of the demands experienced during the perioperative period, allows for quantitative measurement of the capacity of each patient to meet the oxygen demands during the stress of surgical recovery. In fact, Hightower, et al. (2010, p. 470) states, "Systematic expression of CPET data may provide an opportunity to identify even more accurate and precise measures predictive of postoperative outcomes for specific types of surgeries, illnesses, or both" (Hightower et al., 2010, p. 470).

The capacity of a patient‟s physical activity (i.e., functional capacity) has been used as an indicator of survival and perioperative risk (Covinsky et al., 2000; Biccard, 2005). Some clinicians have used Metabolic Equivalent (MET) (1 MET = 3.5 ml O_2/min/kg) to estimate a patient‟s physiologic capacity on the basis of his or her functional capacity. MET is a *generalized estimation* of the body‟s oxygen consumption during a particular activity, but its use to estimate physiologic capacity may misrepresent an individual‟s physiologic capacity because the measured parameters of physiologic capacity represent more than the peak oxygen uptake and utilization achieved during an activity (Wiklund, Stein, & Rosenbaum, 2001,pp. 86-87). The parameters of physiologic capacity define the *efficiency* of oxygen uptake and utilization as measured by the quality of the gas exchange parameters during the activity. Because the parameters of physiologic capacity are unique to each individual at the time of his/her CPET, physiologic capacity is a measured phenotypic quality that is flexible enough to show any real time changes in a patient‟s physiologic capacity over time (Wiklund, Stein, & Rosenbaum, 2001). A practical recognition of this concept is illustrated in the evolution of the New York Heart Association‟s classification of cardiac failure. This classification system was originally based on the subjective evaluation of risk using functional capacity. It was revised in 1994 to include physiologic capacity defined by cardiopulmonary exercise testing as an objective means of patient evaluation (AHA medical/scientific statement, 1994).

Review of Literature

A history of risk prediction

An estimated 30 million individuals undergo non-cardiac surgery in the United States each year. Up to 10% of these patients will experience a major adverse cardiac event (Arora, Velanovich, & Alarcon, 2010, *EPub* ahead of print; Potyk and Raudaskoski, 1998, p. 164). Patients with postoperative myocardial infarction are estimated to have a 50% or greater reduction in their 2-year survival rate (Mangano, 1998, p. 162). The incidence of major adverse pulmonary events after abdominal surgery ranges from 9% to 40% (Arozullah, Daley, Henderson, & Khuri, 2000, p. 847). A United States Department of Veterans Affairs study reported that the occurrence of postoperative complications *independently* reduced the 30-day survival rate and reduced the 8-year survival rate by 69%. (Khuri et al., 2005, p. 326) In the same study Khuri et al. reported that postoperative pulmonary complications and wound infection reduced median long-term survival by 87% and 42%, respectively. (Khuri et al., 2005, p. 336) In addition, the median cost of an operation in general surgery is estimated to increase an estimated 5-fold when major adverse pulmonary events occur. With these statistics in mind, the American College of Physicians published, in the Annals of Internal Medicine, the 2009 guidelines for preoperative evaluation. When asked who should undergo preoperative evaluation, the response was:

> All patients scheduled for surgery should be considered for preoperative evaluation. For very low-risk procedures, such as dental extractions or cataract surgery, the evaluation may only involve the oral surgeon or ophthalmologist confirming the lack of significant risk factors. For more complex procedures, evaluation

> by a physician experienced in preoperative assessment may be judicious. (p. 4)

The challenge to fulfilling this guideline is in the clarification of „significant risk factors‟. Hightower et al. (2010, p. 470) noted that "…assessing surgical risk requires consideration of both the anticipated therapeutic outcome related to the surgical prognosis and the probability of postoperative adverse outcomes unrelated to the surgical prognosis" (Hightower et al., 2010, p.470). Evaluating the latter requires evaluation of the surgical patient‟s physiologic capacity perioperatively. This was the early work of Shoemaker and his associates (1993).

William Shoemaker published a series of articles from 1983 – 1993 encompassing a stream of research investigating the metabolic needs of surgical patients intra- and post-operatively. The findings showed marked differences between survivors and non-survivors in 22 different variables. Notably were VO_2 consumption, O_2 delivery, and cardiac stroke work index values. In 1993 he wrote that these reached critical indexes at 48 – 96 hours postoperatively which includes the time period (3 days post-surgery) when complications most frequently manifest. While Shoemaker set the alpha level at 0.05 and all 22 variables fall under this value, O_2 utilization and delivery and cardiac stroke and work values displayed $< .01$. Shoemaker concluded that the trauma of surgery itself increases flow, oxygen transport, and cardiac index variables. "The increased cardiac index, DO_2, and VO_2 values were significantly greater in those patients who survived and left the hospital alive as compared with those patients who subsequently died during their hospital course" (Shoemaker, 1971, p. 985). He also noted that these values as well as the presence of other complications indicate increased body metabolism after surgical trauma and are also consistent with Moore (Moore, 1995, p.985). Shoemaker asserts that the data shows an underlying physiologic defect, assessed as oxygen debt due to inadequate or maldistributed flow. Furthermore, Shoemaker (1993, p. 987) contends that the O2 debt is "…a major physiologic determinant of postoperative shock, organ failure, and death; it also may be the stimulus for the compensatory cardiac index response" (Shoemaker, 1993, p. 987). Shoemaker continues to note that although his work produced a range of critical metabolic variables associated with postoperative survival, during 1993 it was not possible to test a range, therefore criteria for prospective trials must be defined by cut-points. He contends that these cut points necessarily must be arbitrarily defined. However, more recently, Hightower et al. (2010, p. 469) refers to these cut-points as thresholds and argues that thresholds can be defined using the more advanced equipment and capturing capabilities of today‟s CPET. In fact, it is the aim of the proposed study to identify thresholds for each of three surgical types, which ultimately may be used similarly to Shoemaker‟s „cut-points‟ for preventative interventional therapy goals. Representing a growing consensus, Tang et al. (2007, p. 179) argues, "If a patient has a reduced preoperative physiologic capacity reserve and undergoes high stress as result of surgical trauma, the metabolic and neuroendocrine response to surgery may be insufficient to maintain homeostasis (meet the energy demand), resulting in postoperative complications and possible multi-organ failure" (Tang et al. 2007, p. 179). However, an additional challenge arises when a factor other than surgical trauma is included in the mix of potential influencers.

Cancer compounds the challenge of preoperative risk prediction by adding the unknown risk of the cancer and associated neoadjuvant chemotherapy and/or radiation therapy to the patient‟s preexisting co-morbidities (Lefor, 1999, p. 165S; Thorsen et al., 2006, p. 122). Traditionally, cancer patients are considered for surgery based on the risk–benefit profile of the expected cancer survival outcomes. At the present time, the techniques for identifying individual patients at high risk for morbidity or mortality unrelated to the surgical prognosis are not as accurate or precise as the therapeutic indications for surgery (Hightower, et al., 2010, p. 470).

Limitations of Current Preoperative Risk Assessment Tools and Concepts

Although the American Society of Anesthesiologists‟ (ASA) Physical Status Classification System was *not* originally developed as a preoperative risk assessment tool (Owens, 2001, p. 378), it remains the first and most widely used preoperative general risk assessment tool to date (Aronson, McAuliffe, & Miller, 2003, p. 265 and Garcia-Miguel, Serrano-Aguilar, & Lopez-Bastida, 2003, p. 1749). The ASA system was developed in the early 1940‟s, revised in the early 1960‟s, and has remained essentially unchanged since then (Sidi, Lobato, and Cohen, 2000, p. 329). Garcia-Miguel, Serrano-Aguilar, & Lopez-Bastida describe it as an evaluation tool based on the general clinical impression of the severity of a patient‟s systemic disease. The information used to develop this general clinical impression is derived from multiple sources, including but not limited to, the patient‟s medical history, a problem-focused physical exam, consultations, and diagnostic test results performed on organs or systems of concern (American Society of

Anesthesiologists Task Force, 2002). The patient‟s physical status is *ranked* from 1 through 5 in order of descending physical status with a modifier for emergencies (Owens, Felts, & Spitznagel, 1978, p. 239). Intuitively, a rank indicating a poor physical status results in a higher probability of postoperative morbidity and mortality. Advantages of the ASA classification system include its simplicity and its low cost of implementation. Aronson, McAuliffe & Miller (2003, p, 265) explain its disadvantages include inconsistencies due to the subjective nature of patient rank assignment and Owens, Felts, & Spitznagel (1979, p. 239) contend that its failure includes (as Shoemaker‟s work confirmed) its inability to formally account for the effect of the surgical procedure on patient outcome .

The works of Auerbach & Goldman (2006), Detsky et al. (1986), Gilbert, Larocque, & Patrick, (2000), and Goldman (1983), and all support subjective or empirical preoperative risk assessment tools as focused specifically on predicting postoperative ***cardiovascular*** morbidity and mortality. A study (Gilbert, Larocque, & Patrick, 2000) comparing multiple subjective risk indices (ASA, Goldman, Detsky, and Canadian Cardiovascular) as predictors of postoperative myocardial infarctions and death concluded that each index was better than chance (sensitivity in the 60% range). None was statistically superior to the others when evaluated using Receiver Operating Characteristic (ROC) curves. Charlson, Ales, Simon, & MacKenzie (1987), Prause, Offner, Ratzenhofer-Komenda, Micenzi, Smolle, & Smille-Juttner (1997), and Wolters, Wolf, Stutzer, & Schroder (1996) are all contradictive and controversial as to the credibility of the ASA classification system as well as other subjective preoperative risk assessment tools. In fact, a more recent study by Wolters, Mannheim, Wassmer, & Brunkwall (2006) tested the top four preoperative scoring assessment methods for accuracy in predicting morbidities and mortality in 107 non-randomized patients. The four assessment systems included the American Society of Anesthesiologists (ASA) classification, the acute physiology and chronic health evaluation (APACHE II) , the physiological and operative severity score for enumeration of mortality and morbidity (POSSUM) classification and, finally, the simplified acute physiology score (SAPS) classification systems. Notably, using analysis of variance (ANOVA), multivariate analysis with binary-regression, and receiver operating (ROC) curves to determine sensitivity and specificity, with alpha set at < 0.05, Wolters, Wolf, Stutzer, & Schroder (1996) found " …no significant correlation between risk-scores and outcome. None of the scoring systems used was able to predict mortality" (Wolters, Wolf, Stutzer, & Schroder, 1996, p. 177). His conclusion has echoed the results of the vast majority of researchers who assess subjective methods and express frustration over the situation: "We still lack a system that can be used preoperatively in an individual case and the vascular surgeon still has to build up his own clinical judgment or to transfer a clinical judgment" (Wolters et al., 1996, p. 177).

The American College of Cardiology/American Heart Association (ACC/AHA) cardiac risk classification system and the American College of Physicians (ACP) guidelines for the management of cardiac patients undergoing non-cardiac surgery both provide consensus algorithms with structured guidelines outlining preoperative diagnostic tests for use with **cardiac** patients undergoing non-cardiac surgery. These recommendations are an improvement over empirical risk indices because they consider the past medical history and type of surgery anticipated, along with consensus algorithms for diagnosing cardiac disease. The guidelines are intended to define preoperative risk and optimize the patient"s cardiac condition prior to surgery (Gordon & Macpherson, 200;, Eagle et al., 1996, 2002). However, these methods also studied by Ali, Davison, Picket, & Ali (2000, pp. 10-19), Devereaux, Goldman, Cook, Gilbert, Leslie, & Guyatt (2005), and Gordon and Macpherson (2003) all focused specifically on cardiac assessment. Therefore, they have not been validated in diverse surgical populations, including cancer patients nor do these guidelines include a non-cardiac assessment.

Regarding diagnostic pulmonary or cardiac function test, the American Society of Anesthesiologists Task Force (2002) in addition to DeNino, Lawrence, Averyt, Hilsenbeck, Dhanda & Page (1997, p. 1536), Mangano (1990, p. 153), and Older, Smith, Hall & French (2000, p. 208) all concede that there is no consensus that any traditional preoperative diagnostic pulmonary or cardiac function test is a credible risk predictor in patients undergoing major abdominal surgery. Although diagnostic tests have been developed to diagnose and evaluate organ or system diseases as was the case in the study by Godet et al. (2005), in order to institute effective treatments that improve function prior to surgery, this is not equivalent to predicting organ or metabolic energy systems effectiveness during the dynamic stress of the postoperative period.

On The Forefront

Gas exchange parameters, in conjunction with Cardiopulmonary Exercise Test (CPET), are a relatively new method of evaluating an individual"s physical conditioning (i.e., physiologic capacity). A growing body of evidence suggests that an individual"s physiologic capacity, as defined by CPET, is directly correlated to that person"s levels of health, physical conditioning, and long-term survival (Goffaux et al., 2005; Gulati et al., 2003; Hightower et al., 2010; Myers et al., 2002; and Pate, 1995). Many other studies have illustrated the negative physiologic impact of inactivity (i.e., deconditioning). Inactivity can result in decreased physiologic capacity, *even without a traditional diagnosis of cardiovascular or pulmonary disease* (Smorawinski et al., 2001; Convertino, 1997; NIH Consensus Development Panel on Physical Activity and Cardiovascular Health, 1996). Prolonged inactivity eventually results in multiple organ dysfunctions and a poor response to metabolic stress. This is supported by the studies of Despres (2005), Hahn, Teutsch, Rothenbery & Marks (1986), Kaplan, Strawbridge, Cohen, & Hungerford (1996), Paffenbarger et al. (1993), Pratt and Wang (2000), and Weiderpass et al. (2000). Whether a surgical candidate is deconditioned due to organ disease, chemotherapy and/or irradiation therapy, or behavioral choice, a reduced physiologic capacity may represent a patient"s *inability to physiologically meet the metabolic demands of perioperative stress*. Goffaux et al. (2005, p. 985) contends that physiologic capacity is "…a concept whose time has come" (Goffaux et al., 2005, p. 985). The consistent reproducibility of CPET-derived parameters potentially allows individuals with different disease processes to be objectively evaluated using the common standard of physiologic capacity.

In the textbook Principles of Exercise Testing and Interpretation, Wasserman, Hanson & Sue et al. (1999, chapter 1) explain that cardiopulmonary exercise testing using gas exchange parameters is a noninvasive, dynamic, controlled metabolic stress test. Gas exchange parameters reflect the efficiency of oxygen utilization (an indirect measure of energy production) and the integrated efficiency of the oxygen transport system (cardiopulmonary, vascular, and cellular systems). The American Thoracic Society (ATS) and American College of Chest Physicians" statement on Cardiopulmonary Exercise Testing (ATS/ACCP Statement on cardiopulmonary exercise testing, 2003) is the most comprehensive statement to date on the role of cardiopulmonary exercise testing in medicine. The joint statement suggests a wide range of indications for CPET including establishing levels of exercise tolerance, identifying the pathophysiology of exercise intolerance, and evaluating patients with a variety of known cardiovascular and/or respiratory diseases. The use of CPET as an objective preoperative assessment tool is encouraged for those patients facing lung cancer surgery, lung volume reduction surgery, and evaluations for both lung and heart transplantation. The joint statement, referring to Older et al. (1993), states; "…work has shown that CPET is helpful in objectively assessing the adequacy of cardiovascular reserve and in predicting cardiovascular risk in elderly patients" (STS/ACCP, 2003, p. 212).

Together with several other researchers, Paul Older (1993; 1999) published a series of papers introducing the concept of using physiologic capacity as a cardiac mortality risk assessment tool for elderly patients undergoing major abdominal surgery. These publications identified an Anaerobic Threshold (AT) value of <11 mL/kg/min as the critical component of a patient"s physiologic capacity that identified patients at high risk of postoperative cardiac mortality. Patients at or below this value had an in-hospital cardiac mortality rate of 18%, whereas patients with a higher AT value had a 0.8%

mortality rate (Older, Smith Courtney, & Hone, 1993, p. 703). In a follow-up study, (Older, Hall, & Hader, 1999, p. 356) triaged patients with an AT value of <11 mL/kg/min to receive postoperative care in the Intensive Care Unit (ICU), which reduced the postoperative cardiac mortality rate to 8%. These studies supported the use of cardiopulmonary exercise test (CPET) as a means of objectively stratifying cardiac risk preoperatively and distributing postoperative care resources such as nurses and technicians thereby impacting hospital costs and length of stay. The authors concluded that using cardiopulmonary exercise testing to preoperatively evaluate elderly patients‟ risk of postoperative cardiac mortality and stratify a patient‟s anticipated postoperative level of care is objective, non-invasive, inexpensive, and safe (Older, Smith, Hall & French, 2000, p. 208). Although this study supported the use of CPET for evaluation, its generalizability remains limited to elderly cardiac patients. Other studies are then needed for extended generalizability to additional populations such as cancer patients (the focus of the proposed study).

McCullough, et al., (2006, pp. 715-725) observed that physiologic capacity is useful in predicting a variety of acute postoperative morbidities. These investigators demonstrated that morbidly obese patients undergoing bariatric surgery were at a higher risk of postoperative mortality (6.6% vs. 2.8%) and a multitude of acute postoperative morbidities if their peak VO_2 values were $\leq$15.8 mL/kg/min. Four new studies were recently published evaluating the predictive value of physiologic capacity parameters as preoperative predictors of postoperative cardiopulmonary adverse outcomes. Three of the studies centered on patients undergoing esophagectomy and one enrolled patients undergoing major elective surgeries limited to open aortic aneurysm repairs, aortobifemoral grafts, liver resections, and pancreatic and large retroperitoneal intra-abdominal sarcoma surgery. In Japan, Nagamatsu, et al. (2001) evaluated the usefulness of cardiopulmonary exercise testing as a predictor of cardiopulmonary postoperative outcomes in patients undergoing esophagectomy and concluded that maximum oxygen uptake correlated with postoperative cardiopulmonary complications in this patient population. Nagamatsu, et al., studying the same population type, recommended its use as a preoperative screening test. In the United Kingdom, Forshaw, et al., (20089) questioned the usefulness of cardiopulmonary exercise testing in esophagectomies. In contrast with Older and Nagamatsu‟s studies, Forshaw, et al., concluded that an AT <11 mL/kg/min was a poor predictor of postoperative cardiopulmonary morbidity and the peak oxygen uptake was significantly lower in patients developing cardiopulmonary complications. (Forshaw et al., 2008, p. 299) Furthermore, Forshaw, et al. also concluded that CPET was of limited value in predicting postoperative cardiopulmonary morbidity in the study‟s patient population. Between these three studies, the conclusions concerning the predictive usefulness of cardiopulmonary exercise for esophageal patients were contradictive. Snowden, et al. (2010) employed a submaximal CPET and looked at three specific variables derived from CPET along with several non-CPET variables for prediction of postoperative complications. It is important to note that Snowden et al. utilized Older‟s 1999 predictive value of AT set at <11 mL/kg/min. Over a 2-year period 123 patients underwent one of four major abdominal elective surgeries. Results demonstrated that,

> …in a selected group of major surgical patients with low subjective functional capacity, AT (a measure of cardiorespiratory reserve derived from submaximal preoperative CPET) can predict those at risk for early postoperative complications and may be also useful in predicting hospital length of stay. Furthermore, the use of preoperative noninvasive CPET, adds significant information to the prediction of postoperative outcomes, compared with the use of a subjective algorithmic-based assessment of functional capacity (p. 540 – 541).

Echoing similar sentiment as the majority of studies in this area, Snowden et al. called for, "Further studies will be required to define clinically important levels of cardiopulmonary reserve predictive of postoperative outcomes in other surgical populations" (Snowden et. al., 2010, p. 541).

Research from which proposed study launches

Most recently, Hightower et al. (2010, p. 467) examined a host of parameters, for a range of outcomes, in a population undergoing 8 different abdominal cancer surgeries (esophagectomy, radical cystectomy, and liver included). This study discovered a statistically significant predictive model using two parameters: Delta Heart Rate (ΔHR) and percentage of predicted AT achieved, <75% vs. ≥75% (PAT). The multivariate model produced a sensitivity of 0.813 and specificity of 0.688. Although these findings are encouraging, the greater worth of physiologic capacity parameters are currently thought to be in their clinical significance in that preoperative physiologic capacity can be changed to affect a different postoperative outcome. The remaining gap that Hightower‟s study did not answer is; whether each surgery may, or may not have its own unique predictive parameter(s) and/or threshold(s), nor did it address physiologic capacity as a predictor of collateral consequences from complications such as increased hospital costs and length of stay. This dissertation study seeks to answer these gaps.

In summary, perioperative clinicians have traditionally used independent preoperative pulmonary and cardiac risk factors, consensus algorithms, empirical risk indices and diagnostic tests to predict a surgical patient‟s risk of adverse postoperative outcomes. The results have been controversial, conflicting, and most importantly, have fallen short of the accuracy and precision expected in today‟s sophisticated perioperative environment (Finlayson and Birkmeyer, 2001). The concept of physiologic capacity as a predictor of postoperative risk is appealing. The notion that a patient‟s unique physiologic response to a surrogate stress is an accurate reflection of that patient‟s postoperative risk of morbidity is exciting. This new area of perioperative investigation appears promising, as indicated by the results of the current studies cited in this proposal. These studies collectively suggest that specific predictive parameters of physiologic capacity appear to be independent preoperative predictors of a variety (not limited to cardiac) of postoperative risks in a diverse collection of surgical procedures. The details of this relationship are unknown at present. As we continue to understand the relationship between physiologic capacity and postoperative morbidity, an important product from this area of research would be the identification of a cause and effect relationship. The ultimate product is to understand how to modify a patient‟s preoperative physiologic capacity in order to decrease postoperative risk, thus preoperatively managing risk.

The differences between the proposed study and the above-referenced studies contrast the cited studies, which have begun to lay a foundation in a new direction of risk assessment, to the proposed study, which carries significant differences. These differences are defined in Table 1 below.

Collateral consequences of postoperative complications: hospital costs and length of stay

Predicting hospital costs. A 2007 report by the Congressional Budget Office conveys that healthcare costs will account for 41% of the Gross Domestic Product by 2060. In the Agency for Healthcare Research & Quality‟s (AHRQ) Statistical Brief #86, published in February 2010, the 2007 prices for many outpatient surgeries were up 25% to 41 percent over 2003prices. Overall average of outpatient surgical costs in 2007 was $6100, compared to an average of nearly $40,000 for inpatient surgery. Reporting on these numbers, the Consumer Health Ratings organization warned that consumers will

Table 1

Comparison of Proposed Study to Recent Studies

Differentiations	Proposed Study	Hightower‟s Study (2010)	Older‟s Study (2000)	McCullough‟s Study (2006)	Nagamatsu‟s Study (2001)	Forshaw‟s Study (2008)
Study Population	Cancer patients >18 undergoing esophagectomy, radical cystectomy or hepatectomy	Cancer patients >18 years old undergoing 7 different types of surgeries	Patients >60 years old ,or younger with known cardiovascular disease undergoing a variety of major abdominal surgeries	Morbidly obese patients undergoing bariatric surgery	Smokers with cancer undergoing esophagectomy	Cancer patients undergoing esophagectomy

(table continued)

Differentia-tions	Proposed Study	Hightower"s Study (2010)	Older"s Study (2000)	McCullough"s Study (2006)	Nagamatsu"s Study (2001)	Forshaw"s Study (2008)
Outcomes and End points	Broad range of morbidities and mortalities in three specific surgeries. Also comparison to hospital costs and length of stay.	Broad range of morbidities and mortalities in variety of cancer surgeries	Only cardiovascular mortalities in a variety of different major abdominal surgical procedures	Broad range of morbidities and mortalities in one specific surgery	Limited to cardio-pulmonary morbidity only	Cardiopulmonary and aggregated all non-cardio-pulmonary together
Parameters of Risk Assessment	Consider multiple parameters per surgery as risk predictors with the intent of identifying a risk profile	Identified significant risk predictor as 2-parameter model (PAT + ΔHR)	Identified significant risk discriminator as A T	Identified significant risk discriminator as PVO_2 (measured in mL/kg/min)	Identified significant risk discriminators: VO_2 max and AT + pulmonary factors	Identified significant risk discriminators: Peak VO_2
Test Methodolog y	Bicycle ergometry	Bicycle ergometry	Bicycle ergometry	Treadmill ergometry	Mod. bicycle ergometry	Bicycle ergometry
Surgeries Evaluated	Esophagectomy, radical cystectomy and liver with comparisons	Variety of 7 types of abdominal cancer surgeries with comparisons	Variety of abdominal surgeries – no parameter comparisons	Bariatric surgery only	Esophagectom y surgery only	Esophagectomy surgery only

"..need to adjust the 2007 prices to estimate 2010 facility costs" (p. 1). It is no secret that postoperative complications create additional collateral consequences that result in increased hospital costs (HC) and length of stay (LOS). Administrative impact is seen in resource planning, budget forecasting, and quality indicators. Risk stratification of patients who will and won"t experience postoperative complications may aid hospitals in predicting the budgetary impact, need for resources, and planning purposes. Although investigations are growing regarding assessing the impact of postoperative complications on HC and LOS, forecasting these collateral consequences have largely resulted in confusing and contradictive findings and identifying a valid and reliable predictor has yet to be presented. Even so, there are two commonalities among the published studies: first, that traditional risk assessment methods normally used for predicting postoperative outcomes are being revisited to determine if they can also be used in predicting collateral consequences such as HC and LOS. Second, conclusions repeatedly call for further work to be done in this area.

Kurki, Häkkinen, Lauharanta, Rämö, & Leijala (2001, p. 1187) report that, "Our aim was neither to develop a new score for the economic outcome, nor investigate the impact of individual variables on costs. The impact of the individual risk factors was not investigated since, with the exception of age, we did not have access to single risk factors" (Kurki, 2001,p. 1187). In fact, the Kurki study utilized the Cleveland Clinic preoperative model, which is specifically aimed at patients with known coronary disease scheduled for bypass surgery. This model is subjective in nature and assigns scores for 11 items associated with disease or organ function and two demographic factors of age and weight. Although their findings showed the modeling is possible for prediction of hospital costs and LOS in their population, they also concluded that, "Further prospective studies are needed to evaluate the effects of single preoperative comorbidity factors on LOS values and total costs since their relative impact on costs may be different from their weight on the established risk score" (Kurki, 2001, p. 1187).

Ferraris, Ferraris, & Singh (1998) conducted a study of 1221 patients undergoing cardiac procedures and looked at more than 100 patient risk factors. The study evaluated the relationship between increased cost and in-hospital mortality and serious morbidity. Their findings showed the greatest costs were associated with 31 patients who did not survive the operation and carried between $27,102 and $198,025 in costs with an average of $74, 466. A 95% confidence interval was set for significance. Patients (120) who had serious but nonfatal morbidities saw between $28,381 and $130,897 of increased charges with an average of $60,335. Those 1070 patients who survived the surgery without complications saw costs between $21,944 and $49,849 with an average of $31,459 ($p = 0.001$). A further calculation was computed for correlation with length of stay, however they reported inconclusive evidence because, "…there were many outliers at the high end of the hospital cost spectrum" (Ferris et al., 1998, p. 593). The study concluded that, "… a high-risk patient profile can serve as a target to cost-reduction strategies" (Ferris et al., 1998, p. 603).

Moving from cardiac surgeries to general tertiary care cases, Khan, Wuan, Bugar, Lemaire, Brant & Ghali (2005, pp. 177-180) sought to determine hospital costs and LOS in all incoming patients using a detailed administrative hospital discharge database. Costs and LOS were adjusted for preoperative and surgical characteristics. Of the 7,457 patients undergoing non-cardiac surgery, 6.9% developed at least one postoperative complication. These complications increased hospital costs by 78% and LOS by 114% with confidence interval set at 95%. Analysis showed that pneumonia ranked as the most costly complication accounting for only 3% of patients but carrying a 55% increase in hospital costs and 89% increase in LOS. Conclusions included, "Postoperative complications consume considerable health care resources. Initiatives targeting prevention of these events could significantly reduce overall costs of care and improve patient quality of care" (Khan et al., 2005, p. 180). Within this study, Khan and cohorts set out to determine the independent association of postoperative complications on total cost and LOS. After adjusting for comorbid status and type of surgery (major vs. minor), a list was validated for LOS and hospital costs as outcomes. A positive linear regression line was realized between cost and LOS. Khan also noted, “Evaluation was also conducted for potential clustering at the surgical service level using linear mixed effects modeling” (Khan et al., 2005, p. 178). Although results indicated a correlation and possible causal relationship existed between cost and LOS, the study fell short of providing a predicting variable, a critical first step before implementing prevention measures. This reveals yet another gap in the literature that provides impetus for this dissertation study.

On the other hand, a study by Davenport, Henderson, Khuri & Mentzer (2005) hypothesized that “…preoperative risk factors and surgical complexity predict more variation in hospital costs than complications” (Davenport et al., 2005, p. 463). Beginning from a bases that the impact on complication-related costs of preoperative risk factors being relatively unknown, the team assessed operation complexity by relative value units (RVUs) and utilized the National Surgical Quality Improvement Program to assess preoperative risk factors, surgical complexity and outcomes. A total of 5875 patients on 6 surgical services comprised the random sample. Results showed, “Fifty-one of 60 preoperative risk factors, work RVUs, and 22 of 29 postoperative complications were associated with higher variable direct costs ($P < 0.05$)” (Davenport et al., 2005, p. 471). Risk factors predicted 33%, work RVUs predicted 23%, and complications predicted 20% of cost variations. Surprisingly, risk factors and work RVUs combined predicted 49% of cost variation, which was 16% more than risk factors alone. Therefore, Davenport concluded that,

> Preoperative risk factors and surgical complexity are more effective predictors of hospital costs than complications. Preoperative intervention to reduce risk could lead to significant cost savings. Payers and regulatory agencies should risk-adjust hospital cost assessments using clinical information that integrates costs, preoperative risk, complexity of operation, and outcomes. (p. 471)

Most recently, a study by Hsieh and Chien (2009) produced findings of cost and benefit of esophagectomy for patients with esophageal cancer. Importantly Hsieh and Chien noted that "The incidence of esophageal cancer is increasing all over the world but the cost-and-benefit of esophagectomy for esophageal cancer patients was rarely studied" (Hsieh & Chien, 2009, p.1806). In a total of 310 patients, 149 underwent esophagectomy. The 5-year survival rate and total monthly medical expenses for the surgical group and non-surgical group was monitored. Results showed 36% survival with an average $22,532.8 monthly medical cost was associated with the surgical group. The non-surgical group saw a 10.2% survival rate at 5 years with an average monthly medical expense of $2,101.65. Findings also reported that both esophagectomy and tumor stage could influence a patient‟s survival time. The research team concluded that "…adding economical considerations, esophagectomy is recommended for patients, at least earlier than stage III" (Hsieh & Chien, 2009, p. 1812). While this study provided important information for decisions regarding whether esophageal cancer patients should undergo surgery or not, and consequential costs for each decision, it did not test or evaluate a predictor for hospital costs or length of stay.

Predicting length of stay. Most recently, Snowden et al. (2010) conducted an investigation into the use of submaximal CPET for predicting complications and hospital length of stay (LOS) in patients undergoing major elective surgery. The emphasis of the study fell squarely on the ability of CPET to preoperatively predict patients who would experience postoperative complications. The association to LOS was seen as a default measurement directly related to the presence or absence of complications. No direct correlation or linear regression computations were performed on any univariate or multivariate parameters of physiologic capacity (anaerobic threshold, peak volume of oxygen, and volume of expired carbon dioxide) with LOS. Therefore, while the findings support the growing consensus that CPET parameters are valid and reliable predictors of postoperative complications, the determination of any parameter as predictive of LOS was not completed. Instead, the conclusive statement was more of a deductive nature, "…AT (a measure of cardiorespiratory reserve derived from submaximal preoperative CPET) can predict those at risk for early postoperative complications and *may be also useful in predicting hospital length of stay* [italics added]*"* (Snowden et al., 2010, p. 541). Because Kramer and Zimmerman (2010) recognized "Patients with a prolonged intensive care unit (ICU) length of stay account for a disproportionate amount of resource use…" (Kramer & Zimmerman, 2010, p.1) the study team sought to identify variables that would indicate which patients would experience an extended ICU stay past 5 days. Utilizing a large cohort of 343,555 admissions, Kramer and Zimmerman found that physiologic components reflecting oxygen consumption and utilization (PaO_2:FiO_2 ratio) and some sedation variables on day 5 accounted for 81.6% of the variation in predicted remaining ICU stay. The resulting lesson learned was that a model using physiologic performance data from ICU day 5 accurately predicts a prolonged ICU stay. The suggestion by the study team was that, “The model can be used to benchmark ICU performance and to alert physicians to explore care alternatives aimed at reducing ICU stay” (Kramer & Zimmerman, 2010, p.15). Although the model and approach do not predict who will be assigned to the ICU initially, it is useful in determining who will stay in the ICU for an extended time. Furthermore, it is interesting and not altogether surprising that components of physiologic performance are the predictive variables for extended stay since growing evidence shows them as predictors of who is likely to experience complications and be assigned to ICU after surgery.

Taking a different approach, Marshall, Vasilakis, and El-Darzi (2005) reviewed multiple patient flow models in an effort to enhance the understanding of system activity related to hospital allocation of resources for postsurgical patients. They contend that “…bed occupancy and length of stay activity in hospital wards and how the management of such can be modeled and improved for future allocation of resources…” (Marshall, Vasilakis, & El-Darzi, 2005, p. 218) is the key to reducing some of the most extensive healthcare costs. Reporting that LOS prediction is a product of clinical and operational functions, Marshall and his cohorts argue that the clinical perspective is the most expensive and time consuming of the two functions. They assert that determining the LOS based on clinical measures requires on-site observation and “...models to do so are usually tailor made to the needs of the specific health care setting, and as a result, cannot be easily generalized" (Marshall et al., 2005, p. 213). The team makes a salient point when discussing the LOS from a strategic perspective where long term models must consider changing policies, population demographics and changing demands. A small contingent of models including the Markov models, phase-type distributions and conditional phase-type distribution models were considered for impact on suitability in management within a hospital. The model suggested by the team was a mixed-exponential model based for a compartmental model of patient flow which could be converted to a discrete-event simulation model. Future direction by Marshall predicted hybrid approaches using artificial intelligence, data mining and information technology filling increasingly important roles in the effort to reduce LOS and associated costs. All together, these approaches to managing LOS costs encompass the overall patient population and are recognized as logistical flow methods associated with strategic planning vs. prediction of LOS especially in surgical patients.

In a similar vein, Marshall, McClean and Millard (2004) investigated patient outcome and length of stay to develop a methodology for modeling these factors. As a precursor to the work completed by Marshall in 2005, this study considered the conditional phase-type distribution model. The study aim was to develop a model that anticipates cost of care of the elderly (focus of the study) to be estimated in advance and adjustments for these taken into consideration in the hospital budget. As such, the study observed elderly patients with diagnoses that included and did not include surgery. Not surprisingly, the team reported that the longer the patient stayed the greater the cost, also, transfer patients appear to stay longer in phase 2 of their stay. Concluding that, "A worthwhile exercise would be to investigate the patients in these categories for any *common characteristics that uniquely identify them* [italics added] as absorbing from phase 2. Such further work may provide a useful insight into the patient behavior in hospital" (Marshall, McClean, & Millard, 2004, p. 33), presents possible support for using physiologic capacity parameters as predictors of LOS even in patients not undergoing surgery.

Presented at the Annual Scientific Meeting and Postgraduate Course Program of the Southeastern Surgical Congress in Atlanta, GA during February of 2009, a study by Jacobs et al. (2009) warned that wasted hospital days impair the value of LOS variables in the quality assessment of trauma care. Presenting a significant point, Jacobs and team reminded the meeting attendees that LOS is also impacted by nonmedical factors, which most predictive models fail to recognize. Utilizing data regarding delays in patient discharge to determine the financial consequences and impact on LOS, the team compared actual LOS values with ideal calculated values and determined the per cent increase in LOS. A total of 1517 patients were studied with an actual LOS of 6.54 days. Among the study population, 7% experienced discharge delays resulting in 580 excess hospital days. The ideal calculated LOS was 6.15 days, or 6.34% lower than the actual LOS days. The shocking financial figures showed "Estimated excess patient charges associated with delayed discharges were $4,000,000 to $15,000,000" (Jacobs et al., 2009, p. 800). This was during a 7-month period. The study team also reported that "This figure does not take into lost revenue to the hospital as a consequence of having delayed discharge patients…occupying beds that could be made available to other patients" (Jacobs et al., 2009, p. 800). Lest one jump to a conclusion that the discharge process at the hospital associated with the study was in need of drastic improvement performance measures, the study team also reported that it should be recognized that some discharge delays were associated with untoward clinical outcomes such as prolonged rehabilitation sessions and poor functional outcomes in patients with traumatic brain injuries. Similarly, a study by Cielsa et al. (2008) reported that 85% of their prolonged LOS patients required ICU care. Only 7% of patients were short LOS patients and 41% were moderate LOS patients (Cielsa et al., 2008, p. 83). Both Jacobs and Cielsa studies noted that a majority of trauma deaths (no definition of trauma was given, so it is not known if trauma inferred surgical trauma) occurred early in the hospital course before factors related to discharge delay presented themselves. In conclusion, Jacobs suggested that LOS should "…only be used as a quality metric once it has been corrected for discharge delay, and various other nonclinical factors, as has been suggested by others" (Jacobs et al., 2009, p. 801).

Discussion and Relevance of the Proposed Study and Its Impact on Social Change

This chapter has presented the theoretical principles that underlie the physiology which plays a key role in risk prediction and management of postoperative complications, reviewed the history of risk assessment approaches and their limitations, presented findings of various physiological parameters as predictors (with contradictory findings), and examined studies that sought to identify predictors of hospital costs and length of stay. Given the scope of this information, a complex picture has developed regarding social change for the individual, the clinician, the healthcare institution, and the community if research is able to produce a reliable predictive model of postoperative complications and collateral consequences. This closing section discusses the interrelationships between the presented literature sections, possible lessons, directions of further research necessary to clarify and answer remaining persistent questions, and the overall social change implications.

Inter-Relationships Among Literature Sections

The work of many researchers and scholars such as Hill & Herbst (1920), deVries (1966), Shoemaker et al. (1971, 1973, 1985, 1992, & 1993), McArdle, Katch, Katch (1986 & 2010), Wasserman and colleagues (1999, 2002, & 2005), Smorawinski et al. (2001), and Bouchard, Shephard, Stephens, Sutton & McPherson (1990) blazed the way in identifying the components of metabolic energy synthesis, its grounds in oxygen delivery and utilization, and the beginnings of an understanding of how the combined body systems work together to produce physiologic capacity. The literature then scatters into various tangents as researchers sought to capitalize on this understanding to develop preoperative assessments in order to identify risk of postoperative complications. The lion share of efforts occurred in the cardiology field with a host of various assessment instruments developed and reviewed by researchers such as the American Hospital Association (1994), Ali and colleagues (2007), Aronson (2003), Auerbach and Goldman (2006), Biccard (2005), Detsky et al. (1986), Warner (1990), DeNino et al. (1997), Eagle et al (1996 & 2002), Devereaux et al. (2005), Singh et al. (2005),Trotti (2003), and Thorsen (2006). The assessments of these risk predictive tools have continued into the current year by such researchers as Devereaux et al. (2009) and Arora (2010). Unfortunately, the sentiment expressed by Ashley and Vagelos (2005) continues to echo through many articles,

> The changing paradigm in cardiovascular disease in which atherosclerotic lesions exist in a spectrum of stable to unstable, the *lack of a perfect prediction tool,* (*italics added*), and the paucity of randomized controlled data on appropriate interventions make protection of cardiac patients undergoing thoracic surgery challenging. (Ashley & Vagelos, 2005, p. 272)

On fronts other than cardiology researchers including Butcher & Jones (2006), Goffaux (2005), Goldman (1983), and Prause et al. (1997) set their efforts on developing risk assessment tools for non-cardiac patients. A plethora of risk assessment tools has been developed causing some confusion regarding which tools are best applied for which population groups and in which environments. A commonality, and some (Wasserman, 2005, and Hightower, 2010), contend that a common weakness of these assessment tools lie in the fact that they rely on individual organ functionality, specific disease factors, are inherently subjective, and do not consider the effect of surgery on the entire network of biological systems. In fact, Hightower asserts,

> Perioperative clinicians have traditionally used independent preoperative pulmonary and cardiac risk factors, consensus algorithms, empirical risk indices, and diagnostic tests to predict a

> surgical patient‟s risk of adverse postoperative outcomes. The results have been controversial, conflicting, and most importantly have fallen short of making the accurate clinical predictions expected in today‟s perioperative environment. (Hightower et al., 2010, p. 465)

The continued lack of an accepted valid, reliable, and objective risk assessment tool turned researchers‟ attention toward physiologic capacity as a possible solution. Since physiologic capacity is indiscriminant of surgical type (i.e. cardiac or non-cardiac) and is objective, a risk assessment tool personalized to the individual held great promise for cardiac and non-cardiac patients alike. This new direction provided subsequent and more detailed work from researchers including Forshaw et al. (2008), Godet et al. (2005), Goldman (1983), Nagamatsu et al. (2001), Older et al. (1993, 1999, 2000), Snowden (2005), and most recently, Hightower et al. (2010). However, these studies, while conflicting in results, have supported the overall concept of physiologic capacity as a predictor. Hightower summarized with,

> Taken together, all of these studies suggest that some measurements of PC are associated with postoperative morbidity. The specific details concerning which measures are associated with which postoperative endpoints, and under what conditions are not clear. Clarification of these details will require further studies of these potentially complex relationships. (Hightower et al., 2010, p. 470)

Similar to predicting postoperative outcomes, research has run a wide gamut in identifying predictors for hospital costs and length of stay. While most studies concluded that hospital costs and length of stay are directly associated (Finlayson & Birkmeyer, 2001; Gulati et al., 2003; Hahn, 1990; Khan, 2006; Kurhi et al., 2001 & 2005; and more recently Snowden, 2010), other researchers such as Jacobs et al. (2009) contend that confounding variables such as delays in discharge procedures add substantial increases to hospital costs making it nearly impossible to make accurate reports. Furthermore, Jacobs argued that length of stay should no longer be used as a metric for assessing or predicting quality of trauma care, and by default hospital costs. Without exception, each study reviewed concluded that for surgical patients, the advent of postoperative outcomes increased both hospital costs and length of stay. Notably, and importantly, missing from all studies was a predictor of hospital costs and length of stay. Instead, these factors were calculated *after* surgery (not predicted before surgery) in which complications occurred or did not occur. Prediction was then limited to post surgical information, resulting in a continued gap and opportunity for a preoperative predictor.

Possible Lessons

Perhaps the most important lesson learned is that while research efforts have increased understanding of aspects of physiologic capacity (PC) related to postoperative complications and associated collateral consequences; *more work is needed toward identifying an accepted reliable, valid, and objective predictor of postoperative complications*. While empirical evidence is growing regarding PC parameters as objective predictors for postoperative outcomes, further critical steps are needed to provide definitive answers for clinicians and the 30 million surgical patients each year who are seeking a way to reduce or eliminate their risk of postoperative complications. Hightower et al. (2010) explained, "Continued investigations may ultimately result in the pre-emptive preoperative management of more precisely define physiological risk status, thereby reducing postoperative complications" (Hightower et al., 2010, p. 470). Hightower‟s comment is replete with several major points, namely the plural form of „investigations, ‟ indicating that finding a workable and acceptable solution to the predictive need necessarily requires a sequence of studies of logical steps that bring additional critical knowledge of the exact mechanisms and nature of the relationship between PC and outcomes. Hightower refers to precisely defined risk status. This statement speaks to the confusion and seemingly contradictory results of the various studies that investigated the same PC parameters [anaerobic threshold (AT) set at <11 mL/kg/min and peak volume of oxygen (VO_2)]. The contradictory results created salient questions regarding possible answers for why these findings were not in agreement. Could it be that research to date has tried to force a successful parameter in one study to apply equally successfully to different populations, different surgical types, and different diseases? Put another way are there other PC parameters that are equal or better predictors? Hightower‟s pilot seemed to allude to this possibility with the multivariate model comprised of delta heart rate and predicted max VO_2. Could different PC parameters be predictors for different surgical types? Are there different AT thresholds for diverse procedure types which are significant predictors? Furthermore, could PC parameters predict more than postoperative complications – i.e. hospital costs and length of stay? Lastly, with the knowledge that PC can be improved, pre-emptive intervention measures, for those patients who are at high risk of postoperative complications, may reduce their risk status to low or even eliminate it. While the establishment of PC parameters as predictors of postoperative outcomes is no small finding, the next step (which this dissertation proposal submits) is crucial for answering the essential detailed relationship queries and looming questions that currently remain.

The lesson learned regarding predicting hospital costs and length of stay is one of glaring absence. Currently, no predictive tool exists that preoperatively predicts hospital costs and length of stay. Investigators such as Ferraros et al. (1998); Khan et al. (2005); Kramer & Zimmerman, (2010); Kurki, (2001); Marshall, Vasilakis & El-Darzi, (2005); and Shoemaker et al. (1993) attest to the fact that predicting hospital costs and length of stay are largely determined via calculating costs and stay based on presence or absence of post surgical conditions. Therefore, institutions wait to see if the patient has or does not have a postoperative complication before they forecast collateral consequences and the costs. This then brings us back to the need for a reliable preoperative prediction tool of who will and who will not have postoperative complications. However, Jacobs (2009) posted a strong argument for erroneously associating costs and length of stay solely on presence or absence of complications. He found other confounding nonmedical factors can cause substantial increases in length of stay and costs. In summary, predicting hospital costs and length of stay is primarily dependent on the patient experiencing one or more postoperative complications creating yet another justification for filling the gap for a reliable objective preoperative predictor of postoperative complications.

Perhaps one of the most important lessons to keep in mind regarding the findings of this study is that this is an exploratory study aimed at providing information that will either justify or not justify a larger study. Therefore, the findings of this study are by no means to be generalized to a larger population.

Identified Gaps in the Literature

It is no longer enough to celebrate the advent of the discovery that physiologic capacity holds the key to predicting who will and who will not experience postoperative adverse events. For stopping at this point is akin to stopping at the point where the laws of gravity and lift were discovered; man would never have developed the airplane or space shuttles. Turning again to Hightower; "Systematic expression of CPET data may provide an opportunity to identify even more accurate and precise measures predictive of postoperative outcomes for specific types of surgeries, illnesses, or both" (p. 470). This sentiment is echoed by Snowden (2010) as he wrote, "Further studies will be required to define clinically important levels of cardiopulmonary reserve predictive of postoperative outcomes in other surgical populations" (Snowden, 2010, p. 541). These two quotes are representative of the general consensus of researchers in the field, in that two goals have emerged as next step direction: identify if different PC parameters are associated with different surgical types and identify if there are different threshold measurements that stratify ranges of risk. In fact, the answer to these questions may also provide the answer to the seemingly conflicting findings from different surgeries, different populations, and different parameters. Furthermore, it appears that a reliable objective preoperative risk assessment tool may not only aid in clinical risk management, but may additionally aid in administrative management of resources, costs, bed rotation, and hospital quality measures. It is the expressed goal of this study to address these exact gaps.

Social Change Implications

This study has both immediate and long term implications for social change with the potential for far reaching and dramatic effect. The immediate implication would present a paradigm shift in a priori evaluation of potential surgical patients. Should these finds be validated and accepted, clinicians and hospital administration would receive more accurate and reliable information on each individual patient from which to make data-based decisions regarding the choice of moving forward for scheduling surgery, managing expectations for resources, beds, and hospital costs/revenues. Additionally, since the results of this study found different parameters associated with different surgical types and/or different parameter thresholds associated with various levels of risk for each surgery, similar studies would need to be conducted for other types of surgeries. The latter task could be a life-long endeavor.

Potentially, the two profound social changes may be influenced by the results of this and subsequent sequential studies. The first is for the approximate 12 million non-cardiac non-emergency patients expected to experience one or more postoperative complications this year, the realization that the risk of complications can be reduced or avoided may be welcome news. The second profound social change may impact two national groups: the healthcare industry and health policy makers. When postoperative complications occur, length of stay and hospital expenses rise, and the opposite are true when complications are avoided. Using Arora, Velanovich, & Alarcon (2010) figures that up to 40% of 30 million (12 million) patients undergoing non-cardiac surgery will experience complications each year and using AHRQ"s 2010 Statistical Brief #86 that reports the average inpatient surgical cost of $40K, then adding the average increase of 78% (according to Ferraris, Ferraris & Singh, 1998) the increase in hospital costs due to postoperative complications is a potential staggering $854 billion/year. Recognizing that 100% of the „complication population" will not avoid complications, the savings remains substantial if the estimated complication rate is cut in half; the results garner $427 billion /year in savings. Lest we all rush our legislators for a new law requiring evaluation of physiologic capacity prior to surgery, we must also recognize that a portion of the 12 million patients are emergency surgeries (not elective) and will endure surgery with their current physiologic capacity. Therefore, those emergency surgical patients with poor physiologic capacity would number among the postoperative complication (and subsequent increased cost and length of stay) population and would carry the increased consequences. The extent of societal change in local and national policies, insurance providers, surgical clinicians, hospital administrations, national healthcare administration, budgetary oversight panels, etc. is mind boggling, but cannot be realized unless first, the previous step (application of the present study findings) is taken. Before intervention to improve physiologic capacity can move forward, the correct parameters of physiologic capacity must first be identified along with thresholds of risk stratification. A worthy goal, and worthy of every bit of effort it will take to bring it to pass.

Chapter 3: Research Method

Introduction

This chapter describes the research methods used in the proposed study to explore the relationship between physiologic capacity parameters as predictors of postoperative outcomes and collateral consequences of hospital costs and length of stay among surgical cancer patients undergoing one of three types of procedures. The chapter is comprised of eight sections: The Research Design and Approach (includes Data Collection Design and Justification for Selection of Surgical Types), Population and Sample Size (includes eligibility criteria), Description of Study Variables (includes how variables are measured and operationalized), Instrumentation, followed by the Data Analyses. The chapter also includes a discussion of how Protection of Human Subjects and Dissemination of Findings will be handled, and concludes with a Summary section.

Research Design and Approach

This study continues the exploratory nature and launches from a pilot study in which parameters of physiologic capacity were investigated for risk prediction of postoperative complications *across a group of eight cancer surgeries*. While the findings of the pilot study indicated a multivariate model was a statistically significant predictor in the group of eight surgical types, these findings created two questions as to the predictive ability of parameters in *individual surgical type*s. Therefore, the same basic exploratory design continued in data gathering for the proposed study; however this study initiates two changes. While it continued to explore parameters of physiologic capacity (metrics), continued to evaluate via CPET (measurement tool), and continued to look at the same outcomes (any adverse complication), it focused the exploration on three different surgical types (research question 1) and it investigated stratification of risk ranges (research question 2). In addition, this study also investigated whether physiologic capacity parameters can be utilized as predictors of collateral consequences, specifically hospital costs and length of stay (research question 3).

A retrospective exploratory quantitative analysis study design in the form of a post hoc evaluation was selected to measure the relationship between parameters of physiologic capacity and postoperative complications as well as collateral consequences of hospital costs and length of stay. The dataset was comprised of a non-randomized sample of 103 cancer patients who underwent one of three procedures (esophagectomy, radical cystectomy, or hepatectomy) at M. D. Anderson Cancer Center during 2007 – 2008 and completed a maximal cardiopulmonary exercise test (CPET) during which standard vitals (i.e., heart rate, respiration, blood pressure), EKG, and gas exchange data were collected. Subsequently, data were recorded regarding absence or number of postoperative complications, nature of complications, total hospital costs, and length of stay.

Data Collection

The 103 cases analyzed as part of this study included 22 hepatectomy, 39 radical cystectomy, and 42 esophagectomy cases. This database total includes one hepatectomy and 14 radical cystectomy cases that were extracted from the pilot study and inserted in the total for this study, leaving 89 additional cases added to the database since the pilot study. Inclusion of selected cases from the pilot study serves to enlarge the overall sample and was not expected to adversely affect any results since they fit two of the three specific individual surgical types of the new study focus. Because neither the pilot nor this study involves an intervention in terms of patient diagnosis or treatment, the data from the pilot does not present any difference from the data gathered since the pilot in terms of what is being investigated. Both the selected inserted pilot study data and additional data were gathered according to the same approved protocol design conducted at M. D. Anderson Cancer Center in Houston, Texas under the Principle Investigator Dr. C. Hightower.

Data collection design

The following describes the data collection design and process employed in the gathering of all the data and measures used to reduce study bias at the time the data were collected. Data were collected at three general points in time, pre-surgical time period, intraoperative time period and postoperative time period. The pre-surgical time period included both non-cardiopulmonary exercise data and cardiopulmonary exercise data.

Non-cardiopulmonary exercise data were gathered from an interview, a problem-focused examination, and the preanesthesia evaluation at the appointment before the exercise test and includes:

- Patient demographics
- Patient co-morbidities
- Patient medications
- Patient diagnostic and laboratory test results

- American Society of Anesthesiologists‟ (ASA) Physical Status Classification rank (current standard of care at MD Anderson)
- Surgical procedure and date of procedure.

Cardiopulmonary exercise data were collected during the exercise test (CPET). Each patient‟s raw data was entered into the BREEZESUITE™ program, which translated raw data into usable variable values. These data were then imported to an Excel worksheet, which was uploaded to SPSS® ver. 19.0 for statistical analysis. Data types collected included:

- Pre-cardiopulmonary exercise pulmonary function test results
- CPET gas exchange and resting vitals
- CPET Exercise vitals (includes all gas exchange variables, heart and blood pressure variables)
- Recovery vitals (includes all gas exchange variables, heart and blood pressure variables after exercise portion of test was stopped)

Intraoperative data was collected postoperatively directly from a review of the surgical dictation and the patient‟s anesthesia record then transferred to the postoperative data record and finally to the Excel database:

- Total anesthesia time
- Total surgical time
- All intraoperative complications
- Estimated blood loss
- Urine output

- Intraoperative fluid replacement (type and volume).

Postoperative data were gathered from the patient"s clinical chart by the research nurse and reviewed by two physicians. Data were collected during the acute postoperative observation period (during first 10 days, at 30 days, then at 6 months postoperatively). In keeping with the same process as the previous two time periods, these data were entered into the Excel database:

- Initial postoperative destination
- Actual procedure performed
- Initial postoperative airway status
- Monitors in place at first postoperative destination
- First postoperative destination admission vitals and laboratory test results
- Morbid events during the study"s observation periods CTCAE definitions:
- Mortality during the study"s observation periods CTCAE definitions:
- Total length of Intensive Care Unit and hospital stay
- Total hospital charge to the patient during the surgical admission.

The methodology of data collection utilized a standardization of the classification of adverse events and the reporting procedures by which the Departments of Thoracic Surgery and Urology created an adverse events outcome database (AEOD) that housed data based on the Common Terminology Criteria for Adverse Events (CTCAE), an international method used to classify morbid outcomes (Williams, Chen, Finkelstein, & Okunieff, 2003; National Cancer Institute & National Institute of Health, 2003).

Two teams were involved in gathering data; a preoperative group that completed the Preoperative Data Record and conducted the CPET and the intraoperative/postoperative group that completed the intraoperative forms and Postoperative Data Record. All data contained on preoperative, intraoperative and postoperative forms were entered into the Excel database by this researcher. In an effort to reduce bias in the study the individuals administering the CPET were blinded to the patient‟s postoperative outcomes. All patients underwent their scheduled surgical procedure within one week after CPET. Healthcare providers in the operating room and during the post-operative period were blinded to the results of the CPET. Those individuals identifying postoperative outcomes were blinded to the preoperative results of CPET. Lastly, while the patients were not be blinded to their ASA score (this was available to the patient as part of their clinical record), they were blinded to their CPET results.

Justification for selection of surgical types. Carcinoma of the esophagus is the sixth most common cause of cancer death worldwide (Pisani, Parkin, Bray & Ferlay, 1990). Furthermore, according to a paper published by Ajani et al., (1990) the survival from esophageal cancer remains poor with an overall five-year survival rate of less than 10%. Pisani and team write that "Removal of the esophagus (esophagectomy) has been regarded as standard treatment for patients with resectable esophageal cancer" (Ajani et al., 1990, p. 373). Pisani continues to note that while 5-year survival rates for „healthy‟ patients are typically 25 – 35%, for patients who tolerate surgical therapy poorly, the survival rate declines, resulting in approximating only 30% of patients who will tolerate curative surgery (Pisani et al., 1990, p. 373). While Pisani agrees that "Early, accurate and minimally invasive response evaluation is needed …" (Pisani et al., 1990, p. 378), his cry falls short of recognizing the role that the patient"s physiology may play in the outcome and survival rate. Instead, he maintains a focus on drug therapy and toxicity. This highlights an additional gap in education within healthcare discipline practitioners regarding the role physiologic capacity may play in surgical tolerance. Unless another contributing factor to low-term survival rate is identified (such as physiologic capacity) the future for esophageal cancer patients is short-lived.

Bladder cancer, similar to cancer of the esophagus carries similar statistics. A recent article by Manoharan, Ayyathuri & Soloway (2009) noted that,

> Bladder cancer is the fifth most common cancer in the USA and the fourth most common solid tumour among men, resulting in 13,700 deaths in 2007. The incidence of bladder cancer in the USA is estimated to be 7% of all new cancers diagnosed in men and 3% in women (total 67,000). Although most patients have noninvasive bladder tumours, 20–40% present with invasion or develop invasion during the course of treatment. Radical cystectomy (RC) is considered the optimum treatment for high-grade muscle-invasive bladder cancer. (p. 1227)

Although a few years ago radical cystectomy (RC) was considered a mutilating operation and improvements in surgical techniques have changed that perception, only half of patients are currently cured with surgery and the rate of postsurgical complications continue to remain a challenge (Manoharan et al., 2009, p. 1227). This may be due to the high rate of existing co-morbidities of the majority of patients, ¾ of which are >65 years old. A 25-30% rate of postoperative complications is common according to Manoharan. Interestingly, Manoharan and cohorts also attest to a lack of disease-specific survival studies for RC. This study will add to the current scant knowledge base.

Since the introduction of laparoscopic liver resection (LLR) techniques were applied to solid organ surgery in 1987, hepatectomy (removal of the liver) has remained limited (Trioli et al., 2008, p. 42). Trioli notes that this was largely due to the risk of bleeding, embolism and other complications. A study by Biertho et al. (2002) reviewed 186 laparoscopic liver resections between 1991 and 2001, with a morbidity and mortality rate of 16 and 54% respectively. Trioli (2008) notes that,

> With the evolution of imaging techniques and better understanding of the natural history of hepatocellular tumors, resection of liver cell adenomas (LCA) and focal nodular hyperplasia (FNH) has been progressively restricted. Generally, symptomatic, compressive, or enlarging FNH is considered for resection. Indication to resect LCA is mainly due to the risks of bleeding or the well-documented malignant transformation [5–9]. When surgical treatment is considered for selected patients with benign liver lesions, *absence of postoperative morbidity and mortality are of paramount importance (italics added)*. (p. 38)

However, Trioli also warns that interpretation of results of hepatectomy studies should be read with care due to a "…significant selection bias (absence of retrospective randomized studies comparing OS vs. LLR)" ((Triolo, 2008, p. 42).

Dr. C. Hightower (personal communication, July 18, 2009) explained that a two year internal study for the Department of Anesthesia completed at M.D. Anderson Cancer Center found that 45% of Esophagectomy patients experienced ≥ one complication and a 30-day death rate of approximately 5% per year and 30% of radical cystectomy and hepatectomy patients experienced ≥ one complication and a 30-day death rate of approximately 1% per year. These figures pushed these three surgical procedures to the top of the list for attention toward postoperative complication reduction. Additionally, Dr. Hightower explained that 40% – 60% of patients may receive neoadjuvant chemo-irradiation prior to these surgeries. Furthermore, he indicated that ongoing research is indicating that neoadjuvant chemotherapy or chemo-irradiation may significantly change a patient‟s physiologic capacity prior to surgery (Hightower et al., 2010, manuscript in progress). The treatment path for these surgeries contains a 5 – 8 week recovery period after preoperative neoadjuvant therapy and prior to surgery, which would potentially allow for a risk management intervention to be implemented without an artificial delay in surgery, should this study‟s findings be adopted.

Population and Sample Size. The population that comprises the dataset includes a non-randomized sample of 103 male and female cancer patients >18 years old who underwent a maximal CPET followed within one week by surgical procedure for one of three procedure types. Esophagectomy patients numbered 42; radical cystectomy (bladder) patients numbered 39; and 22 patients underwent hepatectomy (liver). All participants were patients at the University of Texas M. D. Anderson Cancer Center between 2007-2008.

The primary reasons for performing a power calculation are for *prospective* research to assure a sample size with a specified (high) minimum probability of detecting an effect (changes, special causes) if it/they are present, by collecting enough data, and secondly for forecasting what and how much resources in time, money, data collectors, etc. may be required for the research. Performing a power calculation for sample size for this study is of no benefit because the sample size has already been determined according to the number of patients who met inclusion and exclusion criteria and who were willing to sign a consent form to participate in a study and resources have already been expended in gathering the data. According to Dr. W. Fischer, of M.D. Anderson Cancer Center, it is also reasoned that with the given sample size, the "effects" (coefficients, estimated from the data, for each of the physiologic capacity parameters) would only need to be one-quarter the size than if the sample size were doubled (all other factors being equal) in order to be declared significant. However, *if* the parameters" associated p-values *are* equal to or smaller than the individual alpha (0.005), they would be – by definition-significant (personal conversation, December 6, 2010 and Box et al., 1963). In further support of not performing a power calculation, Maxwell, Kelley, & Rausch (2008) stipulate that even though the power of any single test may be low by any reasonable standard, the exploratory nature of the study, which includes conducting multiple tests, makes it highly likely that something of interest will emerge as statistically significant.

Lastly, the pilot study (Hightower et al., 2010) serves as an exploratory study example for the possibility of finding statistically significant findings even in a small sample size. The pilot study collected and analyzed data on 32 patients who completed a CPET within one week of surgery (eight surgical types were included in the pilot study). Analysis showed two univariate parameters and two multi-variant models of physiologic capacity were statistically significant predictors of postoperative outcomes and had higher sensitivity appearing to be better predictors of who is at greater risk of an adverse outcome than the standard American Society of Anesthesiologists (ASA) subjective risk classification score. Additionally, the pilot found that all parameters and models of physiologic capacity had greater area under the curve (AUC) than ASA, indicating greater strength of prediction. While the ASA had higher specificity, suggesting it was a better predictor of who would *not* have a complication compared to physiologic capacity; Hightower et al. pointed out that this could be due to the conservative clinical approach for subjectively assessing the risk score. In other words, it was „better‟ to be wrong about scoring a patient at high risk and they not have a complication than to be „wrong‟ by scoring a patient at low risk and they did have a complication. Therefore, the preference is to score more patients at high risk than low risk deceptively increasing the specificity prediction. Pilot study findings indicated that physiologic capacity may act as a refiner in those cases where the clinical impression may be unknowingly in error, thereby increasing sensitivity to 93% and increasing specificity to 75%.

Eligibility criteria. Inclusion and exclusion criteria are delineated in the table below.

Table 2

Inclusion and Exclusion criteria for qualifying patients from which data were gathered

Inclusion Criteria	*Exclusion Criteria*
1. Patients >18 years of age 2. Patients must sign an informed consent form 3. Patients must be screened in the Anesthesia Assessment Center 4. Patients must be scheduled for one of the following surgeries: • Esophagectomy • Radical Cystectomy • Hepatectomy	1. Any patient that is unable to exercise 2. The patient is deemed unsatisfactory for surgery after preanesthetic evaluation 3. Surgery is cancelled for any reason 4. Suffered a myocardial infarction within 3 months of visiting the preanesthesia clinic 5. Suffered a Cerebrovascular event 6. Suffered a transient ischemic attack within 3 months of visiting the preanesthesia clinic 7. Suffered a pulmonary embolic event within 3 months of visiting the preanesthesia clinic 8. Existing acute or chronic deep vein thrombosis 9. Pregnant patients

Study Variables: Operationalization, Descriptions, and Measurements

Because this study is an exploratory study design the candidate variables under consideration (but not limited to) are listed below with a description of each with the level of measurement. These are based on standard known parameters associated with physiologic capacity and study findings presented in the literature review.

Table 3

Variables: Operationalization, Descriptions, & Measurements

Dependent Variable	Description of Variable	Level of Measurement
Adverse postoperative complication	Presence (how many) or absence of any postoperative adverse complication	Number and type of complications
Independent Variable		
AT	Aerobic Threshold	ml/min and ml/min/kg
%AT (PAT)	Percentage of predicted AT achieved	<75% vs. ≥75% (dichotomized) (Older, 1993)
Blood loss	Blood lost during surgery	Volume of blood in ml
VCO_2	Carbon dioxide output)	L/min., mL/min., or mL/kg/min.
$\%PVO_2$	% of predicted peak VO_2 achieved	mL/min
PVO_2	Peak oxygen uptake	ml/min and ml/min/kg
HR1	Heart rate at AT	beats/min
HR2	Heart rate at 1min. post test stop	beats/min
HR3	Heart rate at Peak VO_2	beats/min
ΔHR1	Heart rate difference between resting and max	beats/min

(*table continued)*

Independent Variable	Description of Variable	Level of Measurement
Time	Time taken for HR to drop to	In minutes and seconds
	100bmp after test stop	
Oxidative energy reserve capacity	difference in O_2 at rest and at AT	ml/min
Physiologic energy reserve capacity	difference in O_2 at rest and at PVO_2	ml/min
PAT	Predicted AT	calculated value in ml/min
VE_3	Minute ventilation at AT	ml/min
ΔHR1+ PAT	Multi-variate model combining ΔHR1 and PAT	calculated model

Instrumentation

Reliability and validity of gas uptake equipment

Medical Graphics Corporation is the manufacturer of the CardiO2/CP™ patented noninvasive cardiorespiratory diagnostic system and BREEZESUITE™ software used to gather the gas exchange and vitals data during cardiopulmonary exercise testing. The system interfaced the gas exchange uptake values with a cycle ergometer, pulse oximeter, and12 lead electroencephalograph (ECG). Blood pressure values were periodically manually captured by the test technologist using standard cuff, sphygmomanometer and stethoscope. The MEDGRAPHIC™ technologies provided direct and precise breath-by-breath metabolic measurement of respiratory flow, airway pressures, analysis of the inhaled-exhaled breath, and 12 lead electroencephalograph (ECG) without compromising for, diverting or turning off bias flow while protecting against cross-contamination. This provided measurement performance of each patient‟s respiratory and cardiovascular system which produced the most complete global indicator of functional capacity. It also meets or exceeds published performance standards for accuracy and reproducibility.

MEDGRAPHICS™ BREEZESUITE™ combines gas exchange and pulmonary function testing capability into this research software. BREEZESUITE is also 21 CFR Part 11 and HIPAA compliant. This technology is used around the world in hospitals, clinics, and universities to diagnose, treat, and prevent heart and lung disease. (http://www.medgraphics.com)

Data Handling

Data transfer, translation, cleaning, coding, and organizing

Data transfer. Upon receiving IRB approval by Walden University, the pre-existing raw data were downloaded from an institutional file owned by Dr. C. Hightower (Principle Investigator of the study data at M. D. Anderson Cancer Center) to an encrypted slip drive and subsequently uploaded to this investigator‟s personal laptop computer into the BreezeSuite® software.

Data translation. All raw gas exchange and vitals data captured during the cardiopulmonary exercise test (CPET) were accomplished via CardiO2/CP™, a patented noninvasive cardiorespiratory diagnostic system manufactured by Medical Graphics Corporation. The MEDGRAPHIC™ technologies also provided direct interface to the BreezeSuite® software that was used to translate the raw dichotomic data into understandable and usable data for statistical analysis. A Microsoft Excel spreadsheet was created by copying the data provided by BreezeSuite® and pasting it into Excel. Once the data were cleaned, complete, and organized they were imported to Spotfire® software (TIBCO Software, Inc., 2011) for graphical analysis and SPSS GradPac Premium statistical software version 19.0 (SPSS Inc., 2011) for statistical analysis.

Data cleaning and discarding. Data transferred from Dr. C. Hightower was scrubbed of all personal identifiers with only study ID numbers, age, gender, and race identifying each participant‟s case. Of special note; no data were missing for any case.

Once the BreezeSuite® program translated the raw data, a variety of formats was available from which to view the data. One of the formats, used in this study, displayed researcher- chosen variables (from a provided list) for all cases, in a table format. A total of 10 variables were selected and the resulting table was subsequently copied and pasted into an Excel worksheet. The systematic process then turned to data cleaning, which entailed a visual comparison of the data displayed in the BreezeSuite® application with the same data displayed in the Excel worksheet for any copy errors, outliers, and discard-able data. No data copy errors were found and no outliers were identified. Although the original dataset included 113 cases, 10 cases were discarded because the patients never went to surgery. This resulted in the final dataset count of 103cases.

Data coding and re-coding.

Dependent variable coding and re-coding. While only one dependent variable (postoperative complications) was considered in this study, it was subjected to a two-step coding process. The first coding process created a dichotomic variable for correlation and logistic regression analysis. A code of "0" was assigned if the patient did not experience any postoperative complications. A code of "1" was assigned if the patient experienced one or more postoperative complications. A re-coding process was limited to all patients who had one or more postoperative complications. Each of the complications was assigned the corresponding Common Terminology for Clinical Adverse Events (CTCAE) standard classification category (see Appendix D) relating to the type of complication experienced. Although this effort was not a focus of the present study, when occurrences for each complication type were tabulated, this approach provided new information (See Exploratory Analysis section in this chapter for detailed results and discussion) regarding trends unknown or not recognized prior to this analysis. No coding problems were observed for the dependent variable.

Independent variable coding and re-coding. The dataset was comprised of a total of 25 independent variables (IVs) that included three demographic variables of age, gender, and race. These variables were used in descriptive statistical analysis and in correlation analysis. Age was categorized as a continuous variable. Gender was coded as a bivariate with "0" assigned to males and "1" assigned to females. Race was categorized as a discrete variable and continued the categorization established from the pilot study (White/Caucasian, African American, Hispanic/Latino, Asian, and Other).

A total of 10 base CPET variables were directly measured during the exercise test and obtained from BreezeSuite®, an additional 10 variables were derived (calculated) from the base CPET variables. Table 6 below lists the base and the derived variables. The remaining 2 variables (hospital costs and total length of stay) were provided by M. D. Anderson"s Patient Business Services Department. The independent derived variable of „PercentofPredictedAT" (measured as mL/kg/min) was re-coded as a dichotomized variable according to who did and did not achieve at least 75% of their predicted anaerobic threshold. Those who did not achieve at least 75% were assigned a "0" and those who achieved $\geq$ 75% of what was predicted were assigned a "1". This dichotomized treatment of predicted anaerobic threshold is one of the two predictive variables that comprised the multivariate model which was a significant predictor from the pilot study. A second re-coding also involved the „HRTime" variable. This variable was originally documented as the actual time it took the individual‟s heart to drop to or below 100 bmp. The variable was re-coded according to the following discrete scale.

0 = achieved heart rate at or below 100bmp in ≤ 1 minute

1 = achieved heart rate at or below100bmp > 1 min. < 2 min.

2 = achieved heart rate at or below100bmp > 2 min. < 3 min.

3 = achieved heart rate at or below100bmp > 3 min. < 4 min.

4 = achieved heart rate at or below100bmp > 4 min. < 5 min.

5 = it took 5 minutes or longer for the heart rate to drop to or below 100bpm

It has been well established in exercise physiology textbooks and cardiology published research (de Vries, 1966, chapter 11; Cole, Blackstone, Pashkow, Snader, & Lauer, 1999) that a good physiologic capacity results in the heart rate returning to pre-exercise levels between 10 – 15 minutes, and at or below 100 bmp within one minute post-exercise. Cole et al. reported that, "A delayed decrease in the heart rate during the first minute after graded exercise, which may be a reflection of decreased vagal activity, is a powerful predictor of overall mortality, independent of workload" (Cole et al., 1999, p. 1351). Until now, this variable (HRTime) has not been considered in research outside of cardiology aimed at identifying an objective preoperative predictor.

After completion of data cleaning, coding, recoding, and organization, descriptives of mean, standard deviation (SD) and p-values were obtained for both demographic data and the 20 physiologic variables considered in the first step toward investigating prediction possibilities. While Table 5 below shows values for the demographic data, Table 6 displays all 20 independent variables (base and derived) with respective mean, SD, and p-values. Because no physiologic independent variable was found to be 0.05 or less (predetermined alpha) in the Esophagectomy cases no further computations were completed for any physiologic parameter for this surgical type

Data Analysis

This research investigated physiologic capacity parameters (PCPs) as potential predictors of postoperative complications, across three surgical procedures and within the three procedures. The approach was a retrospective exploratory graphical and numerical analysis of data gathered on a total of 103 subjects who underwent one of three cancer procedures (42 esophagectomy, 39 radical cystectomy, and 22 hepatectomy) during a two-year time period of 2007-2008. In addition, the PCPs will be evaluated as potential predictors of associated collateral consequences including hospital costs, length of stay and long-term survival rates.

The use of Multivariate Exploratory Graphical Analysis (MEGA) was conducted first using Spotfire® software (TIBCO Software, Inc., 2011) A visual display of the distribution of the data will note the normal vs. skewness (asymmetry), kurtosis (shape of the distribution), and possible outliers (extreme values). This will serve to guide the direction and inform the choices of statistical methods to employ in the numerical analysis.

The numerical analysis is comprised of two phases. The first phase included forward addition and backward elimination stepwise logistic regression to identify statistically significant PCPs that formed statistically significant models with high predictive value for postoperative complications. These models were also tested for prediction of collateral consequences, namely hospital costs and length of stay.

Because this study is exploratory in design, the first phase considered 25 candidate variables thereby requiring multiple analyses. This situation necessarily runs the risk of creating a Bonferroni effect. The use of the Bonferroni correction reduced the likelihood of a Type I error. Therefore, an individual test alpha was set at the standard 0.05 with an overall alpha of 0.10. Although a larger overall alpha is supported by a growing evidence in the body of literature that indicates the null hypotheses for research questions 1 & 2 (listed in Chapter 1 and found in Tables 3 & 4), are false, this study maintained the standard alpha at 0.05 in keeping with published studies. After statistically significant models were generated, phase two began. Each model was ranked using ROC calculations. Clinical preference dictates the willingness to have more false-positives or Type I errors, indicating the patient is at risk for complications when they really are not, than to categorize patients as low risk who really are at high risk of complications. Therefore, in computing the receiver operating characteristic (ROC) curve for determining strength of prediction for sensitivity (who will a have complication) and specificity (who will not have a complication), the specificity was increased by increasing the cut-off level to .62, even at the cost of a lower sensitivity for clinical application purposes (Hightower et al., 2010). This analysis design continues the data analysis methodology utilized in the pilot study by Hightower et al. (2010) and is expected to help identify any additional model(s) that may be predictors in individual surgical types or a better predictor of postoperative outcomes and collateral consequences than the pilot study found.

Table 4.

Statistical Procedures by Research Question

Research Question	Corresponding Hypothesis	Statistical Procedures
RQ1: Are different surgical procedures associated with different predictive physiologic capacity parameters?	H1 Null: Different surgical procedures will have no association with different physiologic capacity parameters, as measured by the CPET test. H1 Research: Different surgical procedures will have significant association with different physiologic capacity parameters, as measured by the CPET test.	Forward adding and backward elimination stepwise logistic regression calculations to determine which univariate and multivariate models are statistically significant. This was followed by computation of receiver operating curve (ROC) and noting area under the curve (AUC) for strength of specificity and sensitivity of predictiveness for each model.
RQ2: Are there different threshold ranges that stratify risk for each surgical type?	H2 Null: Threshold levels that stratify risk of each surgical type, as measured/determined by the associative predictive parameter, will demonstrate no significant difference. H2 Research: There will be a significant difference in threshold ranges that stratify risk for each surgical type, as measured/determined by the associative predictive parameter.	For each variable model found to be statistically significant, observation of the data was conducted to determine if there was a natural break, differentiating a range, where patients had no adverse complications vs. one complication vs. more than one complication.
RQ3: Is there a correlation between risk parameters and collateral consequences including costs and length of stay?	H3 Null: No significant correlation exists between risk parameters as measured/determined by the associative predictive parameter, and collateral consequences as measured by hospital costs and length of stay. H3 Research: A significant correlation exists between risk parameters, as measured/determined by the associative predictive parameter, and collateral consequences as measured by hospital costs and length of stay.	Multivariate regression calculations were performed on PC variables to determine (if any) association exists with the two collateral consequences of hospital costs and length of stay.

Any significant differences in the models (and collateral consequences) due to the three surgical procedures was detected through the use of dummy (indicator) variables (Garavaglia and Sharma, 1998). This uses single regression equations to represent the three groups, thereby preserving the larger sample size. In essence, the dummy variables act like “switches” that turn various parameters on and off in an equation. All statistical analysis will be performed using SPSS® software ver. 19.0.

Potential limitations

Potential limitations and plausible explanations include:

1. The study is not randomized. According to Pagano (2004) and Smith (1983) non-randomization in an exploratory study is widely accepted. Non randomization can be used when the research does not aim to generate results that will be used to create generalizations pertaining to the entire population. Non-randomization is often employed in an initial study which will be carried out again using a randomized sampling. (Pagano, 2004, Chapter 8) Such is the case with this study. Additionally, internal validity is secure due to the objective unbiased nature (derived directly from the patient"s physiology) of the data. Since this study is considered exploratory, external validity may be further supported by a larger study.
2. The study is biased in that only patients willing to complete a maximal exercise stress test were included in the dataset. Because parameters of physiologic capacity are derived from gas exchange uptake variables during a cardiopulmonary stress test, this requirement/limitation is necessary. All of the patients in the study"s database fully completed a maximal exercise stress test.
3. The study is biased in that only patients who underwent one of three surgical types were included in the dataset. This limitation is embedded in the first

research study question which is purposed to answer a question created by the findings of the pilot study.

4. There was no control as to whether a patient significantly increased or decreased his/her level of activity within the 1-week period between his/her CPET and their scheduled surgery. Although there was no control over the patient‟s activity level after the CPET, according to McArdel, Katch, Katch (2010), a person‟s physiologic capacity cannot be significantly increased or decreased in a one-week period by changing their activity level (chapter 21, section 4). Therefore, to ensure the patient‟s physiologic capacity remained the same at the time of surgery as when it was tested during CPET, the study protocol demanded the surgery be performed within 1-week post CPET.
5. This study does not evaluate the degree of variability in patients‟ risk levels. The purpose of this study relative to Research Question 2 is to identify possible threshold ranges of risk stratification for each surgical type. Evaluating the degree of variability in risk threshold levels is beyond the scope of this study.
6. The study is limited to the 103 participants who were patients at the University of Texas M. D. Anderson Cancer Center and were being treated for 1 of 3 specific diagnoses (esophageal, bladder, and liver cancer). Due to the continued exploratory nature of the investigation, including patients outside of MD Anderson cancer center and patients undergoing other types of cancer surgery is beyond the scope of this study.

7. All financial data were limited to the information provided by the business office at the University of Texas M. D. Anderson Cancer Center and were calculated based on the hospital charges (a product of objective standard billing amounts). It is recognized that other institutions may practice different charge amounts for similar or the same services that are a part of this study. However, since this study is not intended to be compared to any other institution, rather limited to exploring a possible link between an objective predictor of physiologic capacity and hospital charges (research study question 3) comparison to other institutions is outside the scope of this study.
8. Evaluation of non-participant patients is not included in this study. A comparison between participants and non-participants is beyond the scope of this study. The study protocol under which the data was gathered did not include obtaining consent from non-participants for demographic or other comparative purposes. Additionally, since the aim of the study is to identify a predictive parameter of physiologic capacity, data to that end cannot be obtained without the patient completing a cardiopulmonary exercise test, which would then include them as a participant.

Research Center

Since the study is comprised of patients attending the University of Texas M. D. Anderson Cancer Center, characteristics of this institution are provided. Among the many attributes of MD Anderson, as publicly published in their institutional profile (http://www.mdanderson.org), are its standing as one of the nation"s original three comprehensive cancer centers (designated by the National Cancer Act of 1971) and one of 40 National Cancer Institute-designated comprehensive cancer centers today. It has been consistently ranked either #1 or #2 among "America"s top Hospitals" by the US News and World Report magazine and achieved the ranking of #1 seven of the past nine years. It invested more than $547 million in research in FY2010, boasts of over 1170 active research protocols, ranks first in the number of research grants awarded and total amount of grant funds given by the National Cancer Institute, and "…encompassing more than 50 buildings stands as the largest freestanding cancer center in the world… featuring the latest equipment and facilities to support growing needs in outpatient and inpatient care, research, prevention and education" (www.mdanderson.org).

With patients coming from across the United States and internationally, MD Anderson expanded additional centers in Florida, Arizona, and New Mexico as well as international centers in Madrid, Spain and Istanbul, Turkey. During Fiscal Year 2010 over 105,000 patients (800,000+ since 1944) were admitted with more than 32,000 being new patients. About one-third continue to come from outside Texas and nearly 10,000 participate in clinical trials, making it the largest such program in the nation. Patients are self-referred, referred by their personal physician, and referred from other hospitals and cancer centers. MD Anderson has a long standing tradition of providing care to low-income residents as testified by the recorded numbers during the last decade (FY00-FY09) of almost $2 billion in unsponsored charity care charges. (MD Anderson Cancer Center, 2011) Because this study is an exploratory investigation, comparison of patients deciding to go to or not go to MD Anderson for treatment is beyond the scope of this study.

Role of the student researcher

The role of this student began as a part of the pilot study team. This student was intricately involved in developing the design methodology and protocol, gathering the original pilot study data, reviewing and interpreting the data analysis, and writing the findings for publication. After the pilot study findings were completed, this student played a critical role in discussion with the principal investigator regarding the formulation of the next step of research (this study). For this study, this student played a major part in gathering and entering the new data in the database and performed the data analysis on the study data. The role of analysis for this study is a critical role from the principle investigator‟s perspective, this student‟s perspective, and the research perspective, as no further steps toward an intervention or other critical research can be undertaken until this segment is completed. In fact, the writing and submission of an R01 federal grant hinges on the findings of this data analysis. As a PhD dissertation project, this student is the only person who has definitively set in writing the theoretical foundations, the exhaustive literature search of support for this study and will do the full analysis and reporting.

Protection of Human Subjects

The data used in this study are derived from an approved extension of a pilot study (see Appendix C for letter from M. D. Anderson acknowledging this student as an approved collaborator on the pilot and extended collection study) and was reviewed and approved by the Institutional Review Board (IRB) of the University of Texas M. D. Anderson Cancer Center with exempt status (IRB approved protocol #20050303) and the approval from the IRB board of Walden University was secured prior to data analysis . Being retrospective in nature the study design presents no risk or harm to any human participant and does not require patient consent forms.

Additional measures have been taken to ensure participant and data security and confidentiality. All data was scrubbed of personal identifiers by the principle investigator at M. D. Anderson with study identifier numbers assigned to each individual‟s set of data. Data is electronic in format and are housed in a double locked environment with access to only those in need of the data on the study. In keeping with the Health Insurance Portability and Accountability Act (HIPPA) of 1996 and requirements of M. D. Anderson, this researcher holds a current Human Research Curriculum certificate from CITIProgram Collaborative Institutional Training Initiative. This training and certification meets all HIPAA human subjects‟ regulations training. A certificate in Good Clinical Practice training is also current from the same institution. (See Appendix A and B)

Dissemination of Findings

Study findings are expected to be disseminated to the University of Texas M. D. Anderson Cancer Center - Anesthesiology and Pain Management Department: Dr. Curtis Hightower and to Walden University via final dissertation paper. Depending on the results of the analysis and interpretation several potential papers will be considered for writing and publication. Possible appropriate journals include The British Journal of

Anaesthesia (the results of this study would be a follow up to the publication of the pilot study results in this journal), various healthcare journals, journals dealing with economics and healthcare policy journals.

Summary

This chapter presented the proposed research methods for analyzing the possible relationship between physiologic capacity parameters and postoperative outcomes and collateral consequences (hospital costs and length of stay) among patients who underwent one of three types of cancer surgery (esophagectomy, radical cystectomy, and hepatectomy). A non-randomized sample of 103 patients who were diagnosed with one of three types of cancer and underwent surgery at the University of Texas M. D. Anderson Cancer Center between 2007-2008 were analyzed according to distinct methodologies of exploratory data analyses. The purpose of the data analyses was to determine whether or not predictive parameters of physiologic capacity are the same or different for each surgical type and if the different surgical types are associated with the same or different variable threshold ranges. Additionally, the data analyses determined whether or not the predictive parameters of physiologic capacity were associated with collateral consequences of hospital costs and length of stay.

Chapter 4: Results

Overview

This chapter describes the data and analysis conducted to address the study‟s three research questions. It consists of four major sections. The Introduction section briefly describes the purpose of the study and reviews the corresponding three research questions. The second section, data handling, describes the data transfer, preparation, cleaning, and organization. The third section, exploratory data analysis, comprises the majority of this chapter and is further subdivided into three sections. The first subsection is descriptive results related to demographics by each surgical type and overall. The second subsection covers the physiologic independent variable treatment and results including collinearity/multicollinearity testing and ROC curves. The third subsection provides an analysis of the dependent variable. The fourth subsection provides the analysis of the collateral consequences: length of stay and hospital costs. The last and final section, Summary of the Findings, provides a comprehensive discussion of how the exploratory analysis was conducted to address each of the research questions and discusses the summary of the findings.

Introduction

The handful of research in this arena generally acknowledges that some aspect of physiologic capacity has a significant correlation to postoperative complications. However, the limited research to date has investigated physiologic capacity parameters in an admittedly scattered approach. Lack of a systematic approach has resulted in confusion and conflicting findings (Forshaw, 2008; Goldman, 1983; Hightower, 2010;

Nagamatsu, 2001; and Older, 1993). Running contrary to a scattered approach, this study launches from a pilot that found a statistically significant two-parameter model predictor for an aggregate population of cancer patients who underwent eight different types of cancer surgery. The resulting research question emanating from the pilot study results asked if there are different physiologic capacity predictors for *individual surgical types*. The present study then, as the next sequential step of the study stream, was developed to address this query. Ironically, it is also the only known study to address this research question. Therefore, the purpose of this study was to explore the relationship between parameters of physiologic capacity and postoperative outcomes among cancer patients undergoing one of three types of cancer surgery (esophagectomy, hepatectomy, and radical cystectomy). A pre-existing dataset containing 103 cases was used in this retrospective analysis to explore the following three research questions:

Research Question 1: Are different surgical procedures associated with different predictive physiologic capacity parameters?

Research Question 2: Are there different threshold ranges that stratify risk for each surgical type?

Research Question 3: Is there a correlation between risk parameters and collateral consequences of hospital costs and length of stay?

Before describing the findings of the study related to the research questions, it is appropriate to describe how the data was handled including; the data translation process, why data was discarded, data cleaning and preparation, and data organization.

Exploratory Data Analysis

The results are presented in four sections with each section displayed by surgical type and as an overall population set. The first section describes and presents results for demographics, the second section describes and presents results for the physiologic independent variables, the third section describes and presents results regarding the dependent variable, and the final forth section describes and presents the analysis of the collateral consequences related to hospital costs and length of stay. It is important to remember that the results of this chapter should not be generalized to any population other than this exploratory study"s population.

Demographic results.

Age. Although the mean age for the overall study population was 61 years, the Hepatectomy population group proved to be the youngest with a mean of 55 years and the Radical Cystectomy population group trailed as the oldest with a mean of 66 years. (See Table 5) Age was not correlated with presence/absence of complications as results of correlation analysis returned *p*-values of .57 for the entire dataset, $p = .51$ for esophagectomy dataset, $p = .64$ for hepatectomy dataset, and $p = .48$ for the radical cystectomy dataset.

Gender. Table 5 shows males comprised the largest portion of the overall dataset with a total of 77 (75%). The esophagectomy group carried the largest portion of males at 38 (90%) and the radical cystectomy group was second with 30 (77%) males. The balance of gender changed slightly for the hepatectomy group with a larger portion of females at 13 (59%). Interestingly, although there were a greater percentage of females in this group, the females comprised the smallest proportion of complications at only 23%. Males comprised 91%, 67%, and 71% of all complications in the esophagectomy, hepatectomy and radical cystectomy groups, respectively. Looking further at females, a greater percentage (56%) of females in the radical cystectomy group experienced complications and half (50%) of the females in the esophagectomy group experienced complications. On the other hand, 53% and 67% of the males in the esophagectomy and hepatectomy groups respectively experienced complications. Only the hepatectomy surgical group showed males with a significant ($p \leq .05$) relation to postoperative complications with a p-value of .043. This may indicate that males face an increased chance of postoperative complications for this specific surgical type. However, when gender was added to a logistic regression equation it was not found to be a significant variable in a predictive model for the hepatectomy group. Further explanation is found later in this chapter. It is worth noting that caution should be used in any conclusions drawn from these results due to the sample size in this exploratory study for this surgical type.

Race. Table 5 below also shows White/Caucasians comprised the greatest portion of the overall dataset at 87 (84%) of a total 103. Hispanics were a distant second with 9 (9%), African American/ Blacks with 5 (5%), and Asians with 2 (2%) comprised the remainder of the dataset. Forty-one (84%) of all complications were experienced by Whites/Caucasians. Breaking down for each surgical type; 51% of White/Caucasians undergoing esophagectomy experienced complications. Likewise 40%, and 46% of White/Caucasians experienced complications in the hepatectomy, and radical cystectomy groups respectively. Of the Hispanics undergoing each procedure, 50% experienced complications for esophagectomies and radical cystectomies and 40% experienced complications undergoing hepatectomy. For African Americans/Blacks 50% of those undergoing esophagectomy and hepatectomy experienced complications and the one African American/Black undergoing radical cystectomy had at least one complication. There were no Asians who underwent hepatectomy and the one Asian who underwent radical cystectomy did not experience a complication. However, the one Asian who underwent esophagectomy did experience at least one complication. Results of correlation analysis for this study population showed no significant relationship exists between race and presence/absence of complications with esophagectomy at .93, hepatectomy at .96, radical cystectomy at .56, and the overall dataset at .95 (See Table 5). Again, due to the small sample size, especially for some of the race categories, the presented results are based on the present study population and no generalization should be construed to a larger population.

Table 5

Frequency distribution of three demographic variables among study subjects (N = 103) segmented by surgical type and overall, and correlation to postoperative complications.

	Esophagectomy $n = 42$	Hepatectomy $n = 22$	Radical Cystectomy $n = 39$	Overall $n = 103$
AGE	$p = .51$	$p = .64$	$p = .48$	$p = .57$
Mean	59	55	66	61
SD	12	13	10	12
Minimum	26	36	[illegible]	[illegible]
Maximum	78	79	[illegible]	[illegible]
Gender	$p = .92$	$p = . .043$	$p = .52$	$p = .28$
Male (% of patients)	38 (90%)	9 (41%)	30 (77%)	77 (75%)
% with complications	20 (53%)	6 (67%)	12 (40%)	39 (51%)

Table continued

Gender	*p* = .92	*p* = .043	*p* = .52	*p* = .28
Female	4 (10%)	13 (59%)	9 (23%)	26 (25%)
% with complications	2 (50%)	3 (23%)	5 (56%)	10 (38%)

Race	*p* = .93	*p* = .96	*p* = .56	*p* = .95
White/Caucasian	37 (88%)	15 (68%)	35 (90%)	87 (84%)
% with complications	19 (86%)	6 (67%)	16 (89%)	41(84%)
African American/Black	2 (9%)	2 (9%)	1 (3%)	5 (5%)
% with complications	1 (5%)	1 (11%)	1(6%)	3 (6%)
Hispanic/Latino	2 (9%)	5 (23%)	2 (5%)	9 (9%)
% with complications	1 (5%)	2 (22%)	1 (6%)	4 (8%)
Asian	1 (5%)	0	1 (3%)	2 (2%)
% with complications	1 (5%)	0	0	1 (2%)
Total complications	22 (52%)	9 (41%)	18 (46%)	49 (48%)

*Significant at $p \leq .05$. *n* = number of cases for the specific surgical type: *SD* = standard deviation.

Physiologic Independent Variable Results

Research Question 1: Are different surgical procedures associated with different predictive physiologic capacity parameters?

Research Question 2: Are there different threshold ranges that stratify risk for each surgical type?

To address Research Questions 1 and 2, the physiologic independent parameter dataset began with 20 independent variables (IVs). Ten „base" variables were directly measured from the cardiopulmonary exercise test and translated through BreezeSuite™. Ten additional variables were derived (calculated) from the measured base variables. Table 6 lists the base and derived physiologic variables that comprised the total dataset. Two remaining independent variables (total length of stay and total hospital costs) were related to the consequences of surgical outcomes, addressing Research Question three and were only considered if statistically significant predictive parameters were found. Table 6 shows means and standard deviations for all IVs by surgical type and overall dataset groups. Also included in table 6 are correlation analysis results (p-values) comparing each IV to presence/absence of complications. (Each independent variable"s acronym is defined and the associated unit of measure can be found in Appendix E.) Interestingly, no variables showed a *p*-value of 0.05 or less for Esophagectomy cases. Therefore, no further independent variable analysis of cases in the Esophagectomy surgical type group was conducted.

Table 6.

Physiologic Independent Variables demographic (mean and standard deviation) and correlation results (p-value) for presence/absence of complications: Directly measured and derived independent variables are segmented for each surgical type and overall.

	Esophagectomy n=42			Hepatectomy n=22			Radical Cystectomy n=39			Overall n=103		
Directly measured IVs	*Mean*	*SD*	*p-Value*	*Mean*	*SD*	*p-Value*	*Mean*	*SD*	*P-Value*	*Mean*	*SD*	*p-Value*
RHR	82	17	.874	81	10	.824	77	13	.399	80	14	.908
MHR	142	23	.770	152	19	.390	133	21	.117	141	23	.447
HRatAT	113	19	.802	118	14	.757	109	17	.133	113	18	.490
$HRatPV0_2$	131	30	.948	144	20	.664	127	20	.149	132	25	.274
HRat stoptest	141	23	.797	152	19	.409	131	21	.132	139	23	.478
HRat1minrec	120	21	.540	127	31	.540	118	20	.051	121	23	.492
$AT_{mL/min}$	1230	319	.728	1080	401	.057	1059	458	.288	1133	399	.930
$AT_{mL/min/kg/}$	11	3	.921	10	3	.014	9	3	.045	10	3	.568
$PV02_{mL/min}$	1697	439	.319	1501	533	.101	1428	460	.300	1553	479	.779
$PV02_{mL/min/kg}$	21	5	.476	19	6	.032	17	5	.167	19	6	.800
Derived IVs												
PMHR	161	12	.507	165	13	.824	154	10	.481	159	12	.521
% PMHRA	88	13	.893	92	10	.318	86	12	.116	88	12	.518
ΔHR1	31	20	.969	37	13	.603	32	13	.286	33	16	.395
ΔHR2	50	33	.400	63	18	.711	50	19	.362	53	26	.263
ΔHR3	20	18	.574	24	26	.496	16	20	.539	19	21	.560
HRTime	3	2	.161	4	2	.037	3	2	.220	4	2	.349
$PredAT_{mL/min}$	1103	285	.264	976	346	.110	928	299	.301	1010	312	.780
$PredAT_{mL/min/kg}$	14	3	.120	12	4	.008	11	3	.167	12	4	.800
$\%PredAT_{mL/min}$	113	18	.155	113	33	.899	113	20	.550	113	22	.371
$\%PredAT_{mL/min/kg}$	83	20	.120	80	14	.880	86	18	.247	83	18	.703

Collinearity and Multicollinearity. All 20 physiologic IVs for the remaining two surgical types were subsequently subjected to tests for collinearity. Collinearity refers to a linear relationship between two variables. For example: a linear relationship is readily known to exist between the predicted maximum heart rate (PMHR) and Age because the PMHR is calculated from 220 minus Age. Another example is the predicted anaerobic threshold (PredAT) and peak volume of oxygen ($PV0_2$) because PredAT is a calculated value using 65% of $PV0_2$ according to the American College of Sports Medicine"s Guidelines for Exercise Testing and Prescription (8th ed). For collinearity, linear regression was used to identify values of .05 or less which indicated a high linear relationship with the comparative variable. All 20 IVs were entered in the linear regression analysis with the one dependent variable – postoperative complications. Once identified, variable sets with low significance ($p > 0.05$) were reviewed for removal (Tabachnik and Fidell, 2007) resulting in a revised list (see Table 7 below) of three remaining IVs that passed the collinearity test and met preset alpha criteria (≤ 0.05): ATkg ($p = 0.014$ hepatectomy and 0.045 radical cystectomy), PV02kg ($p = 0.032$ hepatectomy), and HRTime ($p = 0.037$ hepatectomy).

Table 7

Revised list of independent variables

Surgical Type	Variable Name	*P*-value
Overall	No variables were significant	
Esophagectomy	No variables were significant	
Hepatectomy	HRTime	.037
	$PV0_2$ mL/min/kg	.008
	AT mL/min/kg	.014
Radical Cystectomy	AT mL/min/kg	.045

table continued

Predictive results

Predictive results for Hepatectomy. Logistic regression analysis would be the next logical step toward identifying predictive power in the hepatectomy surgical group; however, logistic regression assumes that no multicollinearity exists among the three candidate variables. Since SPSS does not test for multicollinearity in its logistic regression analysis (Field, 2005), a multiple regression test was performed in order to test the assumption of the absence of multicollinearity among the three variables for the hepatectomy group. Multicollinearity occurs when two or more variables in multiple regression models are too highly related, limiting the ability to analyze the predictive nature of the individual variables (Field, 2005 and Farrar & Glauber, 1967). Again, values of ≤ 0.10 were noted for decision to reject one or more of the highly related candidate variables. A Multiple Regression test provided interesting results in that the variable „HRTime" showed a *p*-value of .05 indicating there is statistical significant association between HRTime with both $AT_{mL/min/kg}$ and $PV0_{2\ mL/min/kg}$ together. To the contrary, HRTime has no relationship with either of the two other variables individually. In fact, Pearson correlation between HRTime and $PV0_{2\ mL/min/kg}$ was 0.139 and the Pearson correlation between HRTime and $AT_{mL/min/kg}$ was 0.251. Therefore, a model with all three variables for the hepatectomy group was rejected. Both $PVO_{2\ mL/min/kg}$ and $AT_{mL/min/kg}$ variables passed collinearity and multicollinearity tests and retained consistent *p*-values of 0.008 for $PV0_{2\ mL/min/kg}$ and 0.014 for $AT_{mL/min/kg}$ in the hepatectomy group. HRTime held a *p*-value of 0.037 when fitted with either $PV0_{2\ mL/min/kg}$ or $AT_{mL/min/kg}$ individually.

Binary Logistic Regression was then conducted to test six combination univariate and multivariate models in the hepatectomy group. Results of the univariate and multivariate model analysis for the hepatectomy group can be seen in Table 8. Univariate model analysis was conducted first for each of the three variables. It should be noted that in the hepatectomy group, all patients who experienced at least one complication had a HRTime >5minutes. This created a perfect prediction for who would have complications. No univariate model showed stronger *p*-values or predictive sensitivity or specificity than multivariate models. Therefore the univariate models for the hepatectomy group were dismissed. Multivariate models were then tested for significance. Each model was produced first using the standard cut-off of .50. A second iteration was conducted using a cut-off of .62. This weighting of specificity over sensitivity was decided based on the assessor propensity to be correct in who doesn‟t have a complication. Whether it is „right‟ or „wrong‟, telling a patient that their risk of having a complication is low and then being wrong is a bitter pill to swallow and adversely reflects poorly on the clinician. To the contrary, if an assessor tells a patient they are at higher risk of having a complication and then none occurs, the „wrong prediction‟ is welcomed and no adverse negative opinion of the assessor is assigned. In other words, it is better to make a type 1 error (false positive) than a type 2 error (false negative). With this in mind, the strongest model that emerged was HRTime+ $PV0_{2\ mL/min/kg}$ (Model B2) which sacrificed some sensitivity (67% - meaning this model would predict with 67% accuracy who will have a postoperative complication) and 92%

specificity (meaning who will not have a complication). The model‟s overall predictive level stands at 82%.

Table 8

Univariate and Multivariate Parameter Logistic Regression Model Analysis Related To Postoperative Outcomes For Hepatectomy Surgical Group. CI= 95%

Variable/Model	X^2	*df*	*p-value*	*Sensitivity*	*Specificity*	*Overall*	*Exp(B)*
Gender	4.265	1	.0.050	0.667	0.769	0.727	.150
$AT_{mL/min/kg}$	7.520	1	0.006	0.556	0.846	0.524	1.002
$PV0_{2\ mL/min/kg}$	8.115	1	0.004	0.667	0.846	0.524	1.340
HRTime	6.259	1	0.012	0.000	1.000	0.591	614.869
Model A: HRTime & $AT_{mL/min/kg}$	4.842	2	1.028	0.556	0.571	0.564	353.763 & 1.770
Model B1: HRTime & $PV0_{2\ mL/min/kg}$	13.632	2	0.001	0.778	0.846	0.818	353.763 & 1.366
Model B2: HRTime & $PV0_{2\ mL/min/kg}$	13.632	2	0.001	0.667	0.923	0.818	353.763 & 1.366
Model C: $AT_{mL/min/kg}$ & $PV0_{2\ mL/min/kg}$	8.115	2	0.004	0.667	0.846	0.773	1.342 & 1.214

X^2 = Chi Square,d *df* = degrees of freedom, *Exp(B)* = parameter estimate (odds ratio)

Predictive results for Radical Cystectomy. Because only one independent variable ($AT_{mL/min/kg}$) displayed significance (0.045) less than the set alpha of 0.05, it alone was tested as the univariate model for the radical cystectomy group. Table 9 below displays the logistic regression model analysis. In keeping with the hepatectomy group analysis, the confidence interval was set at 95%. Although the overall model‟s significance level met the 0.05 criteria, when using a cut-off level of .50 the balanced for both sensitivity (0.556) and specificity (0.571) is not much greater than chance.

However, taking the above discussion in mind regarding weighting toward specificity, Model B set the cut-off at .62, sacrificed sensitivity to 33.3% and improved specificity to 83.3%. The overall model predictiveness showed higher than chance at 64.1%.

Table 9

Univariate parameter logistic regression model analysis related to postoperative outcomes for Radical Cystectomy surgical group. CI= 95%

Variable/Model	X^2	*df*	*p-value*	*Sensitivity*	*Specificity*	*Overall*	*Exp(B)*
$AT_{mL/min/kg}$ Model A	4.842	1	0. 028	0. 556	0. 571	0.564	.732
$AT_{mL/min/kg}$ Model B	4.842	1	0. 028	0. 333	0. 905	0.641	.732

X^2 = Chi Square, *df* = degrees of freedom, and *Exp(B)* = parameter estimate (odds ratio)

ROC /AUC analysis of hepatectomy. Receiver operating characteristic (ROC) curves were used to graphically display the discrimination abilities and to explore the trade-offs between sensitivity and specificity for each of these variables used to predict postoperative complications. The area under the ROC curve (AUC) is frequently viewed as a robust indicator of performance for classification models. It is an overall index of diagnostic accuracy that is not dependent on a decision threshold (Demick et al., 2004). The AUC ranges from 0.5 (no predictive power) to 1.0 (total predictive power); and it is used to estimate the discriminating power of the predictors. SPSS GradPac, version 19 (SPSS, Inc., 2011) was used to assess the difference between ROC, AUC based on the chi-square test developed from the generalized U-statistics theory by DeLong et. Al. (Hightower et al., 2010). Figure 1, shows the ROC and AUC results with a relatively high AUC of 0.8974 for the hepatectomy predictor Model B2.

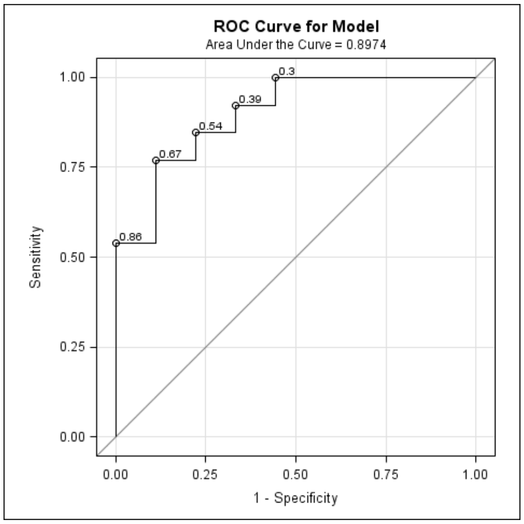

Figure 1. ROC/AUC for Hepatectomy multivariate Model B2 (HRTime + $PV0_{2mL/min/kg}$)

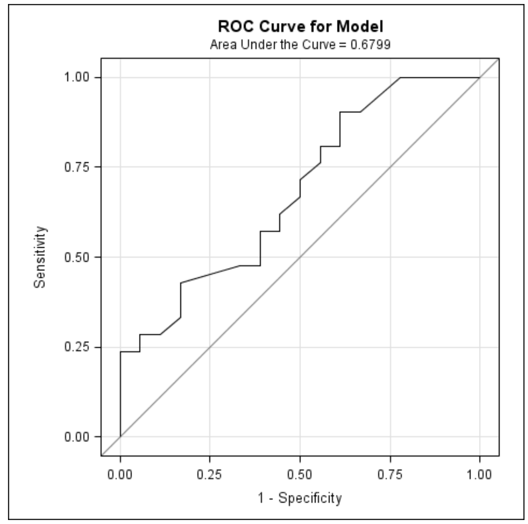

Figure 2. ROC/AUC for Radical Cystectomy univariate Model B ($AT_{mL/min/kg}$)

ROC /AUC analysis of radical cystectomy. The ROC/AUC analysis for the radical cystectomy Model B yielded respectable results of AUC = 0.6799. While the overall AUC may not be as robust as one might like, this finding does suggest clinical significance and provides impetus for further investigation in a larger study population. A more in depth discussion of comparisons for all models with the Anesthesiology Physical Status Classification (ASA), the current risk assessment tool universally used, can be found in chapter 5.

Dependent variable results

Although it was not a part of the stated purpose of this study, a comprehensive descriptive analysis was conducted on the dependent variable of patient complications. Similar to independent variable results, results of dependent variable analysis should not be considered for generalization to any populations other than this study population.

Because this is an exploratory study, results are intended to justify or not justify continued effort in this direction in a larger research study.

Table 10 displays complication rate by surgical type and across all surgeries. Table 11 breaks down the complications by CTCAE classifications. Looking at these two tables, four trends become evident from this study population and would be prudent to follow in a larger study. First, the esophagectomy group captured several „honors" across all three surgical types: highest overall complication rate at 52.3%, highest rate of 2+ complications with 38.1%, highest rate of mortalities with 7.1% deaths, resulting in the lowest percent of survivors at 92.9%. Even though the complication rates appear to be high, the mortality rate is very low in all three surgical types. In other words, even if one or more complications occurred, they were rarely fatal. This data also shows that the highest rate of pulmonary complications (14) were also captured by the esophagectomy group. Although the Radical Cystectomy group „owned" CTCAE 7 category with the most occurrences (10) of ileus, the esophagectomy group was not far behind with 9 occurrences, followed by 6 in the hepatectomy group. Of special note is the fact that no events were attributed to CTCAE categories 3, 4 & 6 in any of the three surgical groups. To the contrary, the fact that all three surgical groups shared commonality in three CTCAE categories of complications (2, 7, and 8) may be an indication that these particular organs or organ systems produce an unwanted response to any surgery. Of the 16 complication categories, 11 were associated with esophagectomy patients. Similarly, six categories of complications were prevalent for hepatectomy patients and eight categories of complications were associated with the radical cystectomy surgery.

These results may indicate the likelihood for a particular type of complication for the specific group of surgical patients at high risk.

Table 10

Patient Complication Rate by Surgical Type and Across All Surgeries

	Esophagectomy *n*=42	Hepatectomy *n*=22	Radical Cystectomy *n*=39	Across three surgical types *n*=103
Total Complications	22 (52.3%)	9 (41%)	18 (46.2%)	49 (47.6%)
3+ complications	11 (26.2%)	4 (18%)	4 (10.3%)	19 (18.4%)
2 complications	5 (11.9%)	3 (13.6%)	5 (12.8%)	13 (12.6%)
1 complications	6 (14.3%)	2 (9.0%)	9 (23/1%)	17 (16.5%)
0 complications	20 (47.6%)	13 (59.1%)	21 (53.8%)	54 (52.4%)
Mortality				
Death	3 (7.1%) 1 < 60 days 2 > 60 days	1 (4.5%) 1 < 60 days	2 (5.1%) 0 < 60 days 2 > 60 days	6 (5.8%) 2 < 60 days 4 > 60 days
Survivors	39 (92.9%)	21 (95.5%)	37 (94.9%)	97 (94.2%)

Table 11

Morbidity and mortality events among patients (N=103) by CTCAE category, for each surgical type and across all surgical types.

CTCAE Complica-tion category	Category Description	N= 42 Total Esophagectomy Patients who experienced each complication type	N=22 Total Hepatectomy Patients who experienced each complication type	N=39 Total Radical Cystectomy Patients who experienced each complication type	Total CTCAEs across all surgical types
CTCAE1	Cardiac: Arrhythmia	6	0	2	8
CTCAE2	Cardiac: General	1	1	3	5
CTCAE3	Coagulation	0	0	0	0
CTCAE4	Constitutional symptoms	0	0	0	0
CTCAE5	Dermatology/skin (ulcer, wound infection)	1	0	0	1
CTCAE6	Endocrine	0	0	0	0
CTCAE7	Gastrointestinal (Ileus, leak, obstruction)	9	6	10	25
CTCAE8	Infection	9	2	3	14
CTCAE9	Metabolic/lab	1	2	0	3
CTCAE10	Hepatobiliary/ pancreas	0	4	0	4
CTCAE11	Neurology	0	0	2	2
CTCAE12	Pulmonary/ Upper Respiratory	14	0	5	19
CTCAE13	Renal/ Hepatobiliary/ pancreas	1	0	1	2
CTCAE14	Vascular	4	0	4	8
CTCAE15	Non-CTCAE: Re-admit, Re-intubation	11	5	4	20
CTCAE16	Death	3	1	2	6
Total events		60 events	21 events	36 events	117 events

Figures 3 through 6 provide a visual depiction of Table 11, displaying the postoperative days in which complications occurred for each of the CTCAE categories of complications and for each surgical type as well as overall. Care should be taken when reading the graphs in relation to the sparseness of some graphs, as stacking of existing points are present, giving the illusion that less complications occurred. Regardless of stacking, it can be clearly seen that complications for esophagectomy patients are clustered from post-op day 1 to around post-op day 25. When compared with surgical patients undergoing either hepatectomy or radical cystectomy, the esophageal patient may have a longer duration of increased energy demand on the physiologic system, thus a longer period to endure before the high risk of complications subsides. The longer duration of required increased energy demand may explain why more complications occur in this surgical group compared to the others. Radical Cystectomy surgery holds the shortest high risk time period with most complications occurring between post-op days 3-15 and very few occurring up to day 21. The risk for complications in the hepatectomy group clustered around post-op days 5-12 but extended out to day 40. Another way to view this data is to observe that an esophagectomy patient is not „out-of-the-woods‟ regarding complications until around post-op day 40. For the hepatectomy patient, the reduced risk occurs around day 17, and for the radical cystectomy patient, reduced risk is a day earlier, on post-op day 16

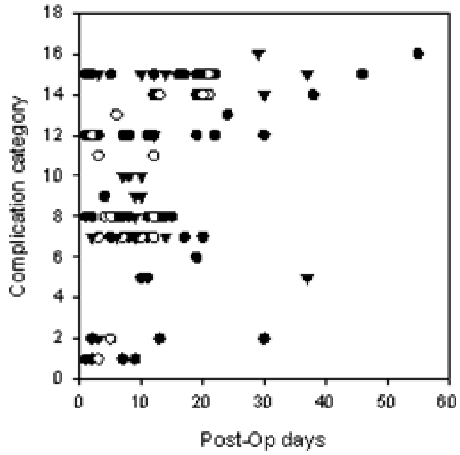

Figure 3. Patterns of days at risk by CTCAE complications in Esophagectomy surgeries (*n*=42)

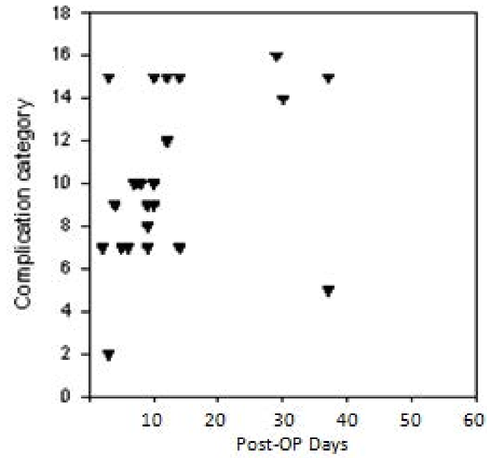

Figure 4. Patterns of days at risk by CTCAE complications in Hepatectomy surgeries (*n*=22)

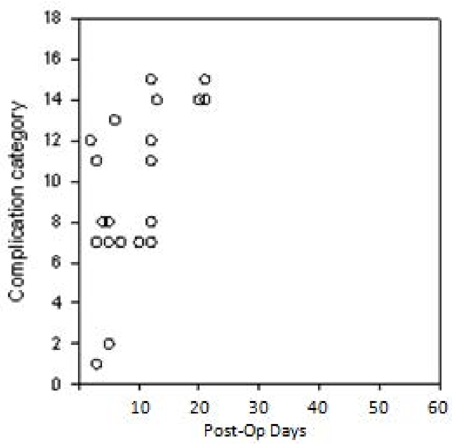

Figure 5. Patterns of days at risk by CTCAE complications in Radical Cystectomy (*n*=39)

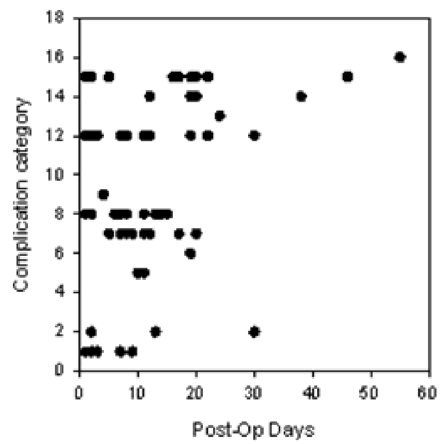

Figure 6. Patterns of days at risk by CTCAE complications in all surgeries (*n*=103)

Analysis of collateral consequences

Research Question 3 asked: Is there a correlation between risk parameters and collateral consequences of hospital costs and length of stay? To address these two issues associated with Research Question 3, correlation regression was conducted to determine if an association existed between LOS and complications as well as hospital costs and complications. Both relationships were found to exist with a p-value of .001

and .008 respectively. Table 12 below shows that for each surgical population group, the occurrence of one or more complications expectantly increased the hospital stay. It is interesting to note that for esophagectomy patients, the hospital stay was longer than the other surgical types whether or not a complication occurred. In reference to the assertion presented by Jacobs et al. (2009), that LOS is often influenced by operational issues delaying the patient discharge and, by default, the additional days are allocated to clinical issues such as complications. Also of importance are two cases which may be viewed as outliers with a 60 day stay (in the esophagectomy group) and a 43 day stay (in the hepatectomy group). The esophagectomy group contained a 55 and a 47 day stay and then a cluster of days in the 30s. The hepatectomy group 43 day stay was more than twice as long as the next longest stay. These data were included in the analysis and not dismissed as outliers due to the fact that the dataset was small and that this study is exploratory in nature. While LOS was strongly associated with complications with a p-value of 0.001, because the esophagectomy group did not have a predictive model, length of stay analysis was limited to comparisons between the complications vs. non-complication groups.

Table 12

Demographic results related to LOS for patients who experienced complications vs. no complications by surgical type.

	Total	Complications	No Complications	*p*-value
		ESOPHAGECTOMY		
Patients (*n*)	42	22	20	
Hospital length-of-stay (days)	Avg: 16 Median: 10 Range: 8-60	Avg: 22 Median: 15 Range: 10-60	Avg: 10 Median: 9 Range: 8-13	.001

table continued

	Total	Complications	No Complications	*p*-value
		HEPATECTOMY		
Patients (*n*)	22	10	12	
Hospital length-of-stay (days)	Avg: 10 Median: 7 Range: 5-43	Avg: 16 Median: 11 Range: 6-43	Avg: 6 Median: 6 Range: 5-8	.008
		RADICAL CYSTECTOMY		
Patients (*n*)	39	18	21	
Hospital length-of-stay (days)	Avg: 12 Median: 9 Range: 6-36	Avg: 16 Median: 14 Range: 7-36	Avg: 8 Median: 8 Range: 6-11	.0001

The next step instituted a t-test to determine if the predictor models for the hepatectomy and radical cystectomy surgical groups were also predictive of length of stay. Table 13 displays the results noting that statistical significance was found to be $p = 0.039$ for the hepatectomy Model B2, and $p = 0.042$ for the radical cystectomy Model B. Model B2 predicted an average 1 day high, for patients predicted to be a low risk for complications and 2 days high for patients predicted to be a high risk for complications. Model B for the radical cystectomy group predicted with 100% accuracy the LOS for the patients predicted to be at low risk for complications and an average of 1 day less (94% accuracy) than the actual LOS average for patients predicted to be a high risk for complications.

Table 13

Comparison of LOS between complications vs. no complication for the three surgical groups and between patients (N = 103) with preserved vs. impaired physiologic capacity (As measured by predictive models).

ESOPHAGECTOMY (N = 42)				
	No Complications	Complications	% Increased LOS	*P*-value
Patients	20	22		
LOS (days) Per patient	10	22	54.5%	.0001

HEPATECTOMY (N = 22)				
	No Complications	Complications	% Increased LOS	*P*-value
Patients	13	9		
LOS (days) Per patient	6	16	111%	.031
	HRTime (<5min) +PV02kg (<20kg)	HRTime(>5min) + PV02kg (≥20kg)	% Increased LOS	*P*-value
Patients	4	6		
LOS (days) Per patient	7	18	54.5%	.039
RADICAL CYSTECTOMY (N = 39)				
	No Complications	Complications	% Increased LOS	*P*-value
Patients	21	18		
LOS (days) Per patient	8	16	44.4%	.035
	ATkg <10kg	ATkg ≥10kg	% Increased LOS	*P*-value
Patients	10	12		
LOS (days) Per patient	8	15	58.3%	.042

The same process was repeated for the analysis of hospital costs for each surgical group. Costs were calculated by the billing department according to standard billing procedures and accounting principles. Both linear correlation and a t-test were conducted to determine if a significant relationship exists between hospital cost and complications and to investigate the possibility that the predictive models for complications also were predictive for hospital costs. Results in Table 14 demonstrate a strong association between hospital costs and complications in all three surgical groups with p-vales of 0.008, 0.011, and 0.006 for esophagectomy, hepatectomy and radical cystectomy respectively. In comparing the LOS data with the hospital cost data, one can readily see that the esophagectomy group took the lead in higher cost figures for complications ($169,545) and the greatest percent of increase due to complications (67.4%). Although the radical cystectomy group was second in line with the costliest tab for complications, the percent increase for complications vs. non- complications were the lowest at 46.3%.

When using the predictive Model B2 in the hepatectomy group to predict costs, it figured an average $6,644 high for patients it predicted to be at high risk for complications and $2,265 high for patients it predicted to be a low risk for complications. Therefore, Model B2 demonstrates an 83% accuracy for predicting (difference of $6,644/ $37,419 avg. actual costs) hospital costs for high risk patients and 97% (difference of $2,624/$89,726 avg. actual costs) accuracy for predicting hospital costs for low risk patients. In the radical cystectomy group, the predictive Model B figured an average of $10, 120 low for patients it predicted to be at high risk for complications and an average $2,200 low for patients it predicted to be a low risk for complications. Model B has an 89% accuracy for predicting (difference of $10,120 / $90,470 actual costs) hospital costs for low risk patients and 95% (difference of $2,200 /$48,546 actual costs) accuracy for predicting hospital costs for high risk patients. It appears that both models predict with greater accuracy hospital costs for high risk patients. However, an 83% and 89% (predictive accuracy for low risk patients) accuracy may not be as high as business administration might like, nevertheless, they are the only known a priori objective predictors for surgical patients undergoing hepatectomy and radical cystectomy. Whatever the final accuracy percentage is, and if it holds steady, adjustments can be made to reflect a more accurate expectation for budgeting purposes. Additionally, this study as the second sequential step in a study stream leaves the possibility for improvement in the predictive abilities of length of stay and hospital costs.

Table 14

Comparison of hospital charges between complications vs. no complication for hepatectomy group and between patients (N = 103) with preserved vs. impaired physiologic capacity (as measured by predictive models).

		ESOPHAGECTOMY (N = 42)		
	No Complications	Complications	% Increased Cost	*P*-value
Patients	20	22		
Hospital Cost Per patient	$55,280	$169,545	67.4%	.008
		HEPATECTOMY (N = 22)		
	No Complications	Complications	% Increased Cost	*P*-value
Patients	13	9		
Hospital Cost Per patient	$37,419	$89,726	58.3%	.011
	HRTime (<5min) +PV02kg (<20kg)	HRTime(>5min) + PV02kg (≥20kg)	% Increased Cost	*P*-value
Patients	4	6		
Hospital Cost Per patient	$40,043	$96,370	58.4%	.032
		RADICAL CYSTECTOMY (N= 39)		
	No Complications	Complications	% Increased Cost	*P*-value
Patients	21	18		
Hospital Cost Per patient	$48,546	$90,470	46.3%	.006
	ATkg <10kg	ATkg ≥10kg	% Increased Cost	*P*-value
Patients	10	12		
Hospital Cost Per patient	$46,346	$80,350	42.3%	.021

Summary of Findings

This section is structured according to each of the three research questions that outlined the purpose of this study. This section concludes a justification and discussion of the dependent variable analysis which was completed in addition to the established research questions.

Research Question 1: Are different surgical procedures associated with different predictive physiologic capacity parameters?

The findings of data analysis support the notion that there are different predictive physiologic capacity parameters for each surgical type analyzed in this study. Analysis revealed the following notable results:

Age:

- The overall range of ages across all surgical types spanned from 26-84 with a mean of 61.
- Radical Cystectomy was shown to be the oldest group with a range of 37-84 and a mean of 66. The youngest group was hepatectomy with a range of 36-79 and a mean of 55.
- Age did not display a statistically significant relation to outcomes (Overall $p = 0.57$, Esophagectomy $p = 0.51$, Hepatectomy $p = 0.64$, and Radical Cystectomy $p = 0.48$)

Gender:

- 75% of all cases were male with the Esophagectomy group containing 90% males. Only the hepatectomy group contained more females (59%) than males (41%).
- A higher percentage of males experienced complications for two surgery types (Esophagectomy = 53% and Hepatectomy = 67%). Only in Radical Cystectomy did females exceed the complication rate over males (56%).
- Gender was not found to have a statistically significant association with outcomes in the overall, esophagectomy and radical cystectomy groups ($p = 0.95$, $p = 0.93$, and $p = 0.56$ respectively) In simple correlation

analysis, gender showed association with complications (*p* = .043). However, when added to a predictive model in linear regression, it did not show as a significant variable (.064) and was not included in a predictive model for the hepatectomy group.

Race:

- 84% of all cases were White/Caucasian with Hispanic at a distant 9%, followed by African Americans/Blacks at 5% and Asians at 2%
- As the largest race group White/Caucasians also captured the highest percentage of complications (Overall 84%, Esophagectomy 88%, Hepatectomy 68%, and Radical Cystectomy 90%)
- Noteworthy are the results showing with fewer cases, 50% of Hispanics undergoing Esophagectomy, 50% of African American/Blacks undergoing Esophagectomy and Hepatectomy experienced complications
- Race was not found to have a statistically significant association with outcomes (Overall $p = 0.95$, Esophagectomy $p = 0.93$, Hepatectomy $p = 0.96$, and Radical Cystectomy $p = 0.56$)

The second phase of analysis focused on the physiologic independent variables. Significant relationships were set at an alpha of $p \leq 0.05$. It was noted that in the esophagectomy surgical group no individual or multiple group of variables were found to meet the set 0.05 alpha, nor did any variable meet a relaxed 0.10 alpha. Therefore, no further effort was given to finding a predictive model for this surgical group. However, this group was included in the dependent variable analysis as well as the collateral consequences analysis. A detailed discussion regarding the lack of significant predictor for this particular surgical group is addressed later in this chapter. Binary Logistic Regression for the hepatectomy and radical cystectomy candidate variables resulted in discovery of two statistically significant models (alpha set at 0.05):

- Three univariate models ($AT_{mL/min/kg}$, $PV0_{2\ mL/min/kg}$, and HRTime) were each found to be statistically significant in predicting outcomes in the hepatectomy group. $AT_{mL/min/kg}$ $p = 0.006$, Sensitivity = 0.556, Specificity = 0.846, and overall = 0.524

  $PV0_{2\ mL/min/kg}$ $p = 0.004$, Sensitivity = 0.667, Specificity = 0.846, and overall = 0.524

  HRTime $p = 0.012$, Sensitivity = 0.000, Specificity = 1.00, and overall =0.591

- Three multivariate models were constructed from the univariates predictors and were all found to be statistically significant predictors in the hepatectomy surgical group.

  Model A: HRTime + $AT_{mL/min/kg}$ $p = 0.028$, sensitivity = 0.556, specificity = 0.571

  Model B: HRTime + $PV0_{2\ mL/min/kg}$ $p = 0.001$, sensitivity = 0.778, specificity = 0.846

  Model C: $AT_{mL/min/kg}$ + $PV0_{2\ mL/min/kg}$ $p = 0.004$, sensitivity = 0.667, specificity = 0.846

  Two scenarios for Model B were produced, first with a standard cut-off level of .50.

Model B1:

(Sensitivity = 0.778, Specificity = 0.846, and Overall model = 0.818)

A second scenario of the model (Model B2) was produced with the cut-off level adjusted to .62 in order to weight specificity over sensitivity per clinical preference.

Model B2:

(Sensitivity = 0.667, Specificity = 0.923, Overall = 0.818, AUC = 0.8974)

- A univariate model comprised of $AT_{mL/min/kg}$ was found to be a statistically significant predictor in the radical cystectomy surgical group. Two scenarios for this model were produced, first with a standard cut-off level of .50.

  Model A:

  (Sensitivity = 0.556, Specificity = 0.571, and Overall model = 0.564)

  A second scenario of this model was produced with the cut-off level adjusted to .62 in order to weight specificity over sensitivity per clinical preference.

  Model B:

  (Sensitivity = 0.333, Specificity = 0.905, Overall = 0.641, AUC = 0.6799)

Increasing the weight toward specificity for both Model B2 in the hepatectomy group and Model B in the Radical Cystectomy group produced higher prediction percentages for who would not have a complication. Without the increased weighting of the radical cystectomy model, its predictive ability is little more than chance, or what one might expect from the flip of a coin. This falls short of the expectations in the perioperative environment. However, with weighting, the model is more palatable in predicting who is a low risk for complications. Weighting toward specificity in both models speaks to the preference of clinicians to avoid a type I mistake of telling a patient they are at low risk for complications and then are proven wrong.

Of special interest to the study findings is the discovery of a new predictive variable, „HRTime". This variable reflects the long standing knowledge held by exercise physiologists (ACSM Guidelines for Exercise Testing and Prescription, 8^{th} ed., Section II, 1210 and Cole, Blackstone, Pashkow, Snader, & Lauer, 1999) that gauges the fitness of a person"s physiology from the time it takes the heart rate at stop test (usually peak heart rate) to drop to or below 100 beats per minute. This variable has not been investigated as a predictor of postoperative complications in any known or published study to date. Further discussion regarding HRTime as a predictor is included in chapter 5.

Research Question 2: Are there different threshold ranges that stratify risk for each surgical type?

Findings from the analysis conducted on the dataset for this study population supports the hypothesis that different threshold ranges stratify risk for two of the three surgical types. In the hepatectomy group peak volume of oxygen ($PV0_{2\ mL/min/kg}$) was found to have a naturally occurring threshold differentiation in the majority of patients, showing those who achieved < 20 mL/min/kg at peak volume of oxygen were at lower risk of complications and patients who achieved ≥ 20 mL/min/kg at peak volume of oxygen were at higher risk of complications. Drilling further into the data, no clear threshold level was apparent which would correspond to the number of complications experienced (i.e. 1, 2, or more than 3). Although the idea of the number of complications being related to various threshold levels of $PV0_{2\ mL/min/kg}$, thereby stratifying risk, was not apparent in this study group, it may be due to the small dataset (n=22). Nevertheless, this theory would be worth investigating in a larger study.

The predictive physiologic variable in Model B for the radical cystectomy group also displayed a naturally occurring break for the majority of patients who achieved < 10 mL/min/kg of oxygen at the anaerobic threshold ($AT_{mL/min/kg}$), were at lower risk of complications and patients, who achieved ≥ 10 mL/kg /min of oxygen at the anaerobic threshold, were at higher risk of complications.

Although the threshold findings in both $PV0_{2\ mL/min/kg}$ and $AT_{mL/min/kg}$ appear to be the opposite of what would be expected based on physiologic principles, i.e. the higher the $PV0_{2\ mL/min/kg}$ and $AT_{mL/min/kg}$ the lower the risk of complications, the data did not indicate this for this particular study population. This creates strong impetus for further investigation.

Research Question 3: Is there a correlation between risk parameters and collateral consequences of hospital costs and length of stay?

The findings from data analysis for this study, supports the hypothesis that the two statistically significant predictive models for the hepatectomy and radical cystectomy surgical groups were also statistically significant predictors for length of stay and for hospital costs in each group.

Summary of findings for LOS. Results of analysis confirmed a strong association for each group with esophagectomy $p = 0.001$, hepatectomy $p = 0.008$, and radical cystectomy $p = 0.001$. The analysis also revealed the esophagectomy surgery not only is associated with the highest number of complications, but also has the longest average LOS at 16 days. For the 52.3% of patients who experienced complications, this surgery carried an average 22 day stay with a range from 10 – 60 for the study population. The hepatectomy surgery group experienced the shortest stay with an average of only 10 days (range = 5-43 days). For the 41% of patients experiencing complications in this surgery, the average stay grew to 16 days. Radical cystectomy surgery was similar to hepatectomy with an average stay of 12 days (range = 6-36 days) and for the 46.2% of patients experiencing complications, the average stay extended to 16 days.

When both models for hepatectomy and radical cystectomy were tested for predictiveness of LOS, both returned statistically significant results: Model B2 for the Hepatectomy surgical type exhibited $p = .039$ with sensitivity = 86%, specificity = 89%; and Model B for the Radical Cystectomy surgical type exhibited $p = 0.043$ with sensitivity = 94%, specificity = 100% compared to actual LOS days.

Summary of findings for hospital costs. As was the case with LOS, results displayed strong correlation between hospital costs and the presence or absence of postoperative complications: esophagectomy $p = 0.008$, hepatectomy $p = 0.032$, and radical cystectomy $p = 0.021$. Not to be unexpected due to the highest rate of complications and resulting highest length of stay, the esophagectomy group also carried the highest average hospital costs for complications at \$169,545 and average cost for no complications at \$55,280. Complications in this surgical group consequently drove costs up 67.4%. The hepatectomy surgical group was not substantially different with complications averaging $89,726 and non-complication cases averaging $37,419. The consequences of complications for this group increased hospital costs by 58.3%. Compared to the hepatectomy group, complications averaged slightly higher at $90,470 in the radical cystectomy group and non-complication cases also averaged higher at $46,346. Although the actual costs were higher than the hepatectomy group, it was the radical cystectomy surgical group who came in at the lowest (46.3%) increase for complications over non-complications.

Repeating the same process as was conducted for LOS, logistic regression was performed to determine if the physiologic predictive models were also predictors for hospital costs. The findings revealed that again, both predictive Model B2 for the hepatectomy and Model B for radical cystectomy group resulted in statistically significant predictiveness for hospital costs. Model B2 exhibit a *p*-value of 0.032 with sensitivity = 93.4% and specificity = 96.4%. Model B exhibited a *p*-value of 0.021 with sensitivity =95% and specificity = 89% compared to actual hospital costs.

These findings are particularly exciting as no preoperative predictive model currently exists in the healthcare field for forecasting length of stay or hospital costs before a patient undergoes surgery. Should these findings be supported in a larger study, the implications for hospital financial planning, logistic scheduling, and improvement in quality indicators may be substantial. Keeping in mind that this study was exploratory in nature and contained a smaller study population than necessary to provide a greater level of confidence in the results and should not be generalized, nevertheless these results are promising and worth subsequent larger studies to either confirm or modify the information this study provides.

Summary of findings for the dependent variable

An extra effort was undertaken to look at the data associated with the dependent variable. Several discoveries shed new light on the complex relationship between physiologic capacity and postoperative outcomes. In many instances, interesting trends were uncovered which brought more questions to light. Three outstanding pieces of information surfaced as the analysis unfolded. First, as seen in Table 11, certain types of complications appear to be common regardless of surgical type: i.e. Complications relating to CTCAE categories 2, 8, and especially 7 were common to all three surgeries, however ileus (from category 7) was found to be the highest complication sort of any in this category. Although the highest rate of category 7 occurred in radical cystectomy surgeries, there was no one surgery that had a substantial preponderance of this complication. That is not the case with category 12 (pulmonary) in which far more esophagectomy patients experienced deep vein thrombosis and other respiratory distresses than patients undergoing any other surgery.

The second trend revealed that patients undergoing esophagectomy surgery appear to have a higher burden and certainly extended demand on the metabolic energy system than the other two surgeries. This was evidenced by the highest percent of complications, the longest and highest average LOS, the highest number of complication categories associated with a surgery, and therefore the costliest. It is perplexing to then discover that no predictive parameter (of those considered in this study) was statistically significant. A host of questions arise to explain these phenomena such as; is there something different about this 42 patient population‟s physiologic makeup that resulted in no predictive parameter? While a new predictive parameter was discovered for hepatectomy, could there be a yet unknown parameter which hasn‟t been tested for this group? Are there one or more other confounding variables that are influencing the dynamics between physiologic capacity and complications (in this surgical type) to the extent that it inhibits the predictive nature of physiologic parameters? Could extraneous variables that have not been identified yet, such as blood loss or total fluids given be predictors?

The third trend exposed each surgical group‟s unique clustering of high risk days in which most complications occurred (as viewed in Figures 3 – 6). For example, for the esophagectomy patient, complication occurrences took place from the operative day through post-op day 25. However, complications continued to occur in a lesser portion of these patients, up to day 60. This was not the case for either of the other two surgeries. If a patient can make it to day 15 for either surgery, they are nearly „out of the woods‟ in regards to occurrences of complications. Hepatectomy also displayed clustering of complications from about day 7 to day 12 with no surprise that the highest portion of these associated with CTCAE category 10 (Hepatobiliary/pancreas). What is happening physiologically a week after the surgery that associates with delayed complications? For radical cystectomy, days 4 and then again on days 11-12 show a cluster of various complications, implying for this population, a complication risk appeared to be delayed more than a week.

As is typical with new research, findings have generated a plethora of new queries in an effort to answer why the results did or did not meet expectations. This study was no different. Questioning is healthy in this environment and creates the path to the next sequential steps in a logical systematic research stream. The interpretation of the findings and limitations of this study are discussed in chapter 5. Recommendations for action and direction of future studies are also discussed. The chapter closes with a discourse of the implications of these findings for social change and a concluding summary.

Chapter 5: Conclusions, Recommendations, and Impact for Social Change

Overview

This chapter is comprised of five major sections that: 1) provide an overview of why and how the study was conducted, a review of the research hypotheses, and a brief explanation of the findings, 2) explore the findings presented in chapter 4, 3) provide recommendations for actions and future studies, 4) discuss implications for social change, and 5) closes with a summary. The introduction explains the impetus for the present study, the role it plays within a larger study stream, and briefly presents the study findings. Within the second section, the findings and conclusions are discussed associated with the three research questions and in conjunction with other research cited in the literature. In the third section, recommendations for next-step actions and future research opportunities are presented. The fourth section contains a discussion of the multifaceted social change impact that this study may generate. The fifth and final section provides a closing summary.

Introduction

The relationship between a patient"s physiologic capacity and the prediction of postoperative complications is an emerging field. As such, research into predictive parameters has been scattered in its approach and unfortunately has resulted in confusion and seemingly contradictive findings. A systematic approach to investigating this issue was started with a pilot study by Hightower et al. (2010), from which the present study serves as the second sequential step in the study stream aimed at ultimately reducing postoperative complications. While the pilot study included an aggregate group of eight surgical procedures, the conclusion questioned the possibility of predictive parameters based on individual surgical types. Therefore, the present study investigated the following hypotheses: 1) Different surgical procedures are associated with different predictive physiologic capacity parameters, 2) Different threshold ranges stratify risk for each surgical type, and 3) A correlation exists between risk parameters and collateral consequences including length of stay and costs. The findings indicate not only are different predictive parameters associated with different surgical types, but it may also be possible to determine the type of complication(s) and when it is most likely to manifest. The ramification of these findings suggests a paradigm change in subsequent research design for this field. Thus, each surgical type must be studied for the specific predictive parameter. The findings also indicate (supporting hypothesis 3) that pre-surgical prediction of length of stay and hospital costs are possible. This possibility, the first of its kind, has implications in the fiscal and operational arenas of healthcare. Taken together, a major change in pre-surgical assessment procedures, operational and fiscal planning, and healthcare policy may be on the horizon. The following sections discuss in greater detail, these findings and potential consequences.

Interpretation of the Findings

The findings of this exploratory study support the hypotheses of all three research questions posed for this study population. As such, it provides strong incentive for the next critical step of a larger confirmatory clinical trial study. For the clinician, these findings give hope that a valid, reliable, and perhaps most importantly, *objective* risk assessment tool may finally come to fruition. Currently, clinicians responsible for determining postoperative risk have been relegated to the same *subjective* risk assessment strategies *regardless of the scheduled surgery type*. The findings of this study indicate that that approach may be unsound. To the contrary, this study brings us a step closer to the time when the burden of an accurate risk assessment may be taken off the shoulders of the clinician and delivered from the patient‟s own body. This paradigm shift in thinking will require a phenotypic assessment of each individual surgical patient and the clinical professional to adopt a change from the nearly 80 years of how preoperative risk has been traditionally assessed.

These study findings are not limited to a tool for establishing postoperative risk of complications; but also potentially impact the operations and financial departments of hospitals, health insurers, payers, and policy makers. It is therefore prudent to explore the findings as they are associated with each study question.

Research Question 1 Findings

Research Question 1 asked: Are different surgical procedures associated with different predictive physiologic capacity parameters?

Esophagectomy group findings. The fact that no statistically significant predictor was found in this study for the esophagectomy surgical group is perplexing in itself, especially in light of the research by Nagamatsu (2001) and Forshaw (2008), which both studied cancer patients undergoing esophagectomy. Nagamatsu found a multivariate model comprised of peak volume of oxygen ($PV0_2$) + anaerobic threshold (AT) as a significant predictor, and Forshaw found $PV0_2$ as a significant predictor. It was anticipated that this exploratory study would lend to clarification of the predictive parameter in the same type population of cancer patients undergoing the same surgical procedure. However, possible population differences (Forshaw in England, Nagamatsu in Japan, and the present study in the USA) may include confounding variables that impacted the results. Such confounders may originate from the surgical techniques, the surgical environment, or the peri- and post-operative treatment of patients. Even so, the logical question follows: Is there something about the physiologic capacity make up of this type of surgical patient that is different from the other two surgical types in this study? Additionally, because there are potentially a hundred or more parameters of physiologic capacity that can be either measured directly or indirectly calculated from gas exchange uptake data during CPET testing, and because investigation into this potential predictor is still young in the evolution of research, not all parameters have been investigated in other studies or in this study. Therefore, is also possible that another gas exchange parameter not considered in the present study may be a significant predictor for this group of patients. Only further research can answer these lingering questions.

Hepatectomy group findings. Quantitative analysis, using logistic regression, identified a unique multivariate model (Model B: HRTime + PVO_2 measured as mL/min/kg) as a statistically significant predictor of postoperative complications in the hepatectomy group. Together with the findings for the radical cystectomy group, these results support the hypothesis for Research Question 1. Although the study by Hightower et al. (2010) included one hepatectomy patient, the analysis aggregated it in with the remaining other seven surgical types. Older et al. (2000) also included hepatectomy patients among several other major abdominal surgical types. The conclusion that aggregating various surgical types produces differing predictive models appears to be born out in a comparison of Hightower et al. vs. Older et al. studies which found different predictive models; ΔHR + PAT and AT, respectively. Given that the present study supports the hypothesis that different physiologic parameters appear to be associated with specific surgical procedures, the seemingly conflicting results between Hightower et al. and Older et al. may be explained due to a large portion of the total study population being a particular surgical type, thereby inadvertently influencing which parameter was shown as the overall predictor. Regardless, the fact remains that the majority of patients undergo only one type of surgery, not an aggregate of surgeries. The present study then supports consideration for a change in pre-operative risk assessment methods to adjust to the specific surgery each patient is scheduled to undergo.

The discovery of a new predictor. As was shown in the Hightower et al. (2010) study, new variables not yet considered in the limited published studies, may be discovered as predictors. To this end, it was decided that a new variable, heart rate time (HRTime: the time it takes for the heart rate to drop at or below 100 bpm from stop test) was included in the list of considered variables. This decision was based on established knowledge taught in basic exercise physiology course work (McArdle, Katch, Katch, 1986 and 2010) and by the American College of Sports Medicine (2010). HRTime was found to be a statistically significant predictor in the hepatectomy group.

In maximal exercise testing HRTime is an indicator of the individual‟s ability to recover from an anaerobic state after strenuous exercise. In the surgical patient, this parameter may be an indicator of the patient‟s capacity to recover from an anaerobic state brought on by surgical stress and continued during the postoperative period. Snowden et al. (2010) showed that maximal exercise stress tests may mimic the stresses of the postoperative period. Additionally, a series of studies by Shoemaker et al. (1973, 1992, and 1993) revealed that patients are subjected to continued high levels of energy demand during the immediate and extended post-surgical period.

The inability to recover (measured by reduced heart rate below 100 bpm within five minutes) may be related to the underlying theory of oxygen utilization. Wasserman et al. (1999) found that the inability to recover from, or repay, the oxygen debt that is experienced in early stress conditions (beginning exercise, or in the patient‟s case, the postoperative period) can result in organ, multi-organ, or system failure. This could explain why, for instance all three surgeries show the highest incidence of complications occurring 3 – 10 days after surgery. In other words, it may be possible that a patient‟s physiologic system is able to maintain high levels of aerobic energy metabolism continuously *for a period of time*. However, it is plausible that between days 3 – 10, patients may no longer be able to supply oxygen at a rate to meet the demand, thereby forcing them into an anaerobic metabolic state. Anaerobic metabolism can only be maintained for a short period of time, thus postoperative complications occur. The time at which anaerobic metabolism can no longer be maintained may distinguish the „complication window‟. The HRTime indicator may give insight into the patient‟s ability to recover from oxygen debt thereby avoiding entry into anaerobic metabolism. To the contrary, those who remain in anaerobic metabolism for an extended time are at higher risk for complications.

While HRTime was by itself a statistically significant predictor, coupled with peak volume of oxygen (PVO_2), (a multivariate model) showed the strongest power for predicting who would (sensitivity = 67%) and who would not (specificity = 92%) experience complications, with an overall predictability of 82%. As mentioned in chapter 4, these percentages are weighted toward specificity to reflect the clinician preference to risk a type I error (false positive) when making surgical risk decisions rather than a type II error (false negative). The physical, mental, emotional, and financial cost in making a type I error (from the clinician‟s perspective) is non-existent compared to a type II error.

Radical cystectomy group findings. Notably, no other published study looking at gas exchange variables as predictors of postoperative outcomes has focused solely on patients undergoing radical cystectomy (liver resection or removal). Results of statistical analysis showed the univariate model of $AT_{mL/min/kg}$ was a statistically significant predictor of outcomes in the radical cystectomy group, showing sensitivity of .33, specificity of .91, and Area Under the Curve (AUC) of .68 (after weighting at .62). It is additionally interesting to note that both studies which included a variety of surgical types, Older et al. (2000) found AT to be a predictor and Hightower et al. (2010) found a function of AT (% of predicted AT achieved) as a predictor. The fact that 14 of the 32 patients in Hightower‟s pilot study underwent radical cystectomy, may explain to some extent, the influence of AT as a predictive variable in the pilot study. Although Older‟s study also involved several surgical types, it is unknown if a majority (like Hightower‟s pilot) were radical cystectomy patients. If this was the case, it may explain why AT was also found to be the statistically significant predictor in that study. One may conclude then that in studies that involved multiple surgical procedures, the predictive parameter of the largest surgical group may influence the overall group predictive parameter. Should this theory be supported in future studies, it would be no small discovery, in fact it may resolve the current conflict and confusion of results in the few studies to date and change the direction for construction of future studies to focus on each surgical type.

Comparing study models to ASA. The American Society of Physical Status Classification System (ASA) is currently the most widely used tool for preoperative risk assessment (Aronson, McAuliffe, & Miller, 2003; Garcia-Miguel, Serrano-Aguilar, & Lopez-Bastida, 2003). It is natural to compare the models from this study to the ASA; however this is problematic at best. As Aronson, McAuliffe, and Miller (2003) point out, while the ASA was not designed to identify anesthetic or surgical risks (p. 265), clinical studies suggesting it correlates with predicting outcomes are met with an equal number which find no correlation, such as Goldstein and Keats (1970), who reported its sensitivity at only 41%. Aronson serves as an example of the growing concern and provides a sound argument for the gross variability of inter- and intra-rater reliability of the ASA. Furthermore, a strong warning of use of ASA as a risk assessment tool for all situations was presented by Dr. William Owens (2001). He argued that while the ASA Physical Status system has been referred to as “ASA risk class”, “ASA values,” and “ASA risk scores,” none of these characterizations are appropriate (pg. 378). Additionally, he warned against using the ASA as such and reminded the anesthesiology body that the authors of the ASA designed it as a *categorization*, *not risk assessment* system for statistical studies and that the Anesthesiologists House of Delegates modified the system several times in the past 59 years but risk was never included in any modification. He concluded by stating, the ASA "…was, and is, a means to stratify a patient"s systemic illness" (p. 378). Although the ASA risk score was assessed as part of the standard of operations at the study"s institution, in light of Owens" warning, the Anesthesiologists House of Delegates lack of including a risk assessment element in their modifications and because it is beyond the scope of this study, I choose not to include a comparison of the risk models to the ASA scores or analyze the ASA for its predictiveness in this study. If indeed the ASA system should not be used for preoperative risk assessment and is unreliable, clinicians needing to assess the patients" risk of complications are left in a quandary. Therefore, a predictive model that is objective, reliable, and unique to each patient presents an exciting change in accuracy and reliability, and may be the answer to the assessor"s dilemma.

Research Question 2 Findings

Research Question 2 asked: Are there different threshold ranges that stratify risk for each surgical type? While both hepatectomy and radical cystectomy findings supported the hypothesis that there are different threshold ranges that stratify risk for each surgical type, the threshold for the hepatectomy group was contrary to what would be normally expected. According to both Older et al. (2000), a $PV0_2$ threshold of >11, and McCullough (2006) a $PV0_2$ >18.5 avoided complications, however, that was not what this study"s data indicated. Instead, data showed 6 of 9 (67%) of patients who achieved a $PV0_2 \geq 20$ $_{ml/min/kg}$ experience complications, and 11 of 13 (85%) of patients who achieved a $PV0_2 < 20$ avoided complications. The result from the present study is unexpected and demands additional investigation. To the contrary, and as would normally be expected, 85% of patients who achieved an $AT \geq 8$ $_{mL/min/kg}$ avoided complications, in the radical cystectomy group. This is similar to Older et al. (1993 and 1999) who found AT a predictor in a variety of abdominal procedures with patients achieving a threshold <11 experiencing complications. One explanation of different threshold levels between Older‟s study and the present study could be that the mixture of abdominal procedures may have influenced the threshold level. Furthermore, given that there are hundreds of surgical procedures, it may be possible that the same predictive variable in two or more different surgeries may carry different threshold levels for determination of risk of complications. Future research is needed to clarify threshold stratifications.

Research Question 3 Findings

Research Question 3 asked: Is there a correlation between risk parameters and collateral consequences including length of stay and costs? The finding that both predictive models for hepatectomy and radical cystectomy surgical groups were also predictive of length of stay and hospital costs is a new finding and may provide advantage in bed management and budgeting functions within a hospital setting. Kramer and Zimmerman (2010), Niskanen, Reinikanen, and Pettila (2009), and Demic et al. (2004) all report the high cost of complications and the inability to preoperatively predict these figures. Demic et al. (2004) speaking of postoperative pulmonary complications (PPC), declared:

> Projecting to national levels, the study determined that more than 1 million patients experienced a PPC in the US in 2008, and these cases were associated with 46,200 deaths, 2.9 million added days on the hospital floor, 1.9 million added ICU days and $11.9 billion in additional costs. (p. 531)

Currently, the cardiology field, specifically the coronary by-pass arena, has been the leader in tackling length of stay and hospital costs prediction (Kurki, Häkkinen, Lauharanta, Rämö, & Leijala, 2001). While the Kurki et al. study associated a higher risk score with greater hospital costs, it limited its predictiveness to a „rough estimate‟ of a patient‟s risk and fell short of predicting the actual costs prior to surgery. Non-cardiac surgery has yet to catch up to their cohorts. Therefore, presently predicting length of stay (LOS) and hospital costs occurs after the outcomes of surgery are known (Niskanen, Reinikanen, & Pettila, 2009). While Kramer and Zimmerman produced a model that predicts LOS *after surgical complications are known*, they readily warn, “We do not recommend using this model to predict a prolonged ICU stay for individual patients” (Kramer and Zimmerman, 2010, p. 14). A prolonged stay in this study was set at >5 days. Interestingly, the authors‟ also warn that the model‟s greatest inaccuracy is the “under-prediction of remaining ICU stays of 2 days or less” (p. 14). The conclusion follows that the model is best used if the patient has a limited ICU stay between 3 – 5 days. This becomes critical when we see (Refer to section on findings for dependent variable below.) that most of the complications in all surgeries for the current study occurred during postoperative days 3 – 10. On the other hand, compared to Jacobs et al. (2009) study of 1517 patients, whose LOS averaged 6.54 days for patients not experiencing postoperative complications, the present study is slightly higher in the non-complication esophagectomy group with an average 10 days, and in the radical cystectomy group with an average of 8 days. Only the hepatectomy group averaged slightly lower with 6 days as compared to Jacobs" study.

Given the substantial collateral consequences associated with major postoperative complications, predicting complications *prior to* surgery would fill a current gap needed for better logistic and budgetary planning. Model B2, used to predict complications in the hepatectomy group predicted LOS as 1 day higher than the actual average for the complication group and 2 days higher than the actual average for the non-complication group. Its accuracy in predicting hospital costs were $2,624 high for the non-complication group and an average of $6,644 high for the complication group. For the radical cystectomy group, Model B was closer in predicting LOS with 100% accuracy for patients at low risk and an average of 1 day for high risk patients. Model B also showed predicting of hospital costs at $2200 high on average for low risk patients, but the gap widened for high risk patients with an average $10,120 low prediction. It is noteworthy to recognize that for both hepatectomy and radical cystectomy groups LOS and hospital costs were much closer to the actual figures in the non-complication group. Keeping in mind that clinicians prefer to be more accurate in predicting who will NOT have a complication, the overall accuracy of 1 day within actual LOS and 6% within actual hospital costs is a far cry closer than the current state of the industry. Additionally, if the differences for high or low prediction hold relatively steady in a larger study, adjustments can be embedded for complication cases to achieve more accurate prediction from which to make bed and budgetary plans.

Compared to the American Health Research & Quality Statistical Brief #86, which reported that in 2007 the average cost for inpatient surgery across the United States was $40,000, the esophagectomy average cost for a non-complication surgery ran more than $15,000 higher, the average hepatectomy group was slightly less at $37, 419 and the radical cystectomy group showed $8, 546 higher than AHRQ‟s figures. If adjustments are made for increased costs from 2007 to 2011dollars, the actual costs shown in this study may be more closely aligned with national figures. Interestingly, the predictive models for both hepatectomy and radical cystectomy were in alignment with the $40,000 from AHRQ‟s 2007 figures.

These findings, although exciting are only an interim step to what is hoped to be a reversal of complications, resulting in a reduction of LOS and hospital costs. For example, in the present study, if only half of the complications in the hepatectomy and radical cystectomy groups were avoided, it would have reduced the LOS by 216 days on average, and translated an average reduction of hospital costs of $1.2 million. Multiplying this study‟s average cost saving by the 5,708 registered hospitals in the United States; one could see a potential costs savings of more than $6.8 billion. This is even more impressive considering these figures only reflect two surgical types.

Dependent variable Findings: Patient Complications

The finding that specific surgical procedures may be associated with increased incidence of specific categories of complications was the result of a limited analysis of the dependent variable. Although this analysis was not part of the predetermined study questions, it gleaned previously unknown trends of when complications for each surgical type most frequently occur and provided insight into the type of complications that are most likely to be experienced. These findings imply that it may be possible to not only predict the risk of postoperative complications but also predict the category and when complications may occur. The implications for interventional measures aimed at specific conditions and at specific times are substantial. Recommendations to include future studies toward further investigation of these aims and others, follows.

Recommendations for Future Studies

The entire study stream follows a sequential and logical series of research questions ultimately aimed at reducing or eliminating postoperative complications. The first exploratory study (Hightower et al., 2010) sought to determine if parameters of physiology capacity (PC) were statistically significant predictors of postoperative complications. With supporting findings, the second exploratory study in the stream (the current study of this dissertation) sought to determine if different predictive parameters were associated with specific surgical types. Again, findings support this hypothesis. It follows then, that a larger study is the next sequential step to confirm/validate the findings of the present exploratory study. Should the findings of the larger subsequent study also support the hypothesis, then, perhaps the most exciting of all studies would finally explore the ultimate goal of the research stream: Can postoperative outcomes be changed by improving physiologic capacity? The basis of this premise emanates from a plethora of research in the field of exercise physiology that historically confirms that physiologic capacity can be improved with consistent aerobic exercise (ACSM Guidelines, 1991 and 2010; McArdle, Katch, Katch, 1986 and 2010; Roy & Irvin, 1983). The implications of purposefully reducing or eliminating postoperative complications are discussed in the next section on societal change.

Recommendations for a consequent larger study would necessarily include a population size that would ensure confidence for inferences to the larger population. It would also be important to duplicate as many of the components of the exploratory study as possible in order to avoid introducing new confounding variables, possibly producing different results. For example, recommendations for a larger study would include employing the same study site, surgical types, surgeons, perioperative procedures, CPET procedures, technical staff to conduct the CPET, BreezeSuite® application for raw data interpretation, and include the same gas exchange variables and new HRTime variable in the analysis (other gas exchange variables may also be included that were not considered in the present study, especially in the case of esophagectomy surgeries). Maintaining these duplications would ensure adherence to sound scientific research standards. Achieving supportive findings of a larger study would finally provide clinicians with a phenotypic, objective, and reliable predictor of postoperative complications for the three surgical types in the present study; thereby satisfying a long-standing cry to meet the high expectations of the perioperative environment.

Other recommendations for future studies include: 1) confirming/clarifying thresholds of risk levels, 2) confirming/clarifying the relationship between the predictive models and collateral consequences of hospital length of stay and costs, 3) clarifying trends for possibly predicting the time frame and type of complication(s) that may be most likely for a patient to experience for each surgical procedure. If indeed different variables of physiologic capacity (PC) are predictive of specific surgical procedures, then each surgical procedure would necessarily need to be studied to identify the associative predictive parameter. That endeavor may prove to be a lifelong study. Additionally, if larger studies confirm number two above, it is possible that the creation of logistic and economic forecasting models may assist planning efforts.

Lastly, should a final study support the notion that postoperative outcomes can be changed by improving PC, hence some patients initially testing at high risk may be re-categorized as low risk and avoid complications; this good news should be taken with some temperance. Not all patients will avoid complications, and for those who do not, further studies in this field may continue to provide insight into when and what complications are most likely to be experienced and generate additional interventions, perioperative therapies, and strategic risk management practices to further reduce complications and their consequences as much as possible.

Implications for Social Change

It is admittedly difficult for some, including me, not to become ecstatic at the potential beneficial changes that this research stream may create in the United States alone. Certainly the findings of this study carry the capacity to promote a social change explosion with a societal change imminent. The clear implications for social change affect the individual, the group, the community, and ultimately the nation. To be sure, without these interim findings we would not know that investigations need to focus on individual surgical types and not aggregate surgical procedures. Therefore, the immediate social change firstly affects the research community in this field; more specifically redirects research design that explores predictors of postoperative complications. However, if future studies continue to include a variety of surgical procedures with the population as the constant (elderly, obese, cancer or cardiac patients), we may very well continue to see conflicting published results thereby creating a lack of trust in physiologic capacity as a predictor, among clinicians responsible for risk assessment.

The social change for the individual surgical patient may be the most profound. The possibility that surgery can be faced without the fear of „what may happen afterward‟, removes a heavy weight of the unknown off the minds of the patient and the family. The future for surgical patients would include assessment and possible intervention (if deemed high risk for postoperative complications) before surgery is scheduled. The result is an uneventful and more pleasant (if possible) surgical experience. If, the risk after intervention remains high, having a window into the type and timing of potential complications can allow for pre-planning and potential mitigation of severity.

Additional implications for social change on an institutional or community level include policy and procedure changes for pre-surgical risk assessment and therapy, hospital standard of care changes, surgical approval and reimbursement policies by insurance providers, financial budgeting policies based on preoperative prediction of hospital costs, and bed management policy changes based on preoperative prediction of length of stay; to name a few.

These potential changes are by no means limited to the local stratum. To the contrary, if adopted in the healthcare and collateral industries across the nation, the changes would essentially impact national healthcare costs and by default, the national budget. To get a sense of the cost savings impact, if the $1.2 million (dollars that could have been saved if the patients in this study were able to avoid complications, in only three surgery types) were duplicated in the 5,708 registered hospitals across the United States (American Hospital Association Resource Center, 2008) more than $6.8 billion dollars could be saved. It is easy to understand then how a national cost savings in non-cardiac surgeries (30 million according to Potyk and Raudaskoski, 1998) could escalate to the projected more than *half-a-trillion* dollars *each year*. There is no doubt that healthcare is a big business directly affecting the national budget. In fact, the Department of Health and Human Services (DHHS), as of June 14, 2011, assessed healthcare spending as representing about 17.6% of the national Gross Domestic Product, compared to an average of 8% spent by other industrialized countries. DHHS also reported that for each dollar spent, 31% goes to hospital care. (www.cms.gov: National Health Expenditure Data, 2011) It is easy to see then how the current healthcare debate over the right to healthcare, access, choice, quality, efficiency and costs impacts the greater economy. Considering the recent passage of the healthcare bill, it is possible that federal legislation may be considered if cost savings from these changes would substantially reduce our national deficit. The willingness to change never comes easily… usually; but with a change in how preoperative assessment is conducted and the potentially astounding benefits, there may be a social and societal rush toward this change.

Summary

Recognizing that the aim of an exploratory study is to see if the results from a small sample provide justification for repeating the research in a larger study, the results of the present exploratory study succeeded in that goal. The findings from this study confirm that predictive parameters of physiologic capacity *change according to the surgical procedure*. The findings also point to the possibility of predicting the type and timing of complications according to the type of procedure. Furthermore, this study found that the same predictive models also predict with surprising accuracy (prior to surgery), the length of stay and hospital costs for each patient. The ramifications of these findings surely provide stimulus for immediate social change in the research community regarding the design of future research of other surgical types for predictors. A flood of social and societal changes that transforms the individual, the clinical staff, institutional direct care operations and strategic planning, collateral industry policies, and possibly national legislative healthcare policy will surely follow.

Taken together, these findings begin to build a larger and clearer picture, a portfolio of sorts, of what the patient, the surgeon, the clinical staff, the hospital administration, quality assessment professionals, policy makers, and insurance payers may expect and use in decision-making. It provides crucial information, from which the ramifications can take the healthcare and associative industries a step further toward a proactive versus reactive approach to surgery and reducing national healthcare costs.

The new frontier of identifying an objective predictor of postoperative complications based on physiologic capacity parameters has possibly moved beyond infancy, but specifics must be definitively clarified before continuing to the ultimate goal. Ultimately, reducing postoperative complications, by accurate assessment and effective intervention can translate into substantial cost savings and deliver a major hammer blow to the economic healthcare burden in the United States. It is achievable, the sooner the better for us all.

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Appendix A

Appendix A. Good Clinical Practice Training Certificate from CITIProgram (expires 01/20/13)

CITI Collaborative Institutional Training Initiative

CITI Good Clinical Practice Gradebook Curriculum Completion Report
Printed on 1/22/2010

Learner: Vicky Woodruff (username: vwoodruff)
Institution: University of Texas Health Science Center at Houston
Contact Information 6400 Fannin
Houston, Texas 77030 USA
Department: Neurosurgery
Phone: 281-546-0413
Email: vicky.woodruff@uth.tmc.edu

GCP:

Stage 1. Basic Course Passed on 01/22/10 (Ref # 4008703)

Required Modules	**Date Completed**	
GCP Introduction	01/21/10	3/3 (100%)
Overview of New Drug Development	01/21/10	5/5 (100%)
International Conference on Harmonisation (ICH): GCP Requirements	01/22/10	4/4 (100%)
FDA Regulated Research and ICH for Investigators	01/22/10	5/5 (100%)
International Conference on Harmonisation - ICH for Investigators	01/22/10	no quiz
Conducting Investigator-Initiated Studies According to FDA Regulations and Good Clinical Practices	01/22/10	3/3 (100%)
Investigator Obligations in FDA-Regulated Clinical Research	01/22/10	5/5 (100%)
Managing Investigational Agents According to GCP Requirements	01/22/10	5/5 (100%)
Conducting Clinical Trials of Medical Devices	01/22/10	3/3 (100%)
Informed Consent-An Ongoing Process	01/22/10	4/4 (100%)
Detection and Evaluation of Adverse Events	01/22/10	4/4 (100%)
Reporting Serious Adverse Events	01/22/10	4/4 (100%)
Audits and Inspections in Clinical Trial	01/22/10	5/5 (100%)
Monitoring of Clinical Trials by Industry Sponsors	01/22/10	8/8 (100%)
Completing the CITI GCP Course	01/22/10	no quiz

For this Completion Report to be valid, the learner listed above must be affiliated with a CITI participating institution. Falsified information and unauthorized use of the CITI course site is unethical, and may be considered scientific misconduct by your institution.

Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Course Coordinator

Appendix B. Human Research Training Certificate from CITIProgram (expires 01/20/13)

THE UNIVERSITY of TEXAS
HEALTH SCIENCE CENTER
AT HOUSTON

CITI Collaborative Institutional Training Initiative

Human Research Curriculum Completion Report
Printed on 1/20/2010

Learner: Vicky Woodruff (username: vwoodruff)
Institution: University of Texas Health Science Center at Houston
Contact Information 6400 Fannin
Houston, Texas 77030 USA
Department: Neurosurgery
Phone: 281-546-0413
Email: vicky.woodruff@uth.tmc.edu

Group 1 Biomedical Researcher and Key Personnel:

Stage 1. Basic Course Passed on 01/20/10 (Ref # 3997628)

Required Modules	Date Completed	
Introduction	12/10/09	no quiz
History and Ethical Principles	01/20/10	7/7 (100%)
Basic Institutional Review Board (IRB) Regulations and Review Process	01/20/10	5/5 (100%)
Informed Consent	01/19/10	4/4 (100%)
Social and Behavioral Research for Biomedical Researchers	01/19/10	4/4 (100%)
Records-Based Research	01/19/10	2/2 (100%)
Genetic Research in Human Populations	01/19/10	2/2 (100%)
Research With Protected Populations - Vulnerable Subjects: An Overview	01/19/10	4/4 (100%)
Vulnerable Subjects - Research with Prisoners	01/19/10	4/4 (100%)
Vulnerable Subjects - Research Involving Minors	01/19/10	3/3 (100%)
Vulnerable Subjects - Research Involving Pregnant Women and Fetuses in Utero	01/19/10	3/3 (100%)
International Research	01/19/10	1/1 (100%)
Group Harms: Research With Culturally or Medically Vulnerable Groups	01/19/10	3/3 (100%)
FDA-Regulated Research	01/19/10	5/5 (100%)
Human Subjects Research at the VA	01/19/10	3/3 (100%)
HIPAA and Human Subjects Research	12/10/09	2/2 (100%)
Workers as Research Subjects-A Vulnerable Population	01/19/10	4/4 (100%)
Hot Topics	01/20/10	no quiz
Conflicts of Interest in Research Involving Human Subjects	01/20/10	0/2 (0%)
University of Texas Health Science Center at Houston	12/10/09	no quiz

For this Completion Report to be valid, the learner listed above must be affiliated with a CITI participating institution. Falsified information and unauthorized use of the CITI course site is unethical, and may be considered scientific misconduct by your institution.

Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Course Coordinator

Return

Appendix C. Letter of collaboration approval from the University of Texas M. D. Anderson Cancer Center

THE UNIVERSITY OF TEXAS
MD Anderson ~~Cancer~~ Center
Office of Protocol Research

Institutional Review Board (IRB)
Unit 1437
Phone 713-792-2933
Fax 713-794-4589

To: Curtis E. Hightower 01/06/2011
From: Virginia M Gonzales
CC: Ashley Smallwood, Deidre Mooring
MDACC Protocol ID #: 2005-0303
Protocol Title: A Study to determine whether Perioperative Energy Dynamics correlates with Postoperative Outcomes
Version: 10

Subject: Administrative IRB Approval -- Protocol 2005-0303

On Monday, 01/03/2011, the Institutional Review Board (IRB) 5 chair or designee reviewed and approved your revision dated 12/07/2010 for Protocol 2005-0303

These Pages Include:

- Collaborator(s) Page -- Document header Date: 12/07/2010

Revision included the following changes:
addition of Vicki D. Woodruff from Walden University as new collaborator.

The revision can now be implemented. Please inform the appropriate individuals in your department or section and the collaborators of these changes.

Please inform the appropriate individuals in your department/section and your collaborators of these revisions.

Please Note: This approval does not alter or otherwise change the continuing review date of this protocol.

In the event of any questions or concerns, please contact the sender of this message at (713) 792-2933.

Virginia M Gonzales 01/06/2011 01:00:18 PM

This is a representation of an electronic record that was signed and dated electronically and this page is the manifestation of the electronic signature and date:

Virginia M Gonzales
01/06/2011 12:59:45 PM
IRB 5 Chair Designee
FWA #: 00000363
OHRP IRB Registration Number: IRB 5 IRB00006023

Appendix D: Common Terminology Criteria for Adverse Events (CTCAE) US National Institutes of Health

Cardiac	
1.0) Cardiac Arrhythmia	**:Conduction abnormality/atrioventricular heart block; (asystole, 1st degree, 2nd degree [mobitz type 1 or 2] , 3rd degree AV Block, sick sinus syndrome, Stokes – Adams syndrome, Wolff – Parkinson – White syndrome, conduction abnormality NOS)** Grade 3, incompletely controlled medically or controlled with device Grade 4, life threatening associated with CHF, shock, etc. Grade 5, death **:Prolonged QTc interval** ; Grade 3, QTc>0.5 seconds Grade 4, QTc>0.5 seconds, life threatening signs or symptoms (arrhythmia, CHF, shock, etc.) Grade 5, death **:Superventricular and nodal arrhythmia**; **(Atrial fib, Atrial flutter, Atrial tachycardia/ paroxysmal Atrial tachycardia, nodal/junctional, sinus arrhythmia, sinus brady, sinus tachy, supraventricular extrasystoles [premature Atrial contractions, premature Nodal/junctional contractions)** Grade 3, incompletely controlled medically or controlled with device Grade 4, life threatening associated with CHF, shock, etc. Grade 5, death **: Ventricular arrhythmia**; **(bigeminy, idioventricular rhythm, PVC's, Torsade de pointes, Trigeminy, Ventricular fib, Ventricular flutter, Ventricular tach, Ventricular arrhythmia NOS)** Grade 3, incompletely controlled medically or controlled with device Grade 4, life threatening associated with CHF, shock, etc Grade 5, death **: Cardiac Arrhythmia- other Specify,___** ; Grade 2, moderate Grade 3, severe Grade4, life threatening Grade 5, death
2.0) Cardiac General	**: ischemia/infarction;** Grade 3, Symptomatic, testing consistent with ischemia, therapy indicated

	Grade 4, Acute myocardial infarction Grade 5, death **: Cardiac troponin T (ctnt);** Grade 2, 0.05 -< 0.1 ng/mL Grade 3, 0.1 -<0.2 ng/mL Grade 4, 0.2 ng/mL Grade 5, death **: Cardiac troponin I (ctnI)**; Grade 3, levels consistent with unstable angina Grade 4, levels consistent with myocardial infarction Grade 5 death **: Cardiopulmonary arrest, cause unknown, non-fatal**; Grade 4, life threatening **: Hypertension**; Grade 3, Recurrent or persistent (≥ 24 hrs) or symptomatic increase by >20 mmhg (diastolic) or to >150/100 if previously WNL requiring continuous IV medication Grade 4, life threatening Grade 5, death **: Hypotension**, Grade 3, sustained (≥ 24 hrs) IV therapy Grade 4, Shock (vital organ impairment, academia) Grade 5, death **: Ventricular diastolic dysfunction**; Grade 3, Symptomatic CHF, responds to therapy Grade 4,refractory CHF, ventricular assist devise or heart transplant indicated Grade 5 death **: Left ventricular systolic dysfunction**; Grade 3, Symptomatic CHF, EF , 40 – 20%, SF <15%, responsive to therapy Grade 4, Refractory CHF or poorly controlled, EF <20% ventricular assist devise, surgery or heart transplant indicated Grade 5, death **: Pericardial effusion, non-malignant**; Grade 3, effusion with physiologic consequence Grade 4, life threatening, emergence intervention indicated Grade 5, death **:Right ventricular dysfunction, cor pulmonale**; Grade 3, symptomatic, responsive to therapy Grade 4, symptomatic, poorly controlled ventricular assist devise or heart transplant indicated Grade 5, death **: Cardiac General- other Specify,___**

	Grade 3, severe, Grade 4, life threatening, Grade 5,death
3) Coagulation	**: Disseminated intravascular coagulation; must have increased split fibrin products or D-dimer**; Grade 3, Lab findings with bleeding Grade 4, Lab findings with life threatening symptoms Grade 5, death **:International Normalization Ratio of Prothrombin Time (INR);** Grade 2, >1.5 – 2.0 × ULN Grade 3, >2 × ULN **:PTT;** Grade 2, >1.5 – 2.0 × ULN Grade 3, >2 × ULN **: Thrombotic microangiopathy (must have microangiopathic changes on blood smear, helmet cells, red cell fragments, schistocytes, etc.)** Grade 3, lab finding + clinical symptoms (renal failure, petechiae, etc.) Grade 4, life threatening symptoms Grade 5, death **: Coagulation-other Specify,___**; Grade 3, severe; Grade 4, life threatening; grade 5, death
4) Constitutional symptoms	**:hypothermia (oral or tympanic);** Grade 3, 32 ->28° C or 89.6 - >82.4° F Grade 4, ≤ 28° C or 82.4° F with life threatening symptoms Grade 5, death
5) Dermatology/ Skin	**: Skin breakdown/ decubitus ulcer**; Grade 3, operative debridement or barometric chamber indicated Grade 4, life threatening, major operative intervention Grade 5, death **: Ulceration**; Grade 3, ulceration ≥ 2cm invasive therapy indicated Grade 4, life threatening major invasive therapy indicated Grade 5, death **: Wound complication, non-infectious**; Grade 3, Incisional separation symptomatic hernia without strangulation or evisceration indicated primary closure by operative intervention Grade 4, evidence of strangulation or evisceration operative intervention indicated Grade 5, death

	: Dermatology / Skin-other Specify,___; Grade 3, moderate; Grade 4, severe; Grade 5, death
6) Endocrine	**:Glucose intolerance (diabetes);** Grade 3, insulin required Grade 4, life threatening (ketoacidosis, hyperosmolor non-ketolic coma, etc.) Grade 5, death
7) Gastrointestinal	**: Ascites, non-malignant**; Grade 3, symptomatic invasive procedure indicated Grade 4, life threatening Grade 5, death **: Ileus, GI, functional bowel obstruction**; Grade 2, Symptomatic altered dietary habits, IV fluids indicated Grade 3, severely altered GI function IV fluids, tube feeding, or TPN indicated≥ 24hrs Grade 5, death **: Leak, anastomotic GI, Esophagus;** Grade 2, symptomatic medical intervention indicated Grade 3, symptomatic, invasive therapy indicated Grade 4, life threatening Grade 5, death **: Obstruction, GI**; Grade 3, symptomatic, altered dietary habits, IV fluids indicated <24hrs Grade 4, severely altered GI function IV fluids, tube feeding, or TPN indicated≥ 24hrs operative intervention indicated Grade 5, death **: Gastrointestinal-Other Specify,___**; Grade 2, moderate; Grade 3, severe; Grade 4 life threatening; grade 5, death
8) Infection	**: Infection with Grade 1or 2 neutrophils, normal ANC**; Grade 3, IV antibiotics, antifungal, or antiviral therapy indicated interventional radiology or operative intervention indicated Grade 4, life threatening consequence Grade 5, death **Grades are for all infections** : Opportunistic infection (Grade 3-5) : Infection select; Colon (Grade 3-5) : Infection-select; Esophagus (Grade 3-5) : Infection-select; Peritoneal cavity (Grade 3-5)

	: Infection-select; Pneumonia (Grade 3-5) : Infection-select; Blood (Grade 3-5) : Infection-select; Catheter-related (Grade 3-5) : Infection-select; Wound (Grade 3-5) : Infection-select; Mediastinum NOS (Grade 3-5) : Infection-select; Pleura (empyema) (Grade 3-5) : Infection-select; Urinary tract NOS (Grade 3-5) : Infection-select; Pelvis NOS (Grade 3-5) : Infection-Other Specify,___ (Grade 2-5)
9) Metabolic / Laboratory	**: Acidosis, metabolic or respiratory;** Grade 4, pH < 7.3, life threatening; Grade 5, death **: Alkalosis, metabolic or respiratory;** Grade 4, pH >7.5, life threatening; Grade 5, death **: Albumin, low serum;** Grade 3, <2g/dL or <20g/dL, Grade 5, death **:Alkaline phosphatase;** Grade 3, >5.0 – 20.0 × ULN, Grade 4, >.20.0 × ULN **: Bicarbinate serum-low** Grade 3, <11 - 8 mmol/L, Grade 4, < 8 mmol/L Grade 5, death **: Glomerular filtration rate** Grade 3, <25% LLN, dialysis not indicated Grade 4, chronic dialysis or renal transplant Grade 5 death **: Glucose serum high;** Grade 3, > 250 -500 mg/dL or > 13.9 – 27.8 mmol/L Grade 4, >500 mg/dL Grade 5, death **: Glucose serum low**; Grade 2, < 55- 40 mg/dL or <3.0 – 2.2mmol/L Grade 3, <40-30 mg/dL or <2.2 – 1.7mmol/L Grade 4, <30 mg/dL or <1.7mmol/L Grade 5, death **: Potassium, serum high;** Grade 2, > 5.5 -6.0 mmol/L Grade 3, >6.0 -7.0 mmol/L Grade 4, >7.0 mmol/L Grade 5, death

	: Potassium, serum low; Grade 3, < 3.0 - 2.5 mmol/L Grade 4, < 2.5 mmol/L Grade 5, death **: CPK;** Grade 2; >2.5 – 5 × ULN Grade 3; >5-10× ULN Grade 4; >10 × ULN Grade 5; death **: Creatinine;** Grade 2 >2.5-3.0 × ULN Grade 3 > 3.0 – 6.0× ULN Grade 4 > 6.0× ULN Grade 5 death **:ALT, SGPT**; Grade 2,>2.5-5.0 × ULN Grade 3, >5.0-20 × ULN Grade 4 >20 × ULN **: Amylase**; Grade 2: >1.5-2.0 × ULN Grade 3 >2.0-5.0 × ULN Grade 4 > 5.0 × ULN **:AST,SGOT**: Grade 2 >2.5-5.0 × ULN Grade 3 >5.0-20 × ULN Grade 4 >20 × ULN **: Bilirubin**; Grade 2 >1.5-3.0 × ULN grade 3 >3.0-10.0 × ULN Grade 4 >10 × ULN
10) hepatobiliary/pancreas	**:Liver dysfunction/failure;** Grade 3, Asterixis Grade 4, Encephalopathy or coma Grade 5, death **:Pancreatitis;** Grade 2, symptomatic medical intervention indicated Grade 3,interventional radiology or operative intervention Grade 4, life threatening Grade 5, death **:Hepatobiliary/pancreas other (specify);** Grade 2, mild Grade 3, severe Grade 4, life threatening, disabling

	Grade 5, death
11) Neurology	**: CNS cerebrovascular ischemia**; Grade 3, TIA, ≤ 24hrs Grade 4, Cerebral vascular accident, neurologic defect >24hrs Grade 5, death **: Seizure**; Grade 3, consciousness alert, with break through seizures despite medical therapy Grade 4, prolonged repetitive difficult to control seizures Grade 5, death **: Neurology -Other Specify,___** Grade 2, moderate; Grade 3, severe; Grade 4 life threatening; grade 5, death
12) Pulmonary/Upper respiratory	**: Adult Respiratory Distress Syndrome (ARDS);** Grade 4, intubation indicated Grade 5, death **: Aspiration**; Grade 2, symptomatic, medical intervention indicated (antibiotics, oxygen, etc) Grade 3, signs of pneumonia or pneumonitis Grade 4, life threatening Grade 5, death **: Atelectasis**; Grade 2, symptomatic, medical intervention indicated (broncoscopy, chest physiotherapy) Grade 3, operative intervention indicated Grade 4, life threatening respiratory compromise Grade 5, death **:Chylothorax;** Grade 2, symptomatic, thoracenteses or tube drainage Indicated Grade 3, operative intervention indicated Grade 4, life threatening Grade 5, death **: Dyspnea**; Grade 4, dyspnea at rest, Grade 5, death **: Fistula, pulmonary/ upper respiratory, Trachea, Pleura, Bronchus, or Lung** Grade 2, symptomatic, tube thoracostomy or medical management indicated Grade 3,symptomatic, altered respiratory function,

	operative intervention indicated Grade 4, life threatening, operative intervention indicated Grade 5, death **: Hypoxia**; Grade 2, decreased O2 sat with activity, intermittent O2 Therapy Grade 3, decreased O2 sat at rest continuous O2 therapy Grade 4, life threatening intubation or ventilation indicated Graded 5, death **: Pleural effusion, non-malignant**; Grade 2,symptomatic, medical tx or up to 2 thoracenteses Grade 3, symptomatic, w/ O2 therapy, > 2 thoracenteses, tube drainage or plurodesis indicated Grade 4, life threatening ventilatory support needed Grade 5, death **: Pneumonitis / pulmonary infiltrates**; Grade 3, symptomatic, O2 indicated Grade 4, life threatening ventilatory support indicated Grade 5, death **: Prolonged intubation, >24hours after surgery;** Grade 2, extubated 24 -72 hrs postop Grade 3, extubated >72 hrs postop prior to tracheotomy Grade 4, tracheotomy indicated Grade 5, death **: Prolonged chest tube drainage or air leak after thoracostomy;** Grade 2, sclerosis or tube thoracostomy Grade 3, operative intervention indicated (thoracostomy) Grade 4 life threatening Grade 5, death **: Pulmonary/Upper respiratory -Other Specify,___;** Grade 2, moderate; Grade 3, severe; Grade 4 life threatening; grade 5, death
13) Renal / Genitourinary	**: Renal Failure**; Grade 3, chronic dialysis not indicated Grade 4,chronic dialysis or renal transplant Grade 5, death **: Fistula, GU;** Grade 3, symptomatic invasive therapy indicated Grade 4, life threatening, operative procedure required Grade 5, death **: Leak, Anastomotic, GU**; Grade 3, symptomatic invasive or indoscopic intervention indicated

	Grade 4, life threatening Grade 5, death **: Renal/Genitourinary-Other Specify,___**; Grade 3, severe; Grade 4 life threatening; grade 5, death
14) Vascular	**:Thrombosis / thrombus/ embolism**; Grade 3, deep vein thrombosis or cardiac thrombosis indicating coagulation, lysis, filter, or invasive procedure indicated Grade 4, embolic event including pulmonary emboli, or other life threatening thrombus Grade 5, death **: Visceral arterial ischemia**; **non myocardial**; Grade 3, prolonged (≥24hrs) or recurrent symptoms invasive intervention indicated Grade 4, life threatening, end organ damage Grade 5, death **: Vascular-Other Specify,___;** Grade 3, severe; Grade 4 life threatening; grade 5, death
15) Non-CTCAE Outcomes of Interest	**: Readmit to ICU; any patient discharged from the ICU after surgery and needing to be readmitted due to complications related to one of the study surgical procedures within that hospitalization.** **: Re-intubation; any patient extubated at the first postoperative destination needing reintubation within the 10 day postoperative observation period.** **: Readmit to hospital in < 30 days after the surgery for a surgery related complication** **: New prescription of home oxygen therapy at discharge**
Death	: not associated with CTCAE term (Grade 5)

Appendix E: Definitions and units of measure for Independent Variables listed in Table 5.

Independent Variable	Definition	Unit of measure
RHR (Resting Heart Rate)	Heart rate at rest	Beats per minute
MHR (Maximal Heart Rate)	Fastest heart rate during CPET	Beats per minute
HRatAT	Heart rate at Anaerobic threshold	Beats per minute
$HRatPV0_2$	Heart rate at peak volume of oxygen	Beats per minute
HRatStopTest	Heart rate at Stop Test	Beats per minute
HRat1minrec	Heart rate at 1minute into recovery	Beats per minute
ATmL/min	Anaerobic threshold	mili-Liters per minute
ATmL/min/kg	Anaerobic threshold	mili-Liters per minute per kilogram of weight
$PV0_2$mL/min	Peak volume of oxygen	mili-Liters per minute
$PV0_2$mL/min/kg	Peak volume of oxygen	mili-Liters per minute per kilogram of weight
PMHR	Predicted maximum heart rate	formula: 220 – age
%PMHRA	% of predicted maximum heart rate achieved during CPET	percent in two decimals
ΔHR1 (Delta heart rate 1)	Difference in heart rate at rest and heart rate at anaerobic threshold	Beats per minute
ΔHR2 (Delta heart rate 2)	Difference in heart rate between rest and heart rate at peak oxygen uptake (PV02)	Beats per minute
ΔHR3 (Delta heart rate 3)	Difference in heart rate at stop test and heart rate 1 minute into recovery	Beats per minute
HRTime (Heart rate time)	How long it took for the heart rate to drop to or below 100 beats per minute after stop test	minutes 0 = <1 minute 1 = ≥ 1 but <2 minutes 2 = >2 but <3 minutes 3 = >3 but <4 minutes 4 = >4 but <5 minutes 5 = ≥ 5 minutes
PredATmL/min	Predicted anaerobic threshold	formula: 65% of AT measured in mili-Liters per minute

PredATmL/min/kg	Predicted anaerobic threshold	formula: 65% of AT measured in mili-Liters per minute per kilogram of body weight
%PredATmL/min	Percent of predicted Anaerobic Threshold achieved	mili-Liters per minute

Curriculum Vitae

VICKY D. WOODRUFF

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PROFESSIONAL EXPERIENCE & ACCOMPLISHMENTS

Research coordination and management

9 years experience:

- Day-to-day coordination of project, teams, facilities, budget, outcomes, and quality control
- Writing /organizing research grant proposals and protocols- shepherd through IRB and submission process (10 years)
- Coordinated and managed participant recruitment, conducting patient interviews and surveys,
- Created and maintained data collection records and maintenance of databases
- Assisted with statistical analysis and interpretation of data
- Wrote quarterly, bi-annual and final progress reports and presentations, to investigative team, granting agencies, and administration. Also created conference posters for presentations at symposiums and conferences

  Accomplishments:
  - 9 years successfully guided research projects within budget constraints
  - Co-authored new software with Institute for Corporate Health for research testing.
  - 80%+ track record of successful grant proposals – Federal, private, professional
  - Reorganized systematic process for participant recruitment and data collection – increased recruitment to 40% and reduced data entry time by 50%

Management

Providing creative solutions with excellent outcomes, where others see no way

- 15 years - institutional consultant and leadership positions
- 15 years – leading teams in project improvement initiatives in academic hospital setting
- 20+ years experience in building internal and external relationships
- 10 years - strategic planning/program and institutional evaluation: Certified Malcolm Baldrige Sr. Examiner with Quality Texas Program

  Accomplishments:
  - Project lead on hospital teams resulting in total ROI saved or generated = >$5,000,000

Examples of projects: staffing, ↑ exam room usage, ↓ infection rate, ↓ postoperative complications, ↓medical errors, ↓ time from test order to results, ↓ cost of disposable surgical instruments.

- Lead project to implement exercise component into patient treatment pathway for diabetic, oncology, and neurologic patients resulted in ↑ revenue and ↓ hospitalization and/or treatment time.
- Created and implemented new service line for major hospital

Research Investigator experience

Clinical research: 6 years experience as research co-investigator on federal and private grant funded projects

- Co-investigator at Oral Roberts University – 2 years
  Fitness capacity determination via max stress test, hydrostatic weighing, & spirometry testing
- Co-Investigator on two research projects at MD Anderson Cancer Center – (2005- present)
  Physiologic capacity as a preoperative predictor of postoperative risk
  Neoadjuvant chemoirradiation affects on physiologic capacity and postoperative risk.

Behavioral research: 2 years experience as PI-investigator on local grant

- PI on behavioral research to assess health needs of Houston 3rd Ward.- Grant funded 2 years
  Assessing health needs of underserved population in 3rd Ward of Houston, Tx.
- Current PhD work under program at Walden University – ongoing effort
  *Physiologic Capacity as a Predictor of Postoperative Complications and Collateral Costs in Three Types of Oncological Surgerie*s

Publications

David, Y., Hyman, W., **Woodruff, V**., Howell, M. (2007). Overcoming barriers to success: Collecting medical device incident data. *Biomedical Instrumentation & Technology,* p.471-475.

David, Y., Hyman, W., & **Woodruff, V.** (2008). Colloquium report: responding to medical device incidents. *Journal of Clinical Engineering,* 33(1), p.16-18.

Hightower, C., Riedel, B., Fieg, B., Morris, S., Ensor, J., **Woodruff, V**., Daily, D., & Sun, X. (2010). A pilot study evaluating predictors of postoperative outcomes after major abdominal surgery: Physiologic capacity vs. the American Society of Anesthesiologists" (ASA) Physical Status Classification system. *British Journal of Anaesthesia, 104*(4), 465-471.

Hightower, C., Riedel, B., Dang, A., **Woodruff, V.** (2009) Effects of neoadjuvant chemo-irradiation on physiologic capacity, affecting postoperative complications (journal has not yet been selected)

Other articles I provided editorial assistance

Riedel, B., Schier, R., (2009) Prognostic Value of Brachial Artery Reactivity Testing in Major Thoracic Surgery. *Anesthesia & Analgesia.* Manuscript submitted for publication.

Grant proposals

10 years experience writing proposals & grant agency reports (R21, R01, K grants, U grants & private foundations)

Awarded grants (some of the many)

- NIH- Transforming Healthcare quality through information technology (2008) MD Anderson Cancer Center
- NIH – Collaboration grant with Children‟s Hospital in Boston- Home for pregnant and parenting teens (5 yr grant)
- Houston Endowment Grants (3 total) $200K for Otra Onda Youth Wave – program grant
- Robert Wood Johnson Foundation (2007) Amos Scholarship grant
- March of Dimes – 2007 & 2008 Leading and Empowering Expectant Adolescent Patients (Project LEEAP)
- Boston Public Health Commission, a Boston Health Start Initiative-2006 (one of 13 sites funded) The Boston Healthy Start Initiative (BHSI)
- Seaton Healthcare Network – (2006) $102K Healthcare Alliance Safety Partnership
- NIH – K grant – Mid-career investigator award in patient research (5 year award – 100K/yr) MD Anderson
- BIRCWH (Building Interdisciplinary Research Career in Women‟s‟ Health) in 2005. Project entitles: Acculturation and Health Risk Behaviors Among Haitian Adolescent Females.
- AHRQ: Partnership for Implementing Patient Safety (2006) MD Anderson Cancer Ctr.
- AHRQ: Alert Sentinel Diagnostic Events (2005) $155K
- AHRQ: Understanding Barriers to incident reporting by nurses: The influence of attitudes, knowledge about the Practice Act, and demographics on intent to report (NUR02-596)
- East Texas Area Health Education Center (2005) HASP $300K
- Houston Endowment Grant - $1M for Episcopal Church - Capital needs for structural building improvements

Other grants

- NIH – (2) Exploratory Grant (2 year award) $500K MD Anderson (currently under consideration by NIH)
- CPRIT – Exploratory Grant (4 years award) $4M MD Anderson (currently under consideration by CPRIT)
- AHRQ -Searching for the final answer: factors contributing to medication administration errors.
  - Nat"l Patient Safety Foundation – Consumer Healthcare Safety Reporting: Moving to inclusive learning systems (2008)
- McDonnell Foundation - $100K Agent Based Modeling in Healthcare. MD Anderson
- National Science Foundation – Pre-doctoral award MD Anderson
- AHRQ – Large Conference Award $250K – MD Anderson
- NIH – Support for conferences and scientific meetings (5 year award) MD Anderson

EMPLOYMENT SUMMARY

UT Health Science Center - *Clinical Research Coordinator II*	12/09 - Present
Woodruff Consulting – *Consultant/Analyst*	07/99 – Present
M. D. Anderson Cancer Center *Sr. Improvement Advisor*	07/03 – 02/09
St. Luke's Episcopal Hospital - *Director*	10/97 – 07/99
Standard Register Co. - *District Operations Manager*	01/95 – 10/97
AT&T/GIS – *Account Analyst/Project Management*	09/93 – 01/95
Saint Francis Hospital - *Manager Physical Performance Center*	03/86 – 08/93

EDUCATION

PhD Health Sciences, Walden University (expected completion 9/2011)
Master of Arts Exercise Physiology/Sports Medicine, The University of Tulsa, Tulsa, Oklahoma
Bachelor of Science Exercise Physiology/Biology, Oral Roberts University, Tulsa, Oklahoma