CHASE, PAUL J., Ph.D. Comparison of Estimations versus Measured Resting Oxygen Consumption in Patients with Heart Failure and Reduced Ejection Fraction Undergoing Right Heart Catheterization. (2014)
Directed by Dr. Paul G. Davis. 152 pp.

Affecting close to 6 million people in the United States, heart failure (HF) represents the final stage of several diseases of the heart and is commonly defined as a reduction in the heart's ability to circulate blood. Cardiac output during right heart catheterization is an important variable used in patient selection for advanced therapies, such as cardiac transplantation and left ventricular assist device implantation. It is common practice to utilize the Fick method to determine the cardiac output (*cardiac output = oxygen consumption [VO_2]/arteriovenous oxygen difference*) inputting estimated VO_2 from one of three published empirical formulae. However, these estimation equations have not been validated in patients with HF. The purpose of this study was to determine the accuracy of three widely used equations for the estimation of VO_2 compared to direct breath-by-breath measurement of VO_2 and determine to what extent clinically significant error occurs in patients with HF and reduced ejection fraction (HFrEF).

Forty-four patients with HFrEF undergoing routine cardiac catheterization (65.9% male, 65.9% Caucasian, 64.5 $\pm$ 10.7 years old) performed 10 minutes of ventilatory gas exchange immediately following catheterization procedures, and averaged results of the last five minutes were compared to the derived estimations by: LaFarge & Miettinen, Dehmer et al. and Bergstra et al. (estimated – measured). Single-sample *t*-tests found the mean difference between the estimation of LaFarge & Miettinen was not significant (-

10.3 ml/min ± 6.2 SE, p=0.053), but significant differences were found with Dehmer et al. (16.0 ml/min ± 6.4 SE, p=0.008) and Bergstra et al. (40.6 ml/min ± 6.4 SE, p<0.001). Bland-Altman plots demonstrated limits of agreement outside of acceptable limits with trends towards overestimation in patients with low VO_2 and underestimation in patients with higher VO_2 for all equations. Bland-Altman plots and single-sample *t*-tests of dichotomous groups (sex, pulmonary hypertension and aldosterone antagonist medication) did not identify a subgroup where any of the equations were acceptable. The rate of ≥25% error in the estimates of the LaFarge & Miettinen, Dehmer et al. and Bergstra et al. equations occurred in 11%, 23% and 45% (respectively) of the patients. Clinically significant error (misclassification) in the cardiac index derived from the Lafarge & Miettinen, Dehmer et al. and Bergstra et al. equations for three clinically important classifications: cardiogenic shock – 20.5%, 22.7% and 31.8%; hypoperfusion – 15.9%, 15.9% and 25%; abnormal – 13.6%, 13.6% and 15.9%, respectively. Exploring possible HFrEF-specific equations, linear regression modeling was performed with 34 patients. Two models were developed: (Model 1) VO_2*=-10.76+(127.74*body surface area)+(aldosterone antagonist [prescribed=1, not prescribed=-1]*22.15)*; (Model 2) VO_2*=149.4+(sex [male=1, female=-1]*25.41)+(aldosterone antagonist [prescribed=1, not prescribed=-1]*28.34).* Bland-Altman plots and *t*-tests with the remaining 10 patients yielded limits of agreement outside of acceptable limits despite lack of significant differences between the estimated and measured VO_2 for Model 1 and Model 2 (11.0 ml/min ± 10.7 SE, p=0.165; 12.4 ml/min ± 0.249, p=0.249). These findings do not support the use of these empirical formulae to estimate the resting VO_2 in patients with

HFrEF undergoing right heart catheterization. The direct measurement of the resting VO_2 should be the primary method applied to the Fick equation for cardiac output.

COMPARISON OF ESTIMATIONS VERSUS MEASURED RESTING OXYGEN CONSUMPTION IN PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION UNDERGOING RIGHT HEART CATHETERIZATION

by

Paul J. Chase

A Dissertation Submitted to
the Faculty of The Graduate School at
The University of North Carolina at Greensboro
in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

Greensboro
2014

Approved by

_____
Committee Chair

APPROVAL PAGE

This dissertation written by Paul J. Chase has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

Committee Chair _____

Committee Members _____

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_____
Date of Acceptance by Committee

_____
Date of Final Oral Examination

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CHAPTER I

INTRODUCTION

Heart failure (HF) is a complex syndrome resulting from any structural or functional disorder that limits the ability of a ventricle to contract (most commonly associated with the left ventricle) and eject blood [HF with a reduced left ventricular ejection fraction (LVEF), or HFrEF] or relax and fill with blood [HF with preserved LVEF (HFpEF)], and represents the severest stage of several disorders/diseases of the heart (Bui, Horwich, & Fonarow, 2011; Hunt et al., 2009; Lindenfeld et al., 2010). In physiological terms, the Heart Failure Society of America describes HF as the presence of elevated cardiac filling pressure (typical finding of HFpEF) and/or inadequate oxygen (O_2) delivery to the periphery (typical finding of HFrEF), either at rest or during stress, that is caused by a cardiac dysfunction (Lindenfeld et al., 2010). As the HF syndrome advances in those (initially) with HFpEF, reductions in LVEF below 45% will occur and will then be considered to have HFrEF.

In the United States HF (HFpEF and HFrEF) represents a major health problem, with a prevalence of approximately 2.4% of the population, or about 5.7 million people (Roger et al., 2012). The prevalence in those $\geq$ 70 years old is approximately 20% (Roger et al., 2012). Annually, about 550,000 new cases of HF are diagnosed each year, and there is roughly a 1 in 5 lifetime risk of developing HF in the United States (Levy et al., 2002; Lloyd-Jones et al., 2010). There are nearly 300,000 deaths per year attributable to

HF, with annual healthcare cost estimations reaching $39 billion in 2010 when the cost of hospitalizations, medications and loss of productivity are considered (Bui et al., 2011).

Cardiac output (while supine at rest) is an important measure in the determination of HF severity and in assessment of the need for advanced therapies (cardiac transplant or left ventricular assist device (LVAD)). Furthermore, cardiac index (cardiac output/body surface area (BSA)) is a more sensitive indicator of the heart's ability to perfuse all the body's tissues. For example, if two patients have the same cardiac output of 5 L/min, but one patient has a BSA of 1.79 m^2 and the other has a BSA of 2.22 m^2, the first patient then has a cardiac index of 2.8 L/min/m^2, where the second patient has a cardiac index of only 2.2 L/min/m^2. A cardiac index <2.2 L/min/m^2 is an indicator for advanced therapies in patients with HFrEF. However, a very low cardiac index (<1.9 L/min/m^2) represents a state of shock and is associated with poor outcomes when considering LVAD implantation as advanced therapy (Ginsberg & Parrillo, 2009; Kirklin et al., 2010; Slaughter et al., 2010). Thus, it is possible that an error as little as 14% in the measure of cardiac index can have significant influence on the patient's disease management.

Though the cardiac index may be a more sensitive indicator of the heart's perfusion performance, the absolute cardiac output is an important variable in the calculation of a number of other derived variables, such as, systemic and pulmonary vascular resistance, total pulmonary resistance, valvular orifice area, and right ventricular stroke work index. All of these variables are used to assist in guiding care and treatment of patients with HFrEF (Lindenfeld et al., 2010) and are strong prognostic indicators of

poor outcomes after cardiac transplant or LVAD procedures (Kirklin et al., 2010; Mehra et al., 2006; Slaughter et al., 2010).

Cardiac output is typically measured during catheterization of the right side of the heart. The most common determination of cardiac output during a right heart catheterization is by the thermal dilution method. This method involves injecting a known volume of cooled saline into the right atrial blood flow, which is then measured distally in the right ventricular outflow tract. The change in temperature is related to the flow of blood. Another common method to estimate cardiac output is by the Fick method, which (by formula) states that cardiac output is equal to the rate of O_2 consumption (VO_2) divided by the O_2 content difference of the arterial and venous blood (a-vO_2Diff). Considering the history of measuring cardiac output, the Fick principle is the "Gold Standard" as it was used to validate other measures, such as thermal dilution. Furthermore, there are several conditions which can cause erroneous cardiac output results with the thermal dilution method that justify the measurement of cardiac output by the Fick method. All of these conditions potentially cause the cooled fluid greater opportunity to have contact with the chamber walls of the right atrium and ventricle effectively warming the fluid above what blood alone would do, which causes an overestimation of cardiac output (Baim & Grossman, 2006; van Grondelle, Ditchey, Groves, Wagner, & Reeves, 1983). These conditions include atrial dysrhythmias, tricuspid valve regurgitation, ventricular dyssynchrony, and low output states (absolute cardiac output <3.5 L/min) (Kendrick, West, Papouchado, & Rozkovec, 1988). Though the low output is the most common of these conditions in patients with HFrEF (Cotter et

al., 2003), these patients are at higher risk of developing any of these conditions. Therefore, it is common practice for physicians performing cardiac output measurements in patients with HFrEF to utilize the Fick method for measuring cardiac output.

Proper measurement of resting cardiac output by the Fick method requires the measurement of VO_2 and gas analysis of arterial and mixed venous blood. It has become common practice to estimate the patient's resting VO_2 utilizing one of three common equations (Narang et al., 2012). All of these assume a constant resting VO_2 based on a set of patient characteristics. As an example, the most common is simply 125xBSA (Dehmer, Firth, & Hillis, 1982), which suggests that the resting VO_2 of an individual is based solely on the patient's estimated BSA. Other proposed formulas, attempt to individualize beyond BSA by including age, sex and/or heart rate into the estimation (Bergstra, van Dijk, Hillege, Lie, & Mook, 1995; LaFarge & Miettinen, 1970). Despite these equations being widely used on patients with HFrEF, a review of the literature indicates that the three most commonly used estimations have not been well validated with patients with HFrEF. Therefore, the purpose of this study was to measure the resting VO_2 in adult patients with HFrEF during right heart catheterization procedures, investigate the accuracy of three widely used equations for the estimation of resting VO_2 compared to the direct breath-by-breath measurement of expired air using a metabolic cart and determine to what extent clinically significant errors occur using estimation equations.

Statement of Problem

It is widely accepted that the Fick method of measuring cardiac output is the most reliable method in patients with HFrEF, which relies on the measurement of VO_2. However, it is normal practice to estimate resting VO_2 in order to calculate the cardiac output via the Fick method utilizing one of three popular estimation equations. Unfortunately, these equations have been derived from selected cohorts that have included very few, if any, patients with HFrEF. Thus, the validity of these equations is unknown in patients with HFrEF undergoing right heart catheterization.

Purpose of the Study

The purpose of this study was to measure the resting VO_2 in adult patients with HFrEF during right heart catheterization procedures, investigate the accuracy of three widely used equations for the estimation of resting VO_2 compared to the direct breath-by-breath measurement of expired air using a metabolic cart and determine to what extent clinically significant errors occur using estimation equations.

Aims & Hypotheses

This study was designed to:

1) Compare the difference between the measured resting VO_2 and estimates from each of three commonly used formulas (LaFarge & Miettinen, 1970; Dehmer et al., 1982; and Bergstra et al., 1995):
    a. Primary Aim – The difference between measured and estimated VO_2 was evaluated for the whole sample.

Hypothesis: The differences between measured VO_2 and the three estimations will each be statistically significant.

b. Secondary Aim (exploratory) - The difference between measured and estimated was evaluated for select grouping variables (e.g., sex, sedation, and etiology). Variables that were found to have a significant effect on resting VO_2 were entered as covariates when comparing measured and estimated VO_2.

Hypothesis: While some variables may improve the comparison between measured versus estimated VO_2 and others may make no difference, it is expected that the differences will remain statistically significant.

2) Determine if the differences between the measured resting VO_2 and the VO_2 estimated by each of the commonly used formulas are clinically significant.

a. Primary Aim - Determined the frequency of $\geq$25% absolute error in the resting VO_2 derived by the three estimations.

Hypothesis: Clinically significant errors will be found in $\geq$15% of the patients studied for each of the three estimation equations.

b. Secondary Aim - Determined the sensitivity and specificity of correctly classifying the cardiac index by each of the estimation equations at the following cut-off values: $</\geq$ 2.6 ml/min/m^2 (low versus normal cardiac index), $</\geq$ 2.2 ml/min/m^2 (hypoperfusion versus no hypoperfusion), $</\geq$ 1.9 (cardiogenic shock versus no shock).

Hypothesis: At each level of cut-off, ≥15% of patients will be misclassified by each of the estimation equations.

3) If the Aim 1 hypothesis holds true for all three estimation equations, then an estimation formula will be derived from the measured resting VO_2 combined with select clinical variables.

   Hypothesis: Though exploratory in nature, the estimation equation can be developed and will include variables beyond what is employed by the three estimation equations being tested.

Study Impact

Whether the above hypotheses hold true or not, this study will provide data to physicians that may help form decisions concerning appropriate clinical treatment. However, if the proposed hypotheses hold true, then the study will influence the current methods used to measure cardiac output in patients HFrEF. However, if the hypotheses are not supported, the study will remain an important contribution to the literature validating the use of these equations in patients with HFrEF.

Delimitations

1) The participants in this study were adult patients (≥18 years old at time of consent) with HFrEF undergoing clinically indicated right heart catheterization.
2) Patients had resting VO_2 measured with breath-by-breath analysis via a metabolic cart while breathing through mouthpiece in a similar fashion as LaFarge & Miettinen (LaFarge & Miettinen, 1970), and others who have re-evaluated these formulas in different patient groups (Fakler, Pauli, Hennig, Sebening, & Hess,

2005; Kendrick et al., 1988; Narang et al., 2012; Narang et al., 2014; Wolf, Pollman, Trindade, Fowler, & Alderman, 1998).

3) Sedation was used in the development of the three equations in question (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970). Therefore, patients were given (operating physicians discretion) no more than standard sedation for the catheterization procedure (not to exceed 2 mg of midazolam and/or 50 μg of fentanyl).

Limitations

1) Patients are generally not accustomed to having breathing monitored, particularly while breathing through a mouthpiece. This may have inherently changed the patient's breathing characteristics and influence resting VO_2 (Perez & Tobin, 1985). However, this is a common method for measuring ventilatory gas exchange and was the method utilized be LaFarge & Miettinen (LaFarge & Miettinen, 1970).
2) Gas exchange was measured breath-by-breath with a metabolic cart (Ultima-CPX, MGC Diagnostics Corp., St. Paul, MN). This is a different method of collecting and measuring ventilation and gas exchange than that performed by LaFarge & Miettinen. Although this may have limited the comparison, this method of measuring gas exchange (compared to Douglas bag method used by LaFarge & Miettinen) is more common in modern laboratories, making it more clinically applicable.

3) Due to the limitation of the system available to measure the resting VO_2, the measurement of gas exchange was not possible while the patient is receiving supplemental O_2. Therefore, if the patient (who is otherwise not prescribed home supplemental O_2) was expected to need supplemental O_2 after receiving sedation were excluded.
4) Most of the study participants were partially sedated during VO_2 measurement. Sedation given to patients prior to catheterization can vary between patients and the patient may need additional sedation during the case. For the safety of the patient, the exact dose was left to physician discretion. The level of sedation can influence the patient's ability to maintain an appropriate seal on the mouthpiece. This problem was minimized through constant observation and appropriate coaching by the primary investigator. In addition, the exact dose of sedation was recorded and patients receiving greater than the standard dosing were excluded from this study.
5) The proposed sample size was sufficiently powered to compare the measured versus the estimated resting VO_2 in the whole sample, similar to previous studies evaluating these estimation equations. However, this sample size is likely too small to evaluate the sex-specific aspects for the formulas of LaFarge & Miettinen and Bergstra et al. This, along with other comparisons, was included as part of the analysis for the secondary aim to Aim 1.

Definitions of Terms

1) Basal Metabolism – The minimum amount of energy required to maintain vital functions at complete rest while in a fasting state.
2) Body Surface Area (BSA) – The area of the external surface of the body. Being difficult to accurately measure directly, BSA is commonly estimated using one of several equations that utilize height and weight measurements. Although developed from only 9 individuals, the formula derived by Du Bois and Du Bois in 1916 has been shown to be surprisingly accurate and remains the most widely used estimation of BSA. (Wang, Moss, & Thisted, 1992)
3) Cardiac Index –Cardiac output per unit of body surface area. Cardiac index relates cardiac performance to the size of the individual. The normal range at rest is 2.6 to 4.2 ml/min/m^2 (Brandfonbrener, Landowne, & Shock, 1955).
4) Cardiac Output – The volume of blood being pumped by the heart per minute. Cardiac output is the product of the heart rate and stroke volume.
5) Cardiomyopathy – A disorder causing structural or functional limitation of the ventricle (Lindenfeld et al., 2010)
    a. Ischemic Cardiomyopathy (ICM) – Identifies the antecedent cause of the cardiomyopathy as the result of ischemia induced by a myocardial infarct (MI).
    b. Non-Ischemic Cardiomyopathy (NICM) – Identifies the antecedent cause of the cardiomyopathy as something other than an MI (i.e., hypertension, viral, peri-/post-partum, genetic, idiopathic, etc.).

6) Ejection Fraction – A measure the fraction of blood squeezed out of a ventricle with every beat, commonly reported as a percentage. Mathematically, it is the volume of blood left in the ventricle at the end of systole (End Systolic Volume) divided by the volume of blood in the ventricle at the end of diastole (End Diastolic Volume). Both left ventricular (LVEF) and right ventricular (RVEF) ejection fractions can be assessed.

7) Fick Principle – Proposed by Adolph Fick in 1870 as a method for measuring cardiac output *in vivo,* it is based on the law of conservation of mass/energy and states that the cardiac output is proportional to the VO_2 divided by the difference in O_2 concentration between the atrial and mixed venous blood (Baim & Grossman, 2006).

8) Heart Failure (HF) – A complex syndrome, representing a common final stage of many different disorders of the heart, which results from any structural or functional disorder that limits the ability of a ventricle to relax and fill with blood and/or contract and eject blood (Bui et al., 2011; Dickstein et al., 2008; Hunt et al., 2009). This cardiac dysfunction leads to neurohormonal and circulatory abnormalities which cause characteristic signs and symptoms such as fluid retention, shortness of breath and fatigue – particularly with exertion (Lindenfeld et al., 2010). Physiologically, it is characterized by increased cardiac filling pressure and/or insufficient peripheral O_2 delivery (Lindenfeld et al., 2010).

    a. HF with Reduced Left Ventricular Ejection Fraction (HFrEF) – Also referred to as HF with dilated left ventricle, it is a categorization of HF

that is characterized by a reduced LVEF and is most commonly associated with left ventricular chamber dilation (Lindenfeld et al., 2010).

b. HF with Preserved Left Ventricular Ejection Fraction (HFpEF) – Also referred to as diastolic HF, it is a categorization of HF that is characterized by normal LVEF and is often associated with incomplete or abnormal relaxation during diastole (Lindenfeld et al., 2010).

9) Heart Transplant – A surgical procedure performed on patients with end-stage HF, where a functioning heart from a recently deceased donor is implanted into the recipient patient. Most commonly, the recipient patient's heart is removed (orthotopic). Alternatively (and much less common), the recipient's heart may be left in to support the donor heart (heterotopic). Five year graft survival was 75% in patients receiving transplants in 2005-2006, and there has been a steady decline in rate of 10-year graft failure (Organ Procurement and Transplantation Network & Scientific Registry of Transplant Recipients, 2012).

10) Resting Metabolism or Resting Energy Expenditure – The amount of energy required while an individual is at rest and typically not in a fasted state. This value is usually slightly higher than the individual's basal metabolism and frequently used as an estimation of true basal metabolism.

11) Right Heart Catheterization – A minimally invasive diagnostic procedure in which a catheter is guided though the right side of the heart and into the pulmonary artery where the heart's pump function and pressures within the heart and pulmonary arteries can be assessed (Baim & Grossman, 2006).

12) Stroke Volume (SV) – The volume of blood ejected from the heart with every beat.

13) Thermal Dilution Method – A common indicator dilution method for measuring cardiac output during a right heart catheterization where an injected bolus of chilled sterile solution in the right atrium mixes with the blood and passes through the tricuspid valve into the right ventricle. A thermistor at the distal end of the catheter measures the change in blood temperature as the blood passes over the catheter tip (Baim & Grossman, 2006). Similar to the Fick method, this method is based on the law of conservation of mass/energy.

14) Ventricular Assist Device (VAD) – A surgically implanted device that helps the heart pump blood from one (left is most common [LVAD]) or both (BiVAD) ventricles. These pumps may be implanted in the body or connected to a pump outside the body. Frequently, used as a bridge to transplant, but increasingly used as destination therapy in those with end-stage HF who do not qualify for a heart transplant.

CHAPTER II

REVIEW OF LITERATURE

The purpose of this study was to measure the resting VO_2 in adult patients with HFrEF during right heart catheterization procedures, investigate the accuracy of three widely used equations for the estimation of resting VO_2 compared to the direct breath-by-breath measurement of expired air using a metabolic cart and determine to what extent clinically significant errors occur using estimation equations.

This chapter discusses the literature reviewed in relation to this topic. The chapter provides information regarding HF, including the epidemiology of the syndrome and its medical and surgical treatment. Furthermore, this chapter discusses in detail the right heart catheterization procedure, cardiac output and how it is determined by the thermal dilution and Fick methods. Then, why the Fick method of determining cardiac output is preferred in patients with HF is discussed. Lastly, the determination of resting VO_2 (a critical value for determining cardiac output by the Fick method) by direct analysis of ventilatory gas exchange and by the three most popular estimation equations is reviewed.

Heart Failure

Heart failure is a complex clinical syndrome with many potential etiologies, and is characterized by elevated mortality, reduced quality of life, frequent hospitalizations and complex medical management (Heart Failure Society Of America, 2006). Heart failure has a high prevalence in the United States and elsewhere, and for most patients it

is a chronic condition. The prevalence of HF is growing due to the aging population and better treatment of antecedent conditions (Bui et al., 2011; Heart Failure Society Of America, 2006). In fact, as part of the Affordable Care Act, the Centers for Medicare and Medicaid Services have begun to penalize hospitals with excessive 30-day re-admission rates for patients admitted with heart attack, HF and pneumonia (Ross, Bernheim, & Drye, 2011). The Centers for Medicare and Medicaid Services has recognized that re-admission rates are too high in these three categories and has determined these conditions as reflective of the treatment of Medicare/Medicaid patients (Ross et al., 2011). Current medical therapy with angiotensin-converting enzyme inhibitor (ACEI), beta-receptor blockade and diuretics can provide reductions or delays in morbid events, and may even lead to some reversal of cardiac remodeling (Heart Failure Society Of America, 2006). Nevertheless, there remains no absolute cure for HF short of cardiac transplantation.

Epidemiology and Definition of Heart Failure:

Heart failure is a significant public health problem in the United States and the world over. Prevalence of HF in the United States is approximately 2.4% of the population or about 5.8 million people, while the prevalence in those $\geq$ 70 years old is approximately 20% (Roger et al., 2012). Data suggests the incidence of HF of roughly 670,000 new cases per year (Levy et al., 2002; Roger et al., 2012). In adults over the age of 45, the lifetime risk of developing HF is approximately 25% (slightly higher in men than women), and approaches 40% in people aged 65 and older (Huffman et al., 2013).

Though limited by healthcare disparities and more advanced disease at first diagnosis, the data indicates that minorities have higher incidence of HFrEF than whites

(Yancy, 2004). Data from the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective cohort study, reports 75% of incidence of HF among African Americans was due to HFrEF, compared to 58% in Hispanics and 60% whites - the latter two showing a non-significant difference (Bahrami et al., 2008). There are significant incidence rate differences between African American, Hispanics and whites: 3.5, 2.1 and 1.5 per 1000 person-years, respectively (Bahrami et al., 2008). In a fairly comprehensive analysis of large population studies found that the unadjusted risk in black men to be highest, and at a lower age than other sex-race groups (Huffman et al., 2013). Interestingly, black men were found to have a lower lifetime risk at age 45 than their white male counterparts (20% vs 30%), which appeared to be related to competing risks of death from non-cardiovascular causes (Huffman et al., 2013).

Due to a wide number and varied causes, HF without an antecedent myocardial infarction causing cardiac muscle dysfunction (sometimes referred to as non-ischemic cardiomyopathy, or NICM) is the most common. In American adults, prevalence of NICM is 36 per 100,000 people and incidence is 5.5 per 100,000 people (Towbin et al., 2006). In adults over the age of 40, the lifetime risk of developing HF due to NICM is 1 in 9 for men and 1 in 6 for women (Roger et al., 2012). Making up a large cohort of the 5.8 million people with HF in the United States, NICM is the most common reason for heart transplant, with an annual care-cost ranging from $4 billion to $10 billion (Roger et al., 2012; Towbin et al., 2006).

It is estimated that an additional 3 million people will have HF by 2030, which represent roughly a 25% increase in the prevalence of HF (Roger et al., 2012). Heart

failure may be the fastest growing cardiovascular disease. For example, between 1979 and 2003 there was a 174% increase in hospitalizations for HF compared to a 16% increase in coronary artery disease (CAD) admissions and 29% increase in admissions due to stroke (Mensah & Brown, 2007). Furthermore, HF has consistently been one of the major cardiovascular disease indications for outpatient office visits and emergency department admissions, second only to hypertension (Mensah & Brown, 2007; O'Connell & Bristow, 1994). When combining the cost of health-care services, medications and lost productivity, the estimated cost of HF exceeded $39 billion in 2010 (Lloyd-Jones et al., 2010; Roger et al., 2012). It is thought that this cost is actually under-estimated as it is based on data with HF as the primary diagnosis or cause of death (Bui et al., 2011).

Heart failure is a complex syndrome representing a common final stage of many different disorders of the heart (Bui et al., 2011). The American Heart Association and the American College of Cardiology, as well as the European Society of Cardiology, define HF as a complex syndrome resulting from any structural or functional disorder that limits the ability of the left ventricle to relax and fill with blood (diastole) and/or contract and eject blood (systole) (Dickstein et al., 2008; Hunt et al., 2009). The underlying disorder causing the structural or functional limitation of the ventricle that leads to HF is referred to as a cardiomyopathy. Symptoms of cardiomyopathies include: shortness of breath, fatigue and/or exercise intolerance (Dickstein et al., 2008; Hunt et al., 2009). In distinguishing between cardiomyopathy and HF additional signs and symptoms of fluid retention must be present (Dickstein et al., 2008; Hunt et al., 2009). The 2008 guidelines from the European Society of Cardiology suggest that an improvement in

response to typical HF treatment is not sufficient to make the diagnosis of HF, but can be helpful when a clear diagnosis is unclear (Dickstein et al., 2008). The definition used by these entities makes the diagnosis of HF more practical, but are somewhat broad. In the last several publications of practice guidelines from the Heart Failure Society of America, the definition of HF has been called a "working" definition (Heart Failure Society Of America, 2006; Lindenfeld et al., 2010). This implies the definition is evolving, and is tied to the continued and developing understanding of this syndrome. As defined by the Heart Failure Society of America, HF is a syndrome resulting from cardiac dysfunction (cardiomyopathy), which leads to neurohormonal and circulatory abnormalities that lead to the characteristic signs and symptoms such as fluid retention, shortness of breath and fatigue - particularly with exertion (Lindenfeld et al., 2010). Physiologically, the Heart Failure Society of America describes the syndrome as being characterized by increased cardiac filling pressures and/or insufficient peripheral O_2 delivery caused by a cardiomyopathy (Lindenfeld et al., 2010).

Expanding the definition further, the 2010 Heart Failure Society of America practice guidelines categorize HF as with either a reduced left ventricular ejection fraction (HFrEF) or a preserved left ventricular ejection fraction (HFpEF) (Lindenfeld et al., 2010). More commonly thought of when the term HF is used, HFrEF (also referred to as HF with dilated left ventricle) is characterized by signs and symptoms of HF and is most commonly associated with left ventricular chamber dilation (Lindenfeld et al., 2010). The reduced LVEF can be thought of as being a result in reduced squeezing of the heart muscle during systole. So, it is still common to see this referred to as systolic HF.

On the other hand, with HFpEF, the signs and symptoms of HF can exist in the presence of a normal, preserved, LVEF (Lindenfeld et al., 2010). This is most commonly associated with a non-dilated left ventricle. Where HFrEF is associated with systolic dysfunction, HFpEF is associated with incomplete or abnormal relaxation during diastole, and has been referred to as diastolic HF in the past. It has been suggested that HFrEF and HFpEF should not be considered separate conditions, but in fact they do not share same pathophysiology (Borlaug & Redfield, 2011; Dickstein et al., 2008). Therefore making the distinction may help direct more appropriate treatment as the majority of the patients enrolled in investigations of HF have been those with a HFrEF of <35-40% (Dickstein et al., 2008). Furthermore, treatments that have shown to be beneficial in HFrEF have not had the same efficacy when studied in patients with HFpEF (Borlaug & Redfield, 2011).

Since, HF is a syndrome that has evolved from another cardiovascular problem, it should never be a patient's only diagnosis and the underlying cause should be sought (Dickstein et al., 2008). Frequently, HF is described as resulting from an ischemic etiology, (ischemic cardiomyopathy, or ICM) or a NICM. Ischemic cardiomyopathies are a result of damage to the myocardium (heart muscle) related to a myocardial infarction, and are associated with the development of HFrEF. Non-Ischemic cardiomyopathy, which may lead to HFrEF or HFpEF, may be genetic (i.e. neuromuscular disorders, familial, inborn errors of metabolism, etc.), lifestyle-related (i.e. hypertension, obesity, hygiene, etc.), or idiopathic (Towbin et al., 2006). From a clinical perspective, distinguishing the etiology of a patient's HF is helpful in determining the course of treatment to prevent further complications by the underlying disease. From a research and

primary prevention perspective, this distinction may also help determine the course and natural history of the disease that lead to the development of HF, which may be helpful in developing strategies to prevent the development of cardiomyopathy and HF.

Risk Factors and Prevention of Heart Failure:

Many risk factors that are related to coronary artery disease (CAD) are also risk factors for the development of either form of HF. In the United States, it has been estimated that more than 60% of the cases of HF in the adult population may be attributable to CAD (He et al., 2001). So, include such risk factors as age, male sex, hypertension, left ventricular hypertrophy, obesity, diabetes, smoking, dyslipidemia, poor diet, sedentary lifestyle and psychological stress (Bui et al., 2011). Additionally, having a myocardial infarction, valvular heart disease, and alcohol abuse are considered risk factors for developing HF. In fact, preventable causes of HF (i.e., hypertension, obesity, smoking, drug or alcohol abuse) before a person is 35 years of age are important antecedents that may be targets for the prevention of HF (Bibbins-Domingo et al., 2009).

Medical and Cardiac Rhythm Management of Heart Failure:

Medical Management: Heart failure is a progressive disease and current practices to treat it are designed to reduce patient symptoms and to slow the progression of disease. These treatments include standard medical treatment with angiotensin converting enzyme inhibitors (ACEI), beta-blockers and diuretics, as well as cardiac rhythm management with electronic pacemakers and implantable cardioverter defibrillator (ICD). Subsequent to these primary treatments, additional medications are frequently used to treat some of the complications related to the development of HF. Advanced therapies, such as heart

transplant or implantation of a ventricular assist device (VAD) are used in the treatment of end-stage HF. Heart transplant has been the best treatment option for patients with end-stage HF for a long time, but technological advancements in VADs and increasing experience with utilizing VAD systems are beginning to improve 1-year survival to levels similar to heart transplant (Organ Procurement and Transplantation Network & Scientific Registry of Transplant Recipients, 2012).

In the pathophysiology of HF, there is an association with reduced myocyte function with alterations such as, reduced Ca^{2+} sequestration by the sarcoplasmic reticulum (due to reduced function and expression of the sarcoplasmic reticulum Ca^{2+} ATPase) and up-regulation of sarcolemmal Na^{+}/Ca^{2+} exchanger (both in function and expression), a reduced affinity of troponin to Ca^{2+}, altered substrate metabolism and impaired respiratory chain activity (Just, 1996; Mohrman & Heller, 2010). These collectively can lead to a decrease in the contractility of the heart and subsequently results in reduced stroke volume (reducing cardiac output), reduced arterial pressure and increased heart rate. Paradoxically, these alterations create changes in the force/frequency relationship such that contractile performance decreases with increasing heart rates; opposite of the normal (Bowditch-Treppe) phenomenon (Just, 1996). The decrease in mean arterial pressure leads to decreased arterial baroreceptor activation; impairing the regulation of the heart rate by the vagus nerve, but the receptors maintain the ability to modulate sympathetic discharge (Floras, 2009). This control of the sympathetic discharge increases central [medullary cardiovascular centers (Mohrman & Heller, 2010)] sympathetic outflow causing a further down-regulation of parasympathetic nervous

system (Floras, 2009). The reduced mean arterial pressure and increased sympathetic stimulation promote the release of renin from the kidneys (Floras, 2009), which converts angiotensinogen to angiotensin I, which then can be converted into the vasoconstrictor angiotensin II (enzymatically controlled by ACE). Angiotensin II also stimulates the release of aldosterone from the adrenal cortex. The decreased activation of the baroreceptors stimulates the release of vasopressin from the posterior pituitary, which (together with aldosterone) causes sodium retention and fluid absorption. Sympathetic stimulation of the adrenal medulla increases the release of epinephrine that further contributes to vasoconstriction (Mohrman & Heller, 2010). The increased circulating epinephrine increases glycogenolysis by the liver, which increases blood glucose levels and raises extracellular osmolarity. This change in osmolarity and the reduced capillary hydrostatic pressure from the increase arterial constriction causes a shift of fluid from the interstitial and intracellular spaces into the intravascular space. The intention of these changes, in response to the loss of cardiac output from the reduced myocyte function, is compensatory responses that are similarly seen in acute cardiogenic shock. This constellation of responses in the setting of impaired of systolic function reflects a net balance between appropriate reflex compensatory responses to the reduced left ventricular function and the stimulus eliciting the adrenergic responses excessive to what is needed to achieve homeostasis (Floras, 2009). When a relatively normal stoke volume and mean arterial pressure can be maintained through increases in left ventricular diastolic volume, then the balance remains shifted toward appropriate compensatory reflexes and plasma norepinephrine levels can be maintained (Floras, 2009). However,

over time, the continued increased volume contributes to cardiac remodeling and further myocyte dysfunction. Furthermore, the chronic norepinephrine release causes a down-regulation in cardiac beta-1 adrenergic receptors, altered beta-receptor signal transduction and a decrease in norepinephrine re-uptake, tilting the balance towards the excessive adrenergic response (Floras, 2009). In other words, in the case of chronic HF, these changes can provide compensation early in the disease, but become pathologic, contributing to the progressive nature of HF.

The clinical guidelines for the treatment and management of patients with HF published by the Heart Failure Society of America, the primary medical management of HF is targeted to the management of the over-activated renin-angiotensin-aldosterone axis and the sympathetic adrenergic system along with resulting volume overload (Lindenfeld et al., 2010). The primary medication used to treat the up-regulated renin-angiotensin-aldosterone axis is ACEI. The Heart Failure Society of America recommends that all patients with HFrEF, whether symptoms are present or not, should be prescribed an ACEI (Lindenfeld et al., 2010). These medications block the conversion of the angiotensin I to angiotensin II by inhibiting ACE. This inhibition reduces the amount of angiotensin II in circulation, limiting its vasoconstrictive effects (reducing blood pressure) and its stimulation of aldosterone release (reducing fluid-retention). Angiotensin II also stimulates thirst centers in the brain, which can exacerbate the fluid-retention in patients with HF. Therefore, limiting the amount of circulating angiotensin II reduces the thirst response. Unfortunately, ACE is an important enzyme in the degradation of bradykinin, and inhibiting it allows levels of bradykinin to build up and

cause a cough and angioedema. In patients that cannot tolerate ACEI due to these side-effects, the Heart Failure Society of America recommends the use of angiotensin receptor blockers (ARB) in place of the ACEI (Lindenfeld et al., 2010). Where ACEI inhibit the conversion of angiotensin I to II, ARB block the angiotensin II type I receptors. Since both ACEI and ARB can similarly affect renal function and increase potassium levels, the Heart Failure Society of America recommends the consideration of hydralazine and oral nitrates in patients who are intolerant of ACEI/ARB due to renal insufficiency or hyperkalemia (Lindenfeld et al., 2010).

Beta-blocker therapy for HF was once considered a contraindication as it was thought this would have a potential to worsen the condition. This concern was based on the fact that beta-blockers decrease the resting and exercise heart rate through the blocking of beta-adrenergic receptors, combined with the decreased LVEF in patients with HFrEF, would further decrease the already compromised cardiac output (Ormiston & Salpeter, 2003). However, as previously mentioned, the patient with HFrEF works in opposition to this phenomenon, and actually improves contractility with a lower heart rate. This has been shown in muscle preparations obtained from normal (donors that could not be used for transplant) hearts and from failing hearts (at the time of transplantation), which showed that the failing heart reached maximum tension at stimulation frequencies between 30-40 bpm and normal hearts reached maximum tension at about 170-180 bpm (Just, 1996). When studies are performed on patients with artificial pacemakers in the catheterization laboratory, patients without HF demonstrate no change in LVEF with increasing heart rates from ~80 bpm to 140 bpm; whereas patients with

HFrEF have dramatic decreases in the LVEF over the same HR range (Just, 1996). Within the same study, patients' contractility was measured as the maximal rate of pressure rise (+dP/dt) over the same heart rate range, which demonstrated a dramatic increase in +dP/dt in patients without HF with no change in +dP/dt in patients with HFrEF (Just, 1996). However, studies of beta-blocker therapy with patients with HFrEF have shown an increase in resting LVEF after as little as three to four months of beta-blocker therapy compared to placebo controls, with about a 29% increase in the relative LVEF (Lechat et al., 1998). By reducing both the left-ventricular end-diastolic volume and the left-ventricular end-systolic volume with an increase in LVEF, which has been demonstrated after four weeks of administration of carvedilol treatment compared to control groups, suggests that beta-blockers may cause a reverse remodeling of the heart (Doughty, Whalley, Gamble, MacMahon, & Sharpe, 1997). Another mechanism where beta-blockers appear to have an effect is an increase in the fibrillation threshold by slowing the heart rate and allowing more Ca^{2+} to be taken back into the sarcoplasmic reticulum by the SERCA pumps and less being removed by the Na^{+}/Ca^{2+} exchangers, which leads to a reduction in the intracellular $[Na^{+}]$ reducing the development of after-depolarization and triggered activity (Just, 1996). Beta-blockers also have beneficial effects on the renin-angiotensin-aldosterone axis. Blocking of renal beta1-adrenergic receptors decreases renin secretion. This, in turn, helps reduce blood volume and pressure, which reduces the amount of work (reduced O_2 demand) of the heart. Through these various mechanisms of reducing the sympathetic over-activation, beta-blockers may contribute to a normalization of down-regulated receptors (or at least slow the

progression of down-regulation of receptors), improve contractile performance and provide cardio-protection (Just, 1996).

This conclusion is evidenced in the large multi-center trials that were performed in the mid- to late 1990's, which demonstrated ~5% reduction in 1-year mortality and reduced the number of hospitalizations in patients prescribed beta-blockers versus those on placebo (Pritchett & Redfield, 2002). The Metoprolol CR/XR (CR: continuous release; XR: extended release) Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) study demonstrated that metoprolol XR provided ~40% reduced risk of sudden cardiac death, ~34% reduced risk of overall HF-associated mortality and hospitalizations, and improvements in New York Heart Association HF functional class and perceived quality of life (Hjalmarson & Fagerberg, 2000). Similar to MERIT-HF, the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial found a risk-reduction of ~31% in HF-related mortality and hospitalizations (Packer et al., 2002). The COPERNICUS trial also demonstrated fewer adverse events, such as worsening HF, sudden cardiac death, ventricular tachycardia and cardiogenic shock (Packer et al., 2002).

Diuretics have a proven efficacy in patients with continued signs and symptoms of volume overload (i.e., orthopnea, abrupt weight gain, shortness of breath) and increased filling pressure (i.e., jugular vein distention, peripheral edema, pulsatile hepatomegaly), with loop diuretics (over thiazide-type diuretics) being the most effective in restoring normal status (Lindenfeld et al., 2010). The common side-effect of loop diuretics is hypokalemia. This is because loop diuretics increase the amount of Na^+ and Cl^- being excreted in the thick ascending segment of the loop of Henley, causing the

membrane potential of the lumen to increase towards the Nernst potential of K^+, which limits the normal re-absorption/recycling of K^+ (Greger, 1997). Due to this, K^+ supplementation is frequently prescribed alongside a loop diuretic (furosemide is the most commonly prescribed of these medications).

Additional medications that can be used in the care and treatment of HF include: aldosterone antagonists, digoxin, and a combination of oral nitrates and hydralazine (Lindenfeld et al., 2010). Aldosterone antagonists further control the renin-angiotensin-aldosterone axis by inhibiting the release of aldosterone by the adrenal medulla. These are recommended for patients with severe HF signs and symptoms, LVEF <35%, in addition to standard medical therapy – including diuretics (Lindenfeld et al., 2010). Digoxin is most commonly used for inotropic support in patients with LVEF <40% who are concomitantly taking beta-blockers and ACEI who remain symptomatic, but can also be used control ventricular rate when atrial fibrillation is present (Lindenfeld et al., 2010). Particularly for African-American patients with HF, the combination of long acting oral nitrates (particularly isosorbide dinitrate) and hydralazine should be considered standard therapy in addition to ACEI and beta-blockers (Lindenfeld et al., 2010). The results of the African-American Heart Failure Trial (A-HeFT), demonstrated significantly lower mortality rates, reduced HF-related hospitalizations and improvements in self-reported quality of life when this drug combination was added to standard therapy compared to a placebo (added to standard therapy) control group (Taylor et al., 2004). In fact, the results of the A-HeFT study were so striking that the study was terminated early and patients enrolled in the placebo group were allowed to begin the drug combination (Taylor et al.,

2004). Further medical management should focus on other co-morbidities such as dyslipidemia, diabetes, and/or concomitant pulmonary disease.

Cardiac Rhythm Management: Devices, such as implantation of an ICD with or without cardiac resynchronization therapy are frequently implemented in the long-term management of HFrEF. Based heavily on the results of the Multicenter Automatic Defibrillator Implantation Trials (MADIT-I and MADIT-II), the United States Food and Drug Administration approved the use of ICD's for protection against ventricular fibrillation/tachycardia events (Moss, 2003). Sub-analysis of the results of MADIT-II indicated between 30-40% of patients with HFrEF as a result of myocardial infarction were found to have inducible ventricular tachycardia/fibrillation during electrophysiology studies performed at the time of implant and about 40% of the patients receiving appropriate defibrillation treatment during the MADIT-II study (Moss, 2003). Though the MADIT-I trial was primarily done as a "proof-of-concept" in patients having suffered a recent myocardial infarction (no inclusion/exclusion for co-existing cardiomyopathy/HF), the study was stopped early by the Data Safety Monitoring Board due to the 54% reduced risk of death in the those receiving ICD. A sub-analysis demonstrated that those with a reduced LVEF <25%, widened QRS complex (>120 ms), or clinical HF received the most benefit (Moss, 2003).

About a third of patients with HFrEF have a left bundle branch block (LBBB) on their 12-lead electrocardiogram, which is indicative of right and left ventricular dyssynchrony and is associated with worse clinical symptoms and left-ventricular systolic function (Shenkman et al., 2002). In a study of 1418 patients with HFrEF first seen in a

community HF clinic, about 34% were found to have LBBB on electrocardiogram (Clark, Goode, & Cleland, 2008). In the patients without LBBB at baseline, the average QRS duration increased significantly from 115 to 118 ms during 1 year follow-up with an 11% incidence of new LBBB (Clark et al., 2008). It is this LBBB sub-population that is the target for cardiac resynchronization therapy. These pacemaker devices are implanted with three lead-wires. One wire is implanted in the right atrium (right atrial appendage), one in the right ventricle (typically in the apex of the ventricle) and one (the left ventricular lead) is advanced through the coronary sinus in one of the venous side branches running along the left posterior-lateral wall of the left ventricle. These systems allow the device to time ventricular contraction after sensing atrial contraction, and to coordinate, or synchronize, the contraction of the left and right ventricles. Due to the occurrence of ventricular arrhythmias in patients with HFrEF, cardiac resynchronization devices commonly contain the ability to perform defibrillation. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial was one of the largest trials investigating the effects of cardiac resynchronization therapy on mortality and hospitalizations in patients with advanced HFrEF and LBBB. This trial found a 34% reduction in the risk of death or hospitalization due to HF in the group receiving devices with defibrillation ability compared to those on optimal medical therapy (Bristow et al., 2004). The study grouped patients into optimal therapy, device without defibrillation or device with defibrillation in a 1:2:2 fashion, and found that there was a 40% risk reduction of the combined end-points in the group with defibrillation (compared to optimal medical therapy), suggesting an additional benefit when defibrillation was

included (Bristow et al., 2004). In the Multicenter InSync ICD Randomized Clinical Evaluation II (MIRACLE ICD II) trial, patients with mild symptomatic HFrEF and LBBB were randomized to receive a cardiac resynchronization device with either the ICD-only or both ICD and cardiac resynchronization therapy activated. This study was done to show if there would be functional improvements in a group of patients with mildly symptomatic HFrEF (COMPANION included only patients with advanced HFrEF) after cardiac resynchronization therapy (Abraham et al., 2004). After 6 months of therapy, there were no significant differences in functional capacity (6 minute walk test and peak exercise VO_2) or quality of life between the two groups, but the patients receiving therapy demonstrated improvement of ventilatory efficiency during exercise and signs of positive cardiac remodeling (decreased left ventricular diastolic and systolic volumes and increased LVEF). In a subsequent study of patients with HFrEF and LBBB that included patients similar to MIRACLE ICD II trial, the MADIT-CRT (cardiac resynchronization therapy) trial found a 35% reduction in all-cause mortality and a 63% reduction in HF-related hospitalizations in patients receiving cardiac resynchronization therapy in addition to defibrillator (Moss et al., 2009). Furthermore, patients in the group receiving cardiac resynchronization therapy had a significant reduction in left ventricular volumes and an increase of ~12% in LVEF (Moss et al., 2009). In September 2010, the Food and Drug Administration released a press announcement approving the indication that patients with HFrEF and LBBB (QRS width >130 ms if LVEF <30% and mild symptoms; or >120 ms if LVEF <35% and moderate to severe symptoms) that are

symptomatic should receive cardiac resynchronization therapy along with an implantable defibrillator (Thompson, 2010).

Advanced Therapies for the Treatment of Heart Failure:

Often, despite these advances in medical and device treatment for the management of HF, the best these treatments can do is to slow the progression of the disease. Some of these therapies (i.e., beta-blockers and cardiac resynchronization therapy) can cause positive remodeling of the heart, but have not been able to cure HF. In turn, a large number of patients eventually require more advanced treatments, such as cardiac transplantation and LVAD.

The number of patients needing a heart transplant is much larger than what is available from donors. For example, in 2011 about 34% of patients on or added to the cardiac transplant waitlist received a transplanted heart and about 8% died while waiting in the United States (Organ Procurement and Transplantation Network & Scientific Registry of Transplant Recipients, 2012). Therefore, strict qualifications have been developed in order for patients to qualify for cardiac transplant. These qualifications are based on the severity of disease (i.e., severity of functional limitation); the effect of co-morbid disease (common co-morbidities are diabetes, pulmonary disease and kidney disease); tobacco, alcohol and illicit-drug use; age; and psychosocial factors. These criteria are designed to ensure patients receiving donor hearts have the best chance for survival. These criteria do seem to be working. Over the past decade, 6 month and 1 year occurrence of graft failure has steadily declined, as has the rate of graft failure at 3, 5 and 10 years (Organ Procurement and Transplantation Network & Scientific Registry of

Transplant Recipients, 2012). The overall graft survival, at the end of 2011, of patients receiving transplants in 2005-2006 was 75% (Organ Procurement and Transplantation Network & Scientific Registry of Transplant Recipients, 2012).

Traditionally, LVADs have been used as a bridge-to-transplant in certain patients waiting for a donor heart to become available. However, developments in LVAD technology are leading to wider use of these devices and are beginning to change the face of advanced HF therapies. Cardiac transplantation still remains the best option for select patients with end-stage HF (Organ Procurement and Transplantation Network & Scientific Registry of Transplant Recipients, 2012), but the newest generation of LVADs are more durable and are beginning to be more widely used as destination therapy (providing an option for patients who do not qualify for transplant or who choose to defer it).

The criteria for LVAD implant should begin with an assessment of functional capacity and should be significantly reduced similar to the peak exercise VO_2 used for transplantation criteria (Slaughter et al., 2010). However, patients with findings of pulmonary hypertension during right heart catheterization who fail acute reversal attempts (irreversible pulmonary hypertension is an exclusion criteria for transplant) during the catheterization, an LVAD can be implanted to determine if mechanical support can reverse the pulmonary hypertension (Mehra et al., 2006), an instance of bridge-to-decision. However, with otherwise no other options, if mechanical support cannot reverse the pulmonary hypertension, the LVAD would seem to be a viable alternative. However, when considering LVAD for destination therapy (otherwise does not qualify for

transplantation or if the patient defers cardiac transplantation listing), the device should be implanted before irreversible end-stage organ disease has been reached (Slaughter et al., 2010). Furthermore, patients found to be in cardiogenic shock have very poor post-surgical outcomes with LVAD, so this should be managed prior to implantation (Slaughter et al., 2010). Since the LVAD assists the left heart and systemic circulation, it is important to determine right heart function with a right heart catheterization procedure. During this procedure, the right ventricular stroke work index (an indicator of the right ventricle's ability to generate pressure and flow; see **Table 1** for formula) can be calculated from the pulmonary artery pressure, central venous pressure, stroke volume and the patient's estimated BSA (Slaughter et al., 2010). Patients with a right ventricular stroke work index of <300 mmHg x ml/m^2 are considered to have poor right ventricular function and are contraindicated for LVAD implantation for destination therapy (Slaughter et al., 2010). Other requirements to ensure adequate right ventricle function include pulmonary vascular resistance <4 Wood units, absence of severe tricuspid valve regurgitation, transpulmonary gradient <15 mm Hg, right ventricular end diastolic volume <200 ml, and right ventricular end systolic volume of <177 ml (Slaughter et al., 2010). All of these measures can be determined during right heart catheterization. So, whether the patient is undergoing work-up for cardiac transplantation or LVAD for destination therapy, undergoing a right heart catheterization is important for the proper care and treatment of the patient with HF.

Right Heart Catheterization

Right heart catheterization was once performed on every patient presenting to a cardiac catheterization laboratory (Baim & Grossman, 2006). This procedure is the only way to obtain the pulmonary capillary wedge pressure (PCWP, a measure of mean left heart filling pressure), detect pulmonary hypertension and detect left-to-right intra-cardiac shunts. Additionally, measurement of cardiac output by thermal dilution is routinely done during the right heart catheterization procedure. Due to the little added information from the right heart catheterization, the routine use of this procedure is discouraged in patients with a primary diagnosis of CAD (Baim & Grossman, 2006; Bashore et al., 2001). However, in patients with HF, other evidence of depressed left ventricular function or valvular disease, the quantification of hemodynamic function justifies the performance of the right heart catheterization (Baim & Grossman, 2006). In the case of patients with HF the quantifying hemodynamic function is useful in guiding therapy with diuretics, vasodilator and inotropic support (Slaughter et al., 2010) and is indicated for all patients being considered for LVAD and/or cardiac transplantation listing (Mehra et al., 2006).

In order to perform this procedure, a femoral vein puncture is administered. However, the internal jugular vein may also be used, particularly when exercise hemodynamics are being measured. For this discussion, femoral vein access will be discussed, unless otherwise noted, as described in the 7th edition of Grossman's Catheterization, Angiography and Intervention (Baim & Grossman, 2006). Once entry to the venous lumen has been accomplished, the puncture needle is removed and a sheath is

threaded over a guide-wire into the lumen. After removing the guide-wire, the sheath is flushed with a heparinized saline solution and secured in place. It is through this sheath that a thermistor-equipped, balloon-tip, double-lumen catheter is advanced towards the heart through the inferior vena cava and into the right atrium (RA). From this point, the catheter can be advanced or withdrawn through the right cardiac anatomy and the pulmonary arteries in order to obtain the various measurements necessary. Common measurements obtained during a right heart catheterization include; determination of left-to-right shunt, RA pressure, right ventricular (RV) end-diastolic pressure, PWCP, pulmonary artery (PA) pressure and cardiac output.

The right heart catheter allows for blood sampling at the point where the distal tip of the catheter is placed. Therefore, the evaluation of left-to-right shunt can be evaluated by simply drawing a blood sample when the catheter tip is in the superior vena cava, and after flushing the catheter, advancing the catheter into the PA and drawing a blood sample. Comparing the O_2 saturation from these two locations identifies the shunt. That is, the O_2 saturation of blood coming back to the heart from the systemic circulation should not change until it enters the pulmonary capillary bed where gas exchange occurs. Therefore, if the PA saturation is higher than what is measured from the superior vena cava, then oxygenated blood from the left side of the heart must be traveling through a shunt into the right side of the heart, increasing PA saturation. The presence of a left-to-right shunt suggests the presence of an atrial or ventricular septal defect.

When the catheter is advanced into the RA, systolic and diastolic pressure measurements can be performed and the mean RA pressure can be derived. The mean RA

pressure is used in the calculation of systemic vascular resistance by equation 1 in **Table 1**. Systemic vascular resistance is expressed in arbitrary resistance units of mm Hg/L/min. These units are also referred to as hybrid resistance units or Wood units. Though these units are still frequently used to report findings in the United States, in Europe and in growing numbers in the United States, these numbers are presented in the metric units of dynes-sec/cm^5. Wood units can be converted to dynes-sec/cm^5 by multiplying the Wood units by 80. Normal mean RA pressure ranges from about 2-6 mm Hg, where normal systemic vascular resistance ranges from 11-18 Wood units (900-1440 dynes-sec/cm^5). High systemic vascular resistance occurs with hypotension and reduced cardiac output, which trigger baroreceptor responses, alpha-adrenergic pathways and release of vasoconstrictor hormones. Low vascular resistance is seen in high output states (high blood flow), such as severe anemia or arteriovenous fistula.

Table 1. Select Variables Derived during Right Heart Catheterization and the Formulas to Derive the Variable.

Variable	Formula	Units
Right Ventricular Stoke Work Index	((*m*PA - *m*CVP)*SV)/BSA	mmHg*ml/m^2
Systemic Vascular Resistance	(*m*Ao - *m*RA)/C.O.	Wood Units
Valvular Orifice Area (Gorlin Formula)	(C.O./([DFP or SEP]*HR))/44.3C*√ΔP)	cm^2
Mitral Valve Orifice Area	(C.O./(HR*DFP))/(44.3*0.85*√ΔP)	cm^2
Total Pulmonary Resistance	*m*PA/pulmonary C.O.	Wood Units
Pulmonary Vascular Resistance	(*m*PA - *m*LA)/Pulmonary C.O.	Wood Units

*m*PA = mean pulmonary artery pressure; *m*CVP = mean central venous pressure; BSA = body surface area; *m*Ao = mean aortic pressure; *m*RA = mean right atrial pressure; C.O. = cardiac output; DFP = diastolic filling pressure; SEP = systolic ejection pressure; HR = heart rate; C = constant; ΔP = mean pressure gradient across the valve; *m*LA = mean left atrial pressure.

When the catheter tip is advanced from the RA, through the tricuspid valve and into the RV, systolic and diastolic RV pressure can be measured. Measured at the end of diastole, the diastolic pressure has shown to provide indication of impending HF decompensation and poor prognosis (Voelkel et al., 2006). Therefore, it is common practice to only measure the end-diastolic RV pressure. Normal ranges of end-diastolic RV pressure range from 0-8 mm Hg. It has been shown that there is an inverse correlation between end-diastolic RV pressure and RVEF (Bleasdale & Frenneaux, 2002). Measurements of RVEF in patients with HF have been shown to be prognostic independent of the LVEF (Bleasdale & Frenneaux, 2002; de Groote et al., 1998).

Advancing the catheter from the RV through the pulmonic valve, the catheter can be advanced into a small pulmonary arterial branch where it can be wedged. According to Baim, the appropriate "wedge" positioning can be confirmed when the catheter can no longer be advanced; even after having the patient cough (Baim & Grossman, 2006). Additionally, visual inspection of the resulting waveform (compared to a standard waveform) and/or $\geq$95% O_2 saturation of sampled blood through the catheter can confirm a true wedge position (Baim & Grossman, 2006). A normal PCWP can range from 6-12 mm Hg. In patients with HF, a PCWP <16 mm Hg has been associated with improved outcomes. An appropriately confirmed PCWP has been shown to be a reliable measure of left atrial pressure. This is due to the continuity of the pulmonary circulatory system transmitting the left atrial pressure signal back through pulmonary veins and capillaries (Baim & Grossman, 2006). That is, when the catheter is wedged, the pulmonary vasculature forward of the catheter tip acts like an extension of the catheter, providing useful information about the left atrial pressure. This can provide information regarding changes in left atrial compliance. Furthermore, this relationship is helpful in avoiding the direct measure of left atrial pressure, which requires a trans-septal approach that is associated with serious complications. It is necessary to have the left atrial pressure in order to quantify the trans-mitral pressure gradient and mitral valve area (Lange, Moore, Cigarroa, & Hillis, 1989). However, this has come into question in patients with existing mitral valve stenosis, as it consistently overestimates the transmitral pressure gradient and, therefore, the severity of the mitral stenosis in these patients (Hildick-Smith, Walsh, & Shapiro, 2000; Nishimura, Rihal, Tajik, & Holmes, 1994). Despite this, when the

appropriate wedge position is confirmed with the oximetry method stated previously (Alpert, 1989), a relatively small error in left atrial pressure is seen (Lange et al., 1989). The formula for calculating any valve orifice area (Gorlin Formula) is used for the measurement of mitral valve orifice area (**Table 1**), whereas the specific equation for the measurement of the mitral valve orifice area is exampled in **Table 1**. In the equation presented in **Table 1** the empirical constant (C) 0.85 accounts for the coefficient of velocity and the coefficient of orifice contraction.

Once the PCWP is obtained, the catheter is often withdrawn into a more proximal (to the heart) left or right PA. At this point the PA pressures can be recorded. The PA diastolic pressure is a reliable indicator of a patient's volume status. This value is particularly important in the determination of total pulmonary resistance and pulmonary vascular resistance (**Table 1**).

As can be seen in the preceding four equations (summarized in **Table 1**), the cardiac output is used in all these. This makes the accurate and reliable measure of cardiac output key to quantifying the full cardiac hemodynamic function in those patients undergoing right heart catheterization. Currently, there are two methods in determining cardiac output utilized in the catheterization laboratory.

One method of measuring cardiac output (indicator dilution method) is performed while the catheter tip is in the PA (typically at the same location where PA pressure is measured) and involves the injection of a nontoxic injectant the concentration of which can be accurately measured. Dye dilution methods are used, but cool-fluid (thermal dilution) methods are most common. Regardless of the method, the dilution of the

indicator (dye concentration or temperature change) is used to determine the cardiac output based on the Henderson-Hasselbach equation, which can be seen in **Table 2** (Baim & Grossman, 2006). The second method of measuring cardiac output is based on the Fick equation (**Table 2**), which involves the measurement or estimation of resting VO_2 and the measurement of the a-vO2diff. Each of these two techniques will be discussed in detail in following sections. However, it may be beneficial at this point to discuss cardiac output in greater detail.

Table 2. Formulas for Calculating Cardiac Output with Thermal Dilution and Fick Methods.

Method	Formula
Henderson-Hasselbach Equation	$V_I(T_B - T_I)(S_I*C_I/S_B*C_B)60(sec/min)/ \Delta T_B(t)dt$
Fick Equation	$VO_2/((Ao\ sat - SVC\ sat)*(Hgb*(1.36)*(10)))$

V_I = volume of injectant; $T_{B\ or\ I}$ = temperature of blood or injectant; $S_{B\ or\ I}$ = specific gravity of blood or injectant; $C_{B\ or\ I}$ = specific heat of blood or injectant; $\Delta T_B(t)dt$ = change in temperature of the blood downstream from the injection site; Ao sat = aortic oxygen saturation; VO_2 = oxygen consumption; SVC sat = superior vena cava oxygen saturation; Hgb = hemaglobin concentration.

Cardiac Output

As illustrated in **Table 1** there are several hemodynamic measurements that can be made or estimated during a right heart catheterization. Among these is the estimation of cardiac output. Cardiac output is typically defined as the quantity, or volume, of blood delivered to the systemic circulation per unit of time, and is normally expressed in liters per minute (L/min). In other words, this is the volume of blood that is flowing through the body per minute, which is responsible for the transporting of substances to and from

the body's tissues. Corresponding with cardiac output is venous return, which is the volume of blood that is flowing back into the heart (right atrium) from the peripheral circulation. When cardiac output is unchanging, venous return is equal to cardiac output. However, when cardiac output is changing, these two values will vary temporarily (for at least a few heartbeats) as blood is being stored or removed from capacitance vessels (i.e. medium to large veins), the lungs and the heart. It is generally accepted that a typical, resting cardiac output is about 5 L/min and can increase to levels $\geq$35 L/min during heavy exercise in elite endurance athlete. In a classic study, Brandfonbrener and colleagues found a mean cardiac output of 5.08 $\pm$ 1.51 L/min in 60 patients between the age of 19-86 years-old (mean 52.5 years) who were absent of cardiac disease using a dye dilution method (Brandfonbrener et al., 1955). It was further found that cardiac output decreases with age ~1% per year between 20 and 89 years of age (Brandfonbrener et al., 1955).

When considering cardiac output as a clinical variable, it is often better to index it to BSA. Dividing cardiac output by BSA (cardiac index) provides a better indicator of the heart's performance as a pump to circulate O_2 and nutrients to the body's tissues. For example, a person with a cardiac output of 5 L/min and a BSA of 1.79 m^2 would have a cardiac index of 2.8 L/min/m^2. However, a person with the same cardiac output and a BSA of 2.22 m^2 would have a cardiac index of 2.2 L/min/m^2. Thus, it may be a more sensitive indicator of cardiac function than the absolute cardiac output. The normal range of cardiac index is about 2.6-4.2 L/min/m^2, with a mean of ~3.0 L/min/m^2 in normal health adult subjects, with no significant difference between males and females (Brandfonbrener et al., 1955). Similar to what was found with cardiac output, the cardiac

index decreases with age of ~1% per year in adults (Brandfonbrener et al., 1955). A cardiac index of <2.6 L/min/m^2 is considered abnormal and is consistently found in patients with HF (Carlsson et al., 2012; Cotter et al., 2003). Clinically significant hypo-perfusion is considered when the cardiac index becomes <2.2 L/min/m^2 and cardiogenic shock is considered when the cardiac index falls below 1.9 L/min/m^2 (Ginsberg & Parrillo, 2009). Cardiogenic shock is associated with early death (within 3 months) after implant of LVAD (Kirklin et al., 2010), and is therefore important to take steps to improve this situation and attempt to improve cardiac index towards 2.2 L/min/m^2 (Slaughter et al., 2010).

Though the measurement of the cardiac output and deriving the cardiac index are clinically important, the measurement of cardiac output is an important variable in the calculation of a number of derived variables (as described above in the description of the right heart catheterization procedure and summarized in **Table 1**). In the use of right heart catheterization in the decision for candidacy for heart transplantation, the measurement of the pulmonary vascular resistance (absolute or indexed to BSA) is important in risk stratification for successful post-transplant outcomes (Mehra et al., 2006).

Thermal Dilution Cardiac Output

One of the methods used to obtain cardiac output is an indicator dilution technique. The most common of these techniques is the thermal dilution technique, although dye-dilution techniques using indocyanine-green dye have been used (these have fallen out of favor due to difficulty with obtaining the dye). The thermal dilution

technique uses a cold fluid as the indicator, which is then diluted (warmed) by the circulating blood. There are two techniques used during any indicator dilution methods: continuous-infusion and single-injection techniques. The single injection technique is the most widely used and is the technique used in catheterization laboratories (Baim & Grossman, 2006). Therefore, the single injection technique of the thermal dilution method will be discussed. All indicator dilution techniques capitalize on the Law of the Conservation of Mass-Energy, which states that mass, or energy, cannot be created or destroyed. That is, they are simply applications of the general Fick principle. In fact, in the VO_2 method, the indicator is the O_2 that is inspired into the lungs continuously. There are four fundamental requirements for the single injection method (Baim & Grossman, 2006).

The first requirement states that the nontoxic injectant should mix completely with the blood and its concentration should be able to be accurately measured (Baim & Grossman, 2006). In the thermal dilution method, the injectant is either a saline solution (5% dextrose mixed in water can also be used) which is either cooled to a pre-determined temperature (most common) or is at room temperature. It is important to point out that temperature is the indicator in this method, and in order to measure its "dilution" one needs to know the starting temperature. Originally, the thermal dilution method was done with a dual-thermistor set-up. However, most commercial systems utilize a single thermistor catheter, but dual thermistor systems have been re-visited and have demonstrated superiority over single thermistor systems (Lehmann & Platt, 1999). Despite this evidence, single thermistor systems still persist and remain the most common

set-up. The single thermistor system requires measurement of the temperature of the injectant prior to injection and that temperature needs to be corrected by a known constant to account for catheter warming. However, the value of this constant has come in to question, particularly because it does not account for the variation in warming due to the operator's hands (Lehmann & Platt, 1999). In an important study by Lehmann and Platt, they measured single and dual thermistor cardiac outputs in 50 non-emergent patients (totaling 960 cardiac outputs) with and without definite indications for right heart catheterization (Lehmann & Platt, 1999). They found wide variation in the resulting cardiac output with single thermistor technique compared to Fick VO_2 (Fick) cardiac output (mean error of about 25%) versus the dual thermistor cardiac output compared to the Fick cardiac output (mean error of about 17%). Although single thermistor techniques are still used, dual thermistor techniques appear to provide a more accurate measurement of the injectant temperature at the injection site, and therefore more accurate measurement of the dilution.

The second requirement for the single-injection method is that the indicator substance is not added to or subtracted from the blood between the injection site and the sampling site. In the thermal dilution method, the change in temperature is related to the injectant being diluted by the warmer blood. Therefore, the thermal dilution method meets this requirement in most patients. However, this may not be true in patients with low output states (van Grondelle et al., 1983). In a set of 16 patients with Fick cardiac outputs $\leq$3.5 L/min (van Grondelle et al., 1983), the thermal dilution method overestimated cardiac output compared to the Fick cardiac output in all the patients,

reaching an overestimation of cardiac output of >35% in patients with cardiac output <2.5 L/min. These results suggest a systematic error in the measurement in these patients, which means that either the Fick method underestimates true cardiac output or the thermal dilution overestimates it in this patient group. However, as mentioned above, in such low output states, the a-vO_2diff is increased. This makes the relative errors in its measurement small, and in turn, provides the Fick cardiac output greater accuracy (van Grondelle et al., 1983). It is postulated in such low flow, low output states that there is loss of indicator (temperature) that is related the warming of the blood by the walls of the heart chambers and surrounding tissue (Baim & Grossman, 2006; van Grondelle et al., 1983). That is, the integrated signal that is sampled demonstrates a greater temperature increase due to the greater time the indicator is exposed to the cardiac tissues (van Grondelle et al., 1983). This theory is supported by the evidence of prolonged circulation time in patients with HF (Morris et al., 2007). In a study of 30 patients with chronic systolic HF, resting lung-to-lung circulation time was measured by determining the time taken for a bolus of inhaled acetylene to travel from the lungs, through the systemic circulation and back to the lungs (Morris et al., 2007). The results of this study demonstrated that the severity of HF increased with increased lung-to-lung circulation time (Morris et al., 2007).

The third requirement is that the majority of the indicator must pass the sampling site before it is re-circulated (Baim & Grossman, 2006). When the indicator is injected into the RA (or less commonly the vena cava) the blood flow must travel forward into the RV and into the PA. Therefore, it is logical that regurgitant flow through the tricuspid

valve will cause the indicator to be re-circulated back into the RA before it can be sampled. Similar to situations of low output, the indicator is exposed to the blood and cardiac tissues for a longer period of time. This will cause an increase in the temperature at the sampling site and then overestimate cardiac output. Tricuspid regurgitation occurs in about 15% of men and 18% of women in the general population in the United States (Roger et al., 2012). This is a common exclusion criterion in studies measuring thermal dilution cardiac output (Bergstra et al., 1995; Berthelsen, Eldrup, Nilsson, & Rasmussen, 2002; Dehmer et al., 1982; Lehmann & Platt, 1999). As such, it is recommended that this technique should not be used in patients with severe tricuspid regurgitation (Baim & Grossman, 2006).

The fourth and last requirement for the single injection method states that the indicator must traverse some part of the central circulation where mixing of all the blood from the body occurs (Baim & Grossman, 2006). As stated previously, the two most common sites of injection are the RA and the vena cava. In patients with sinus rhythm and remaining in a steady resting state, demonstrate a relatively constant stroke volume with each cardiac cycle. Therefore, mixing of the blood is very consistent; making injection just outside (vena cava) or within the RA meet this criteria. However, in situations where variations in RV filling times and stroke volume cause the cardiac output to become cyclic. For example, Østergaard et al. compared 25 patients with atrial fibrillation and 22 patients with sinus rhythm and found that patients with atrial fibrillation had a 55% higher random error (less precise measure of cardiac output) compared to patients with sinus rhythm (Østergaard, Nilsson, Nilsson, Rasmussen, &

Berthelsen, 2005). Additionally, they were able to measure cardiac outputs in 8 patients in atrial fibrillation group after they converted to sinus rhythm, which demonstrated improved precision to a level more comparable to those in the sinus rhythm group (Østergaard et al., 2005). It was postulated in this study that their results likely show much greater random error because of the compounding effect of the random error associated with the single injection method (same for both groups) and the variable cardiac output that results from atrial fibrillation (Østergaard et al., 2005). However, the patients in atrial fibrillation in this study had controlled ventricular rates, which may have improved the overall precision in this group (Østergaard et al., 2005). Though atrial fibrillation is problematic, in situations where there is good rate control, performing more cardiac outputs injections and taking an average of these may provide a better idea of the patients overall cardiac output. It is common practice to perform three to five thermal dilution cardiac outputs in all patients with an average of the closest three to four measurements (Nilsson, Nilsson, Skovgaard, & Berthelsen, 2004). In patients with atrial fibrillation, it may be necessary to perform even more measurement trials.

Fick Cardiac Output

As mentioned above, the Fick equation for measuring cardiac output is an application of the Law of Mass/Energy Conservation (same as indicator dilution methods), where the indicator is the O_2 that is inspired into the lungs continuously. That is, the theoretical principles proposed by Adolph Fick in 1870 are the common underpinning to both the thermal dilution and Fick VO_2 techniques. The simplified Fick equation for measuring cardiac output is: *Cardiac Output = VO_2/a-vO_2diff.*

When determining cardiac output with the Fick Method, the measure of VO_2 through metabolic gas exchange measured at the mouth is considered the gold standard. In fact, prior to the introduction of the thermistor-equipped catheter in 1971, the Fick cardiac output was the standard method.

Measurement of Resting Oxygen Consumption

Measurement by Ventilatory Gas Exchange:

Ventilatory gas analysis is the most common method used for both quantifying metabolic rate and energy expenditure, and metabolic carts that measure gas exchange from expired breath during rest and exercise are widely available from commercial manufacturers. In order to calculate metabolic data, all of these systems need to measure fractional concentrations of O_2 and carbon dioxide in expired air along with minute ventilation. Although hardware and software specifications vary, all systems contain the basic components of flow/volume transducer and gas analyzers. From these, VO_2, carbon dioxide production, and the respiratory exchange ratio can be calculated as frequently as breath-by-breath in many commercial systems.

The major source of error relating to the Fick method for estimating cardiac output is the assessment of VO_2 with an average error of the measurement of 4 - 6% (Armstrong & Costill, 1985; Novitsky, Segal, Chatr-Aryamontri, Guvakov, & Katch, 1995). During the measurement of VO_2 at rest, prior to catheterization, the primary contributors of error are sedation (Wolf et al., 1998) and the changes in breathing patterns related to the instrumentation (Perez & Tobin, 1985).

Sedation given to patients prior to catheterization can vary between patients and is often left to physician discretion. Any sedation will cause a decrease in metabolism, reflecting in a decrease in VO_2 (Wolf et al., 1998). However, in the context of the right heart catheterization, it is important to obtain the resting VO_2 under the conditions of the right heart catheterization.

It is well established that changes in tidal volume and breathing frequency occur when a patient's breathing is being monitored (Perez & Tobin, 1985). This appears to be particularly true when a patient breathes through a mouthpiece with nose clips blocking the nose, where increases in tidal volume can exceed 20% (with a particular increase in length of time for inspiration) and decreases in breathing frequency can reach 7% or more (Perez & Tobin, 1985). These alterations in breathing can change the work of breathing and influence the resting VO_2. Despite these limitations, the use of the mouthpiece and nose clip during the measurement of VO_2 is quite common and many ways is better than the alternative methods. For example neoprene facemasks and hoods that cover the entire face and head have demonstrated similar changes in breathing patterns as seen with mouthpiece and nose clips (Perez & Tobin, 1985). Facemasks cannot provide an appropriate seal in those with flattened facial features or those with facial hair around the mouth and chin. Hoods, however, significantly reduce the risk of air leaks, but may allow the mixing of "room air" with exhaled air within the hood space and are associated with greater anxiety due to claustrophobia (Wolf et al., 1998). When the instantaneous collection of breath-by-breath gas exchange is performed, the instantaneous display of gas exchange values for each breath can be displayed and allows the technician an

opportunity to recognize the air leak and correct it. Furthermore, in the post-test analysis, data from leaked breaths can be excluded when collected breath-by-breath reducing the error related to air leaks.

Partly due to these limitations and, likely more importantly, the ease of using standardized equations have led researchers and clinicians to develop estimation equations as a surrogate to measuring the VO_2 in the calculation of cardiac output by the Fick Equation. In the catheterization laboratory, the main purpose of the estimation equations were a back-up when the measurement of resting VO_2 was determined to be inaccurate or unreliable during an individual procedure (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970). However, most catheterization laboratories have adopted the practice of using one of three popular estimation equations (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970) exclusively over measuring VO_2 (Narang et al., 2012). The estimation equations capitalizing on the accepted and well demonstrated fact that the resting VO_2 per unit body mass is greater in males than in females, greater in children than in the aged, greater in small individuals than in large ones, and higher under stress conditions (Brooks, Fahey, & Baldwin, 2005), all three of the widely used estimation equations include BSA in the calculation (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970). Two of the equations have used age, sex and heart rate at the time of measurement in order to improve estimated accuracy (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970). The formulas for each of the estimations is listed in **Table 3.**

Table 3. Equations Used to Estimate Oxygen Consumption.

Estimation Equation	Formula
LaFarge & Miettinen (1970) - Male	(138-(11.49*ln(Age))+(0.378*HR))xBSA
LaFarge & Miettinen (1970) - Female	(138-(17.04*ln(Age))+(0.378*HR))*BSA
Demer, Firth & Hillis (1982)	125*BSA
Bergstra, van Dijk, Hillege, et al. (1995)	(157.3*BSA)+(100*Sex[0 for female; 1 for male])-(10.5*ln(Age))+4.8

ln(Age) = natural log of age; HR = heart rate; BSA = body surface area (Du Bois and Du Bois (1916) formula)

Before discussing each of these estimation equations, it is important to have a brief discussion of the calculation of BSA. Referring back to **Table 1**, the right ventricular stroke work index is indexed to BSA, referring back to the discussion of cardiac output it is often indexed to BSA in order to standardize cardiac output and provide information concerning the effectiveness of the measured cardiac output, and lastly all the estimation equations have utilized BSA in the estimation of VO_2. Though there are several estimations of BSA from different authors, the most widely used (including all the authors of the VO_2 estimation equations) is the equation of Du Bois and Du Bois (Verbraecken, Van de Heyning, De Backer, & Van Gaal, 2006). The estimation of BSA by Du Bois and Du Bois was based on cadaver studies of 9 European adult males (Du Bois & Du Bois, 1916), which would certainly seem to limit how the equation could be generalized across ethnicity, sex and age. Furthermore, studies performed on larger cohorts of individuals have determined that the formula by Du Bois and Du Bois consistently underestimates BSA (Haycock, Schwartz, & Wisotsky, 1978; Verbraecken et

al., 2006). In obese (BMI $\geq$ 30 kg/m^2) adults, the DuBois and DuBois formula underestimate BSA by 2.7% in males and 4.5% in females (Verbraecken et al., 2006). Considering determination of conditions like cardiogenic shock are partly determined by a reduced cardiac index (cardiac output/BSA), underestimating the BSA in this calculation would result in a higher cardiac index and result in inadequate treatment (Verbraecken et al., 2006). Despite these findings, the estimation by Du Bois and Du Bois remains widely used in the cardiac catheterization laboratory (Baim & Grossman, 2006), and (as already stated) is employed in the most widely used VO_2 estimations. The formula from Du Bois and Du Bois (Du Bois & Du Bois, 1916) is:

$$BSA=0.00718 * Height\ (cm)^{0.725} * Weight\ (kg)^{0.425}$$

Equations Derived by LaFarge & Miettinen:

In 1970, LaFarge & Miettinen published their findings of the indexed VO_2 (VO_2/BSA) in 879 patients undergoing cardiac catheterization (LaFarge & Miettinen, 1970). To date, this study contains the largest cohort of patients undergoing cardiac catheterization where VO_2 was measured. Prior to this publication, other researchers had published results (with prediction equations and nomograms) for infants, children and adults in the basal condition, basal metabolic rate. LaFarge & Miettinen suggested that utilizing results from these previous studies to predict resting VO_2 in those undergoing cardiac catheterization would lead to erroneous results. One of their primary arguments was that patients undergoing catheterization are not in the basal state, because the patient can be under some stress from undergoing the procedure (LaFarge & Miettinen, 1970). In

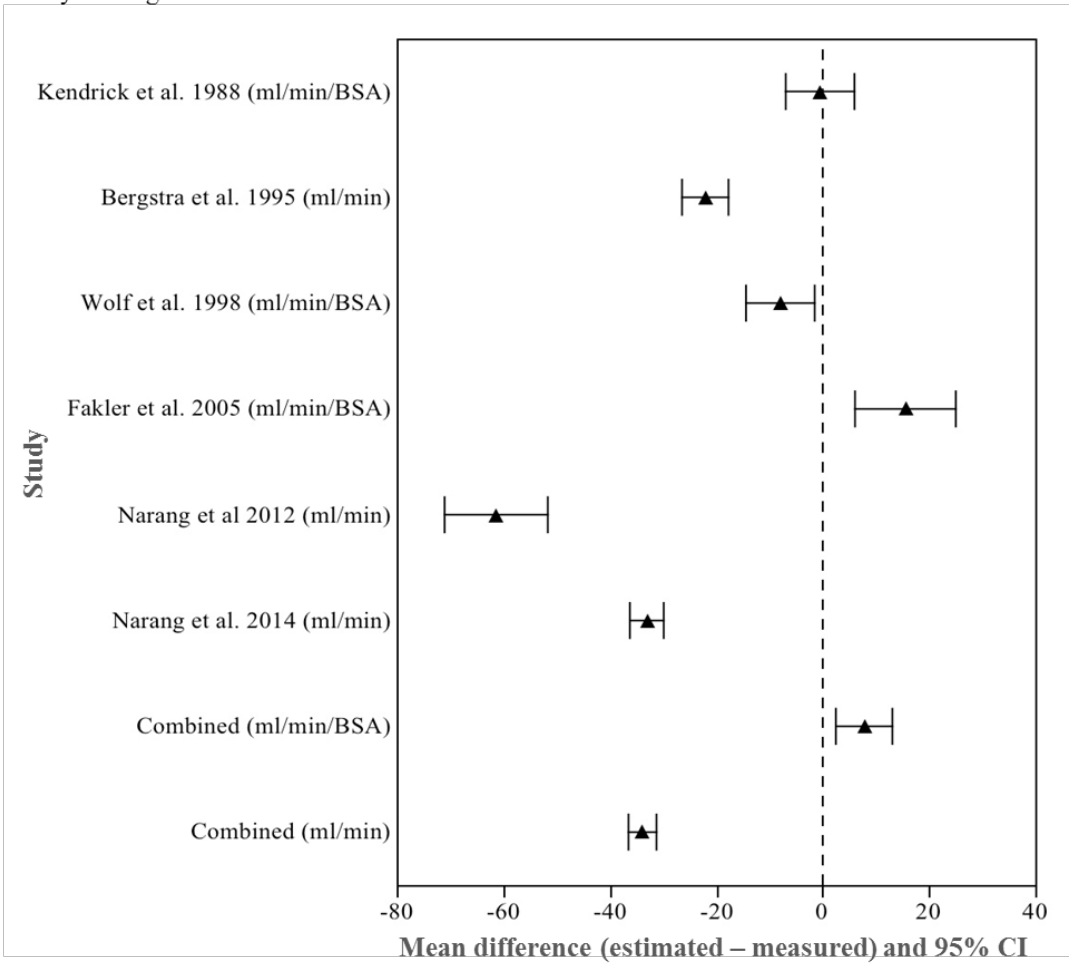
1970, the most widely used estimate for resting VO_2 was from Rudolph and Cayler (Rudolph & Cayler, 1958). In this older study, the authors reported an age-specific estimate of basal VO_2. With the estimate derived from 126 patients, one of the limitations to this older study is the small cohort and its exclusive assessment with pediatric populations (Rudolph & Cayler, 1958). Furthermore, LaFarge & Miettinen argued that estimating VO_2 from age alone is insufficient, and that other variables such as sex, heart rate, a-vO_2diff and arterial saturation (along with age) influence VO_2 (LaFarge & Miettinen, 1970).

In their study, all patients between the ages of 3 and 40 years old undergoing cardiac catheterization over an almost six year period were included, which resulted in a total of 879 patients. Expired air was collected for all patients over a three-minute period into a Douglas bag by way of a two-way valve and mouthpiece/nose clip. The concentration of O_2 in the expired air (in the Douglas bag) was measured by a pO_2 analyzer, and the volume of air was measured by evacuating the Douglas bag through a Collins Tissot spirometer. Room air was assumed to contain 21% O_2. After obtaining the data, fitted regression models were run which included variables such as age, sex, heart rate, arterial O_2 saturation, a-vO_2diff and BSA. Standard error was computed for each model derived and the estimates were compared to zero. The best-fit equations for males and females can be found in **Table 3**. Interestingly, the measured results were never compared to the nomograms of Rudolph and Cayler, which were reportedly widely used during this time period (LaFarge & Miettinen, 1970). Another major limitation to the

study is the lack of patients over the age of 40, and with a mean age of 13 years for the sample implies a majority of pediatric patients.

Several studies have revisited the findings of the formulas developed by LaFarge & Miettinen. In these studies, the VO_2 was either measured through metabolic gas exchange (Fakler et al., 2005; Kendrick et al., 1988; Narang et al., 2012; Narang et al., 2014; Wolf et al., 1998) or calculated by back calculating the VO_2 from the dye-dilution cardiac output (Bergstra et al., 1995; Dehmer et al., 1982). **Figure 1** summarizes the findings of these studies with a plotting of the mean difference of the estimated VO_2 by the formulas of LaFarge & Miettinen minus the measured VO_2, with variance represented by the 95% confidence interval. Overall, studies with primarily adults (Fakler et al. enrolled primarily pediatric patients) show that in a wide variety of patients the formulas derived by LaFarge & Miettinen underestimate the resting VO_2 (**Figure 1**). However, in all the studies reported, including the relatively small difference reported by Kendrick et al. (mean difference -0.44 ml/min/m^2), mean differences were found to be significantly different than zero by *t*-test analysis (Bergstra et al., 1995; Fakler et al., 2005; Kendrick et al., 1988; Narang et al., 2012; Narang et al., 2014). Furthermore, all studies analyzed the agreement between the measured and estimated VO_2 utilizing the methods of Bland & Altman (Bland & Altman, 1986), and found a systematic error in the formulas of LaFarge & Miettinen where lower values of VO_2 were overestimated and higher values of VO_2 were underestimated, which results in poor agreement between the two measures.

Figure 1. Summary of the Mean Difference in Resting Oxygen Consumption Estimated by LaFarge & Miettinen versus Measured.



Importantly, the studies by Kendrick et al., Wolf et al. and Narang et al. (2014) utilized primarily adult patient groups representative of type of patient seen in an adult cardiac catheterization laboratory with measurement of resting VO_2 with gas exchange similar to the method of LaFarge & Miettinen. In the study by Kendrick et al., 80 adult patients (age 59 $\pm$ 8, range 38-78 years) were undergoing routine left and right heart catheterization as part of their assessment for various (no specific conditions mentioned) cardiac disorders (Kendrick et al., 1988) and it is likely that at least some of these patients

had reduced systolic function. None of the patients received sedation prior to catheterization, which is unlike the methods of LaFarge & Miettinen. The age range of the patients starts at the upper end of the range analyzed by LaFarge & Miettinen. One reason for such agreement between the measured and estimated VO_2 may be related to the fact the expired gas exchange was collected into a Douglas bag through a two-way valve and mouthpiece and analyzed (room air O_2 was assumed at 21%) in a similar fashion to the methods described by LaFarge & Miettinen (LaFarge & Miettinen, 1970). Where patients were sedated in the LaFarge & Miettinen study, the reduction in VO_2 caused by the use of sedation in their younger cohort may have been off-set by the older age of the patients studied by Kendrick et al. In fact, this would be consistent with the trend in the findings of LaFarge & Miettinen that demonstrated a decrease of ~0.4 $ml/min/m^2$ per half-decade after the age of 20. If this trend remains beyond the age of 40, then the results from Kendrick et al. are consistent with LaFarge & Miettinen. Likewise, the patients in the study by Wolf et al. were also primarily adult patients (mean age 52.2, range 16-68 years old) with diagnosis of cardiomyopathy (47 patients), valvular disease (3 patients) or post cardiac transplant (7 patients) who were scheduled to undergo maximal cardiopulmonary exercise testing (Wolf et al., 1998). Prior to beginning exercise testing, patients' resting VO_2 was measured by breath-by-breath respiratory gas exchange while lying in a supine position (Wolf et al., 1998). These methods utilized are quite different than those described by LaFarge & Miettinen, particularly in the methods used to analyze the metabolic gas exchange (computerized metabolic cart vs Douglas bags) and the fact that these patients were preparing to undergo an exercise stress test instead of

a cardiac catheterization. Measuring the gas exchange through breath-by-breath analysis of inspired and expired air is well validated and may provide some advantage of detecting air leaks on the mouthpiece. Measuring the resting VO_2 prior to exercise testing indicates these patients did not receive any sedation. So, it is not surprising that the estimated VO_2 by LaFarge & Miettinen underestimated the resting VO_2. Most recently, Narang et al. (2014) published results from a retrospective analysis of 10 years' worth of data. Resting VO_2 was measured by the Douglas bag method in 535 adults patients (mean age 55 $\pm$ 13.5 years) undergoing routine right heart catheterization (Narang et al., 2014). Among the 535 patients, 102 (19%) had a diagnosis of HF, but no sub-analysis was performed on this particular subgroup. Where Kendrick et al. and Wolf et al. reported their findings indexed to BSA, Narang et al. (2014) reported their findings in ml/min making the comparison difficult. When roughly indexing the mean difference in resting VO_2 by an estimated average BSA of 1.89 m^2 (from the reported average height and weight), the results of Narang et al. (2014) still show a greater underestimation than Wolf et al. (-17.5 vs. -7.9, respectively). Narang et al. (2014) make no mention of sedation, which limits the understanding of these results.

Prior to the results reported in 2014, Narang et al. (2012) reported results from 75 lean and obese adults (median age of 39 years old, mean BMI 33 kg/m^2) prior to exercise testing during their participation in two other studies. Though the measurement of gas exchange was done in the same manner as LaFarge & Miettinen (expired air collected into Douglas bags through a mouthpiece), 27 participants were standing during the resting data collection and the remaining 48 subjects were seated on a recumbent bike

(Narang et al., 2012). So, again the absence of sedation and the additional deviation of body position and body habitus are likely contributors as to why these findings are so divergent from the other studies (**Figure 1**). However, the results between the 2012 and 2014 analyses appear to be what would be expected. That is, non-patient volunteers undergoing exercise stress testing will have a higher resting VO_2 than patients undergoing cardiac catheterization (assuming sedation was given to the patients).

Equation Derived by Dehmer, Firth and Hillis:

Of the three equations presented here, the 125 x BSA equation is probably the most widely used. Primarily, this is related to the fact that it has been put forth as an acceptable estimation for resting VO_2 in authoritative texts and statements of clinical practice (Baim & Grossman, 2006; Bashore et al., 2001; Summerhill & Baram, 2005). However, none of these publications offer any reference for the origins or validation of this equation. A recent publication references the "Parkland Equation" to a 2005 review paper by Summerhill and Baram (Narang et al., 2012). The review paper lists the equation in a table (with no reference), and suggests using it when measuring VO_2 is not possible (Summerhill & Baram, 2005). The expert consensus statement from the American College of Cardiology and the Society for Cardiac Angiography and Interventions recommends use of either "established reference table or the following formula: $[VO_2] = 125\ mL/min/m^2\ BSA$" (Bashore et al., 2001), but again offer no reference to origins of this equation. During some investigation into previous editions of Grossman's Cardiac Catheterization, Angiography and Intervention textbook, a reference to research performed by Dehmer et al. (Dehmer et al., 1982) was cited as the source of

this formula. This finding was confirmed with the second paper published by Narang in 2014, where the authors no longer refer to it as the “Parkland Formula”, but the “Dehmer Formula” (Narang et al., 2014).

Dehmer et al. sought to determine the variability of resting VO_2 in a sample of 164 adults between the ages of 21-75 years old (mean age of 50 years) who were referred for cardiac catheterization (Dehmer et al., 1982). Though patients were referred for cardiac catheterization for clinical indications, patients with valve regurgitation, inter-cardiac shunting or low cardiac output (<3.5 L/min) were excluded from their analysis. Instead of measuring VO_2 with ventilatory gas exchange, the resting VO_2 in each patient was back calculated from the measured cardiac output and a-vO_2diff through the Fick Equation. There were more than 50 patients that did not receive sedation and on average had higher resting VO_2 measurements than did the remaining patients who received sedation. In the study by LaFarge & Miettinen, all patients received some level of sedation. Unfortunately, Dehmer et al. did not estimate resting VO_2, and therefore there was no direct comparison between their measurement of VO_2 and that estimated by the equations of LaFarge & Miettinen. Although they found an average, indexed to BSA, VO_2 of 126 $\pm$26 ml/min/m^2, which was similar to what can be derived from the data reported by LaFarge & Miettinen in their adult cohort (126 $\pm$15 ml/min/m^2, derived from the data presented in LaFarge & Miettinen, 1970), they also reported a large range of 65-250 ml/min/m^2. This large range led them to conclude that with such a wide range, estimating the VO_2 on an individual may be severely inaccurate, and the subsequent

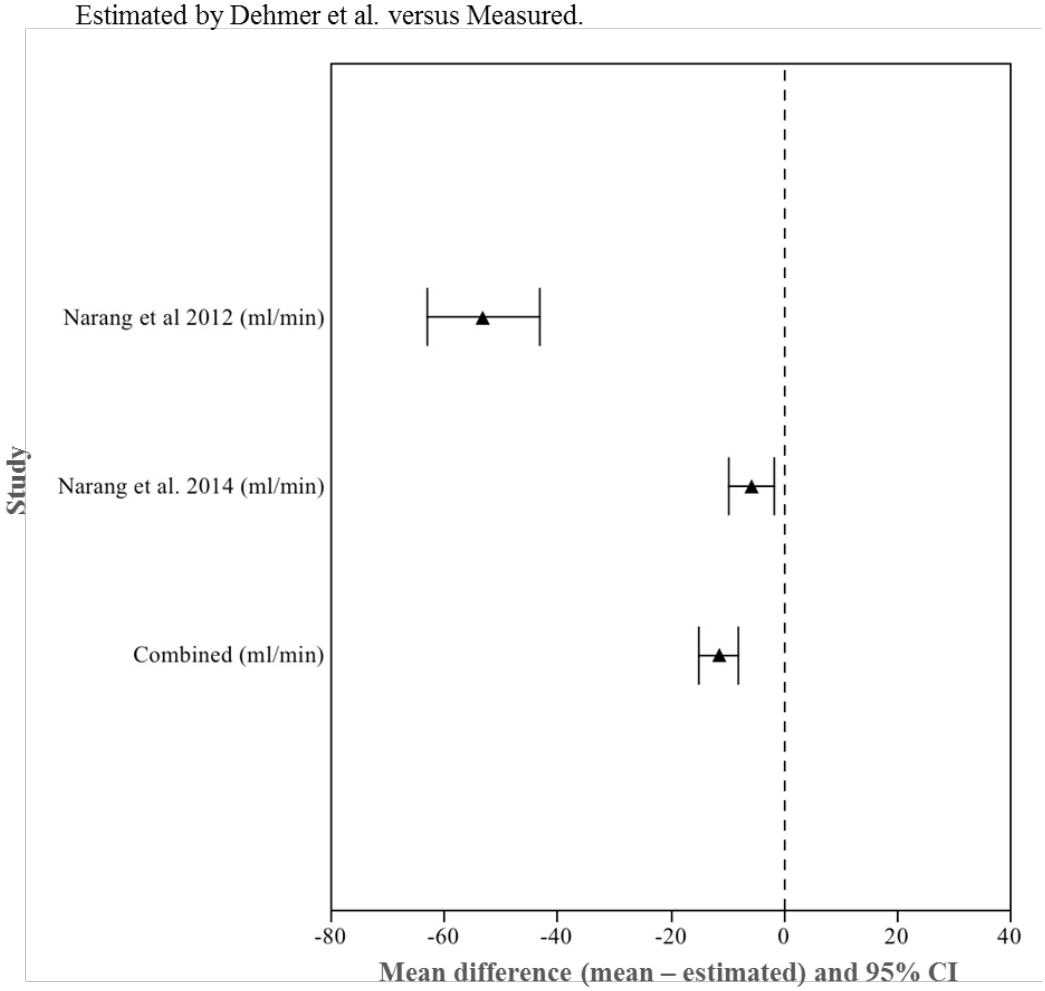
computing of cardiac output would lead to significant miscalculation of valve area, regurgitant fraction and vascular resistance (Dehmer et al., 1982).

This study was not performed with the intention of developing an estimation equation and, in fact, the study did not offer an estimation equation. The authors report the average indexed VO_2 among the 108 patients in the study was 126 $\pm$26 ml/min/m^2 with a large range of values between 65-250 ml/min/m^2 (Dehmer et al., 1982). However, regardless of the findings and conclusion of the study, their results gave an average of 126 ml/min/m^2, not 125 ml/min/m^2. So, it still remains a question as to where the estimation used originates. The lack of referencing to original work makes this equation difficult to evaluate in regard to its ability to estimate VO_2, bringing its wide use into question. It is unfortunate this equation can be perpetuated without substantial validation.

The only studies that could be found that used this formula in comparison to measured resting VO_2 are those performed by Narang et al. (Narang et al., 2012; Narang et al., 2014) and are summarized in **Figure 2**. Again, as mentioned before, the major complication of 2012 results is they were obtained prior to performing maximal exercise tests and were retrospectively consolidated from two other studies where resting VO_2 was not a primary variable under consideration. This certainly would affect the findings and may not be the most valid design to evaluate the accuracy of a formula to estimate resting VO_2 during a catheterization procedure. The results from their 2014 report make for a better comparison, but regardless they found a significant difference (underestimation) between the measured and the estimated VO_2 (Narang et al., 2012; Narang et al., 2014). Furthermore, they reported a trend of overestimation when resting VO_2 was <200 ml/min

and an underestimation of VO_2 when the measured VO_2 was $\geq$250 ml/min (Narang et al., 2012; Narang et al., 2014). Comparing the 2012 and 2014 data, again the effect of the methods and patient selection appear to be apparent.

Figure 2. Summary of the Mean Difference in Resting Oxygen Consumption Estimated by Dehmer et al. versus Measured.



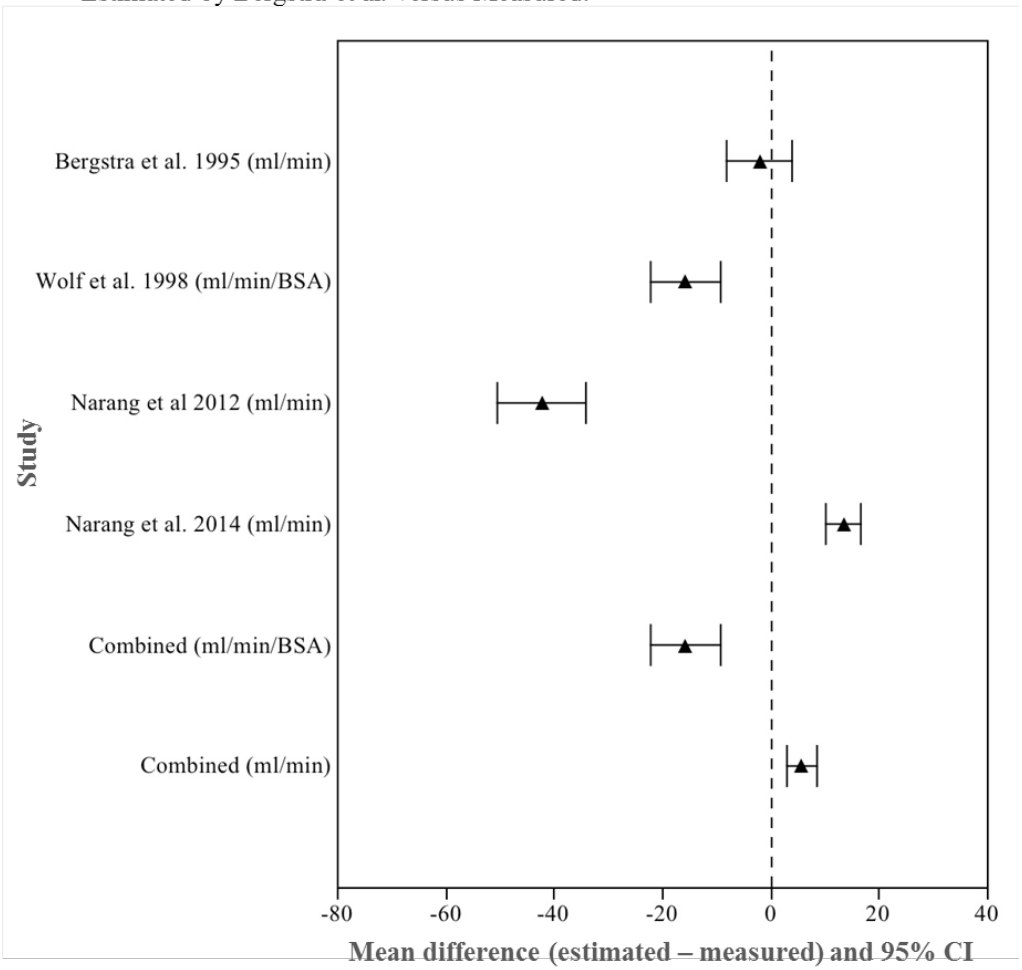
Equation Derived by Bergstra, van Dijk, Hillege, Lie and Mook:

Bergstra et al. divided 310 patients with congenital and acquired heart disease undergoing right and left catheterization into a "control group" (n=250) used to develop

the prediction equation, and a validation group (n=60) used to validate the equation (Bergstra et al., 1995). In their laboratory, the authors note that when an estimation of VO_2 is needed they use the formulas derived by LaFarge & Miettinen, but find disparity when compared to the dye dilution (indocyanine green) method that has been performed in their laboratory since the 1960s (Bergstra et al., 1995). They hypothesized that the disparity, in part, was due to the fact they more frequently perform catheterization on adult patients, where the formula by LaFarge & Miettinen was based primarily on a pediatric population (Bergstra et al., 1995). Therefore, they compared 130 patients from the control group, matching for the age range used by LaFarge & Miettinen (4-40 years), to the equations by LaFarge & Miettinen in order to determine if this was a source of error (Bergstra et al., 1995). Similar to Dehmer et al., these authors back-calculated the VO_2 from the measured cardiac output by the dye dilution method. Therefore, it is inherent that they excluded certain patients, including those with atrial fibrillation and atrioventricular block (Bergstra et al., 1995). Within their matched control sample of 130 patients, they found that the estimation by LaFarge & Miettinen underestimated VO_2 when compared to the derived value from the dye dilution method (**Figure 1**). However, from the 230 patients in their control group they developed an estimation equation and validated it with the 60 patients in the validation group by comparing the VO_2 estimation against the dye dilution derived VO_2. This demonstrated very good agreement (**Figure 3**), with a mean difference of (dye dilution – estimated) of only 2 ml/min and 95% confidence interval of -4 – 8 ml/min (Bergstra et al., 1995).

Three studies were found comparing VO_2 measured by metabolic gas exchange and estimated by the formula of Bergstra et al. (1995), the results of which are summarized in **Figure 3** (Narang et al., 2012; Narang et al., 2014; Wolf et al., 1998). These studies, already described above, have their limitations. Again the study by Wolf et al. (1998) was performed with patients including those with HFrEF, but prior to cardiopulmonary exercise testing, therefore not sedated (Wolf et al., 1998). The study by Narang et al. (2012) was done on obese adults without cardiovascular disease prior to cardiopulmonary exercise testing (again not sedated) and in either a standing or seated position (Narang et al., 2012). Lastly, the best comparator was the results from Narang et al. (2014) as these were done on a clinical population undergoing cardiac catheterization. Between these studies (excluding Bergstra et al.), Wolf et al. demonstrated the smallest mean difference utilizing a patient group that included patients with HFrEF (similar to the patients used by Bergstra et al.) and raises the question of what the results would have been if the patients analyzed by Wolf et al. were sedated. However, under the conditions presented by Narang et al. (2014), the estimation of Bergstra et al. grossly overestimates the resting VO_2. The most likely explanation is Bergstra et al. excluded patients with valvular heart disease, whereas Narang et al. (2014) included 72% of patients with valvular heart disease. Again, patient selection appears to be contributing to these findings.

Figure 3. Summary of the Mean Difference in Resting Oxygen Consumption Estimated by Bergstra et al. versus Measured.

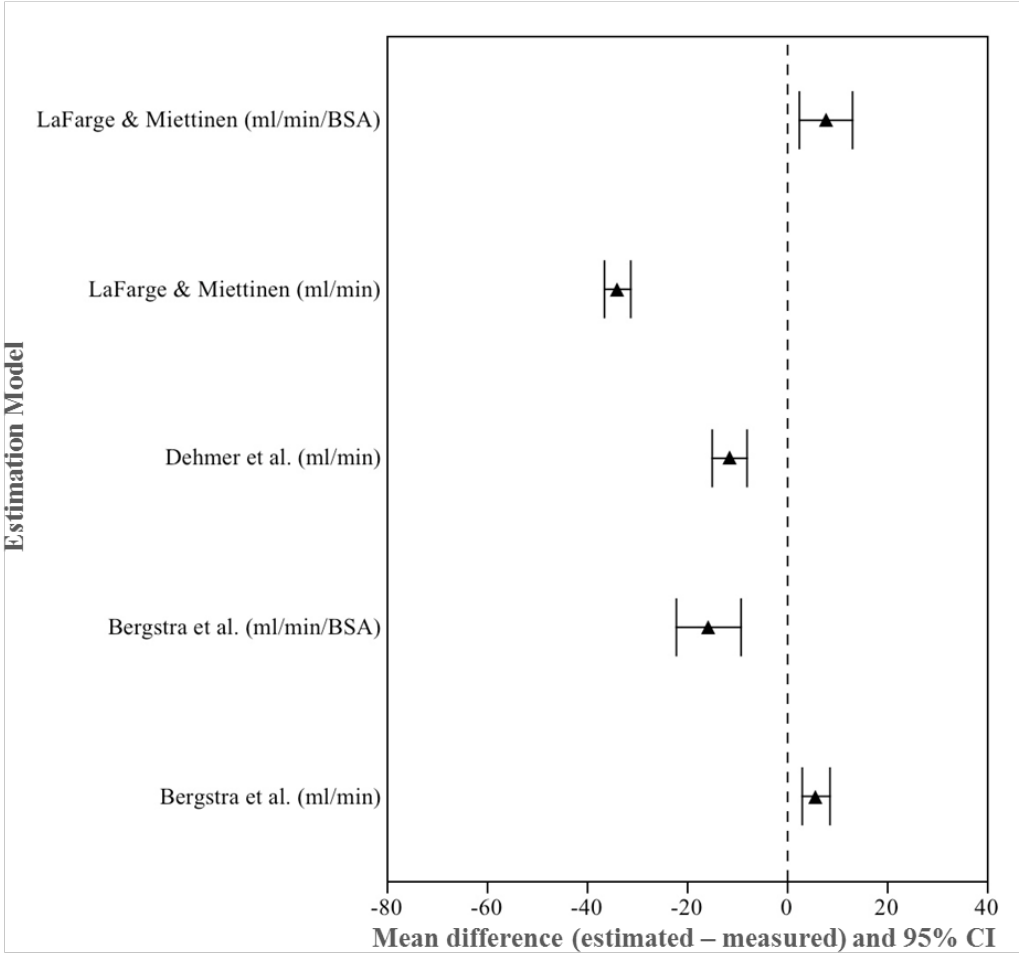


Summary of Estimation Equations:

As summarized in **Figure 4**, all estimation equations appear to under- and overestimate the resting VO_2. This variability appears to be dependent on patient selection, methods for deriving the "measured" VO_2 (gas exchange or dye dilution) and conditions the measurements are performed. The estimation by LaFarge & Miettinen appear to give a larger mean difference than the other measures, but being most studied formula it has been tested with the widest variety of patients. However, based on the

available literature, it is difficult to develop an appropriate hypothesis of whether estimating resting VO_2 in patients with HFrEF is appropriate or (if appropriate) which estimation equation would provide the "best" estimation. The studies of Kendrick et al. and Wolf et al. would suggest that the formulas by LaFarge & Miettinen are likely to result in the smallest mean difference in patients with HFrEF. On the other hand, the results of Narang et al. (2014) would suggest that it would be the estimation by Dehmer et al. Regardless, they all suggest that the mean difference would remain significantly different than zero. Even if the mean difference is significantly different than zero, it needs to be determined if these differences are clinically significant, that is, should the differences found (whether or not statistically different from zero) influence clinical decisions?

Figure 4. Summary of Mean Differences Found in the Studies Evaluating Estimated Resting Oxygen Consumption versus Measured. (grouped by the prediction equation)



Wolf et al., suggested that an error of >25%, calculated by differences between the measured and estimated VO_2 divided by the mean of measured and estimated VO_2, were clinically unacceptably large error (Wolf et al., 1998). Kendrick et al., suggested that an error $\geq$10% was large enough to potentially err clinically (Kendrick et al., 1988). Kendrick et al. based this minimum error on results reported by Selzer and Sudrann (1958) that compared two measurements of resting VO_2 and two measures of the a-vO_2diff during a cardiac catheterization procedure (Selzer & Sudrann, 1958). However,

Selzer also found a 95% confidence interval that approaches 20% error at the upper end (Selzer & Sudrann, 1958). Kendrick et al. noted this and estimated a compounding error from estimating BSA of ~5% (3-5% has been reported more recently (Verbraecken et al., 2006)), and subsequently suggested an error >25% as the level where significant clinical error would definitely occur (Kendrick et al., 1988). The estimation of VO_2 by the LaFarge & Miettinen equation resulted in 59% of the patients with >10% error and a total of 16% with an error exceeding 25% in the study by Kendrick et al., 25% of the patients exceeding 25% error in the study by Wolf et al. and 26% of patients exceeding 25% error in the 2014 Narang et al. study (Kendrick et al., 1988; Narang et al., 2014; Wolf et al., 1998). Although mean differences were significantly different than zero, both Kendrick et al. and Wolf et al. reported the lowest mean difference using the LaFarge & Miettinen and suggested the use of this equation when measured VO_2 results are unavailable or suspect, with careful consideration taken concerning this error (Kendrick et al., 1988; Wolf et al., 1998). Narang et al. (2014) found the smallest error with the Dehmer et al. equation, but concluded that the estimation of VO_2 in the calculation of cardiac output was inappropriate and did not endorse any of the formulas. Wolf et al. also reported that 40% of the patients exceeded 25% error when the estimation by Bergstra et al. was used and cautioned that this formula should not be used (Wolf et al., 1998).

Lastly, all the authors of the reported estimation equations (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970), most of the authors of the validation studies (Fakler et al., 2005; Kendrick et al., 1988; Narang et al., 2012; Wolf et al., 1998), and the authors of clinical practice guidelines and recommendations (Baim & Grossman,

2006; Bashore et al., 2001; Summerhill & Baram, 2005) suggest that VO_2 should be measured and only estimated when error in the measurement is suspected or measurement is not possible. Surprisingly, the clinical practice guidelines and recommendations suggest the use of the 125*BSA equation, which appears to be the least validated (Baim & Grossman, 2006; Bashore et al., 2001; Summerhill & Baram, 2005). In patients with HFrEF, it appears the formulas by LaFarge & Miettinen provide the lowest mean difference (Kendrick et al., 1988; Wolf et al., 1998), but with potentially more than 25% patients having clinically significant error in their estimated VO_2 (Narang et al., 2014; Wolf et al., 1998).

Conclusion

Heart failure represents the final stage of several diseases of the heart and is defined as a reduction in the ability of the heart to contract and eject blood (Bui et al., 2011; Hunt et al., 2009; Lindenfeld et al., 2010). Heart failure represents a major health problem, affecting 5.7 million people in the United States, and may be the fastest growing cardiovascular disease with an estimated 25% increase in prevalence by 2030 (Roger et al., 2012). Medicines and cardiac rhythm management devices are used to manage HF, but cardiac transplantation remains the only treatment that comes closest to a cure. Left ventricular assist device systems are also becoming increasingly more advanced and are providing an option beyond the traditional bridge-to-transplant to use as destination therapy for those patients who do not qualify for transplantation. For both of these therapies, appropriate patient selection is essential in order to provide the patient with the best potential outcome and manage limited resources. One of the many

measurements used to determine candidacy for these advanced therapies is the cardiac output determined during right heart catheterization. The measurement of cardiac output is particularly important because it is used to derive several other variables that could influence the decision of candidacy and/or the overall management of the patient's syndrome. Though thermal dilution is the most widely used method of determining cardiac output in the catheterization laboratory, it has been shown to over-estimate the cardiac output in patients with HF, particularly HFrEF. So, it is common practice to utilize the Fick method to determine the cardiac output, which requires measurement of resting VO_2. Though the direct measurement expired gas exchange is the best method measuring VO_2, estimation equations are most commonly used during right heart catheterizations. However, the three most widely used estimation equations have not been validated using patients with HFrEF. With potential clinically significant errors >25% in the studies that have utilized patients with HFrEF (Narang et al., 2014; Wolf et al., 1998), the potential to affect the patient's candidacy for advanced therapies and/or the patient's subsequent disease management. Therefore, the purpose of this study was to measure the resting VO_2 in adult patients with HFrEF during right heart catheterization procedures, investigate the accuracy of three widely used equations for the estimation of resting VO_2 compared to the direct breath-by-breath measurement of expired air using a metabolic cart and determine to what extent clinically significant errors occur using estimation equations.

CHAPTER III

METHODS

The purpose of this study was to measure the resting VO_2 in adult patients with HFrEF during right heart catheterization procedures, investigate the accuracy of three widely used equations for the estimation of resting VO_2 compared to the direct breath-by-breath measurement of expired air using a metabolic cart and determine to what extent clinically significant errors occur using estimation equations.

Participants

This study was conducted in conjunction with the Advanced Heart Failure Program and the LeBauer Cardiovascular Research Foundation at Moses Cone Hospital, Greensboro, NC. All study procedures were concurrently approved by the institutional review boards of the Cone Health Network and the University of North Carolina at Greensboro. All patients provided written informed consent prior to any study-related procedures. It was anticipated that up to 54 patients would need to be enrolled in order to obtain 44 complete data sets. Forty-eight patients (75% male, age: 63.6 $\pm$ 11.3 years, LVEF: 22 $\pm$ 6.4%) were enrolled in this study. There was no exclusion based on sex, race or ethnicity. All patients scheduled for a right heart catheterization were considered for inclusion in this analysis. All patients had a history of a LVEF $\leq$40% within the previous 6 months, with continued signs and symptoms consistent with chronic HF, and had not

received intravenous inotropic therapy within the previous seven days of the right heart catheterization.

Patients were excluded from participating in the study if they had received sedation prior to written informed consent being obtained or were otherwise unable to provide informed consent (consent was not obtained from healthcare power of attorney). Furthermore, patients were excluded if they were determined to have severe lung disease (diagnosed as such in the patient's medical history or, if spirometry data was available, a forced expiratory volume in 1 second (FEV_1) $\leq$ 1 L and/or a FEV_1 to forced vital capacity ratio of $\leq$ 0.50, or required use of home O_2). Patients with significant lung disease undergoing right heart catheterization have not been validated with these equations and, in the case of this analysis, might have confounded the results. Sedation has been shown to reduce resting VO_2 (Dehmer et al., 1982) and was used in the development of the three equations in question (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970). However, heavily sedated patients may not be able to maintain an appropriate seal on the mouthpiece and are likely to have difficulty following instructions given to them. Therefore, patients were excluded if they were expected to receive more than standard sedation (>2 mg of midazolam and/or >50 μg of fentanyl). Due to the limitation of the system used to measure the resting VO_2, the measurement of gas exchange was not possible while the patient was receiving supplemental O_2. Therefore, patients were excluded if supplemental O_2 was expected to be needed after receiving sedation (in those who otherwise were not prescribed home supplemental O_2).

Once enrolled in the study, it was possible for patients to subsequently receive more than standard sedation, require the use of supplemental O_2, or withdraw their consent to participate. For the current analysis, four patients were withdrawn from the study. Two patients required sedation beyond what was considered standard doses midazolam (one patient received 4 mg) or fentanyl (one patient received 100 μg). One patient became hypoxic during the catheterization procedure and needed supplemental O_2. Although, the fourth patient had an echocardiogram the week prior to catheterization with an LVEF <35%, the operating physician performed a ventriculogram that revealed a LVEF of >40% (reported as 40-45%). Therefore, the operating physician and the primary investigator decided the patient should be withdrawn. All remaining patients completed the 10 minutes of breathing without difficulty or complication. No patient asked to be withdrawn once data had been collected.

Sample Size Justification

The proposed sample size was estimated using the statistical software, G*Power version 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007). Estimation of the sample size needed was determined based on the existing literature for each of the three estimation equations. Since each of the equations was compared individually, the sample size needed to be based on the estimation that requires the most subjects. As can be seen in **Table 4**, the estimation of LaFarge & Miettinen was estimated to require the greatest number of patients. To establish the appropriate sample size, the effect size determined in **Table 4** was used to calculate the sample size at three power levels; 80%, 90% and 95%. The results of this analysis can be found in **Table 5.** From these calculations the

enrollment goal was 44 patients completing the resting VO_2. Up to a maximum of 54 patients were expected to be enrolled to ensure that there were 44 complete data sets.

Table 4. Results of Sample Size Estimation for Each of the Three Estimation Equations.

	LaFarge & Miettinen	Bergstra et al.	Dehmer et al.
Mean Difference	20.6	21.7	52.9
Standard Deviation	41.0	29.0	43.2
Effect Size	0.502	0.748	1.225
Critical t	2.035	2.120	2.365
Degrees of freedom	33	16	7
Sample size	34	17	8
Actual power	81.1%	82.5%	84.2%

Two tale *t*-test of mean difference of single sample. Power (1-β) = 80%; $\alpha = 0.05$

Table 5. Results of Sample Size Estimation using Data for the Lafarge & Miettinen Estimation Equation.

	Power (1-β)		
	80%	90%	95%
Critical t	2.035	2.017	2.006
Degrees of freedom	33	43	53
Sample size	34	44	54
Actual power	81.1%	90.3%	95.2%

Two tale *t*-test of mean difference of single sample. Effect size = 0.502; $\alpha = 0.05$

Patient Flow through Catheterization Laboratory

The patient flow through the catheterization laboratory from registration (out-patient) through entry into the catheterization procedural laboratory was dependent on

which laboratory the patient's procedure was being performed (Main Catheterization Laboratory or Joint-Venture Catheterization Laboratory) and if the patient arrived to the lab as an in-patient or an out-patient.

Main Catheterization Laboratory:

Out-patient (n=7): The patient arrived at Moses Cone Hospital's Short-Stay Center and was registered about 2 hours prior to scheduled procedure. After being registered, they were brought to the Short-Stay holding area where the patient changed into a hospital gown and the patient's intravenous lines were started. From the Short-Stay Center the patient was transferred to the catheterization laboratory department and taken into one of the procedure rooms. Inside the procedure room, the patient was draped and the planned insertion area was prepared. When the operating physician arrived, a "time out" was performed, where correct patient, procedure and insertion site were confirmed. The operating physician evaluated the patient and ordered sedation to be given.

In-patient (n=9): When ready to perform the patient's procedure, the catheterization laboratory notified the hospital unit where the patient was receiving care. The patient was transported from the patient room to the catheterization laboratory. Once in the catheterization laboratory, the in-patient process was the same as for the out-patient.

Joint-Venture Catheterization Laboratory (n=32):

The Joint-Venture laboratory performed catheterization procedures on an out-patient basis only. The patient arrived to the Moses Cone Hospital Heart and Vascular Center about 1 hour prior to the procedure and was registered in the waiting area. Once

registered, the patient was brought to a holding bay in the Joint-Venture Laboratory, allowed to change and was prepared for the procedure. At this point, the process was the same as the main catheterization laboratory.

Data Collection

Appropriate medical history was obtained in order to determine the patient's candidacy for participation in the study, which included the date and results of the patient's last LVEF measure and the method by which it was obtained (i.e., echocardiography, cardiac MRI, ventriculogram, etc.), date and results of the last pulmonary function test (if available), co-morbidities (such as lung disease) as listed in the patients electronic medical record, a list of currently prescribed medications (as listed in the electronic medical record), and results (and date) of the last measure of BNP/Pro-BNP (if available). Age, sex, height and weight were collected. The results of the catheterization were also obtained following the procedure.

Body surface area, using the patient's measured height in centimeter and weight in kilograms, was calculated according to the formula by Du Bois and Du Bois (Du Bois & Du Bois, 1916):

$$BSA\ (m^2) = 0.007184 x weight(kg)^{0.425} x height(cm)^{0.725}$$

The above estimation of BSA was used in the development of each of the estimation equations being investigated (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970) and, therefore, was the only estimation of BSA that could be applied when using these formulas. So, despite the reported limitations of this equation,

particularly consistently under-estimation of BSA (Haycock et al., 1978; Verbraecken et al., 2006), utilizing any other estimation of BSA would have inherently invalidated the results of this analysis.

Resting VO_2 was measured utilizing a commercial, open-circuit, breath-by-breath gas analysis system (Ultima-CPX, MGC Diagnostics Corp., St. Paul, MN). System calibration was performed prior to each study according the manufacturer's specifications. After the completion of the catheterization procedure and while the patient remained in the catheterization laboratory procedure room (supine on the laboratory table), the patient breathed through a pneumotach attached to a mouthpiece with a nose-clip occluding nasal ventilation. After a 5-minute run-in phase (to acclimate the patient to the mouthpiece and nose-clip), sampling was performed for an additional 5 minutes. Utilizing the mouthpiece and nose-clip instead of alternatives such as a facemask or hood allowed for the study to more closely replicate that of LaFarge & Miettinen (LaFarge & Miettinen, 1970). The other two equations were based on the back calculation of VO_2 from the measurement of cardiac output from dye dilution methods (Bergstra et al., 1995; Dehmer et al., 1982), but studies attempting to validate these estimations have used expired gas analysis with mouthpiece and nose-clip, as well (Kendrick et al., 1988; Narang et al., 2012; Narang et al., 2014; Wolf et al., 1998). Furthermore, the estimation equations were developed with patients receiving sedation, while in a supine position and in the catheterization laboratory (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970).

Estimated resting VO_2 was calculated according to each of the three widely used empirical formulae:

1) LaFarge & Miettinen:

   For males: $VO_2=(138.1-(11.49*ln(age)*0.378*Heart\ Rate))*BSA$

   For Females: $VO_2=(138.1-(17.04*ln(age)*0.378*Heart\ Rate))*BSA$

2) Dehmer et al.:

   $VO_2=125*BSA$

3) Bergstra et al.:

   $VO_2=(157.3*BSA)+(10*sex[male=1;female=0])-(10.5*ln(age))+4.8$

Data Analysis

All statistical analyses and creation of figures were done with JMP Version 10 (SAS Institute Inc., Cary, NC). With the exception of the mean differences, all continuous variables are reported as mean $\pm$ standard deviation (SD) and categorical variables are reported as the total number (percent of total). The mean differences, in the context of the Bland-Altman plots are also referred to as biases, are reported as mean $\pm$ standard error (SE).

Primary Aim 1:

The results from each empirical formula for estimating resting VO_2 were compared with the measurement of VO_2 with gas exchange. The Bland-Altman method (Bland & Altman, 1986) for comparing methods of measuring the same parameter was used to assess the agreement between measured and estimated VO_2. This method not only allows the assessment of agreement, it also allows for the visualization of trends in over- or under-estimation of the equations. A common finding in studies evaluating these estimation equations in different patient groups have demonstrated trends of overestimation with lower resting VO_2 (<200 ml/min) and underestimation with VO_2 above 250 ml/min (Bergstra et al., 1995; Fakler et al., 2005; Kendrick et al., 1988; Narang et al., 2012). In accordance with this method, the difference of the measured minus estimated for each patient was plotted against the corresponding average of the measured plus estimated. The limits of agreement will be the mean difference +/- 1.96 SD.

Another aspect of the Bland-Altman analysis is to determine bias in the measurement, or the mean difference. However, Bland & Altman do not provide any recommendation of objectively determining if the bias is significant. A single-sample *t*-test was also performed to compare the mean of differences (estimated minus measured), or bias, against the hypothetical mean difference of zero, and was considered statistically significantly different when $p \leq 0.05$. This analysis is consistent with previously published research attempting to validate these estimation equations (Bergstra et al., 1995; Fakler et al., 2005; Kendrick et al., 1988; Narang et al., 2012; Wolf et al., 1998).

However, in both studies by Narang et al. absolute mean (Narang et al., 2012) and absolute median (Narang et al., 2014) differences were subjected to single-sample *t*-tests. This method ignores the assumption of the Bland-Altman analysis, which suggests the results of the method being tested will have some variability above and below zero, or no difference (Bland & Altman, 1986).

Secondary Aim to Aim 1:

The patients were dichotomized based on select characteristic variables (e.g., sex, sedation, and etiology). When dichotomization resulted in two groups of $\geq$10 patients each, the groups' measured VO_2 was compared utilizing unmatched paired *t*-tests. When measured VO_2 between the groups were found to be significantly different, then both assessments done for Primary Aim 1 were repeated for this secondary aim.

Primary Aim 2:

Although statistical differences are important in clinical research, these differences may or may not impact clinical decision-making. Therefore, the question of the clinical relevance, or clinical significance, was important to consider. Furthermore, statistical significance is often based on the mean with little regard to the individual, but clinical significance is often considered at the individual patient level. In order to establish if differences between the measured and estimated VO_2 were clinically significant, the absolute percent error (direction of the error was ignored) in the estimate was calculated by dividing absolute difference (estimated - measured) by the mean of the measured. Based on previously published data, an absolute percent error exceeding 25% was considered clinically significant, and was reported as the percentage of patients at or

above 25% error (Bergstra et al., 1995; Narang et al., 2012; Narang et al., 2014; Wolf et al., 1998).

Secondary Aim to Aim 2:

Another way to consider the clinical significance of differences found between measured and estimated VO_2 is to consider the impact of these measurements on derived variables such as the cardiac index (cardiac output/BSA). The a-vO_2diff was collected from each patient's catheterization procedure. This value was used to calculate cardiac output and cardiac index based on the Fick equation for the measured and estimated VO_2. Sensitivity and Specificity determinations were performed for each estimation equation (cardiac index based on measured VO_2 will be the reference) with three prognostic cardiac index cut-off levels: $</\geq 2.6$ ml/min/m^2 (low versus normal), $</\geq 2.2$ ml/min/m^2 (hypoperfusion versus no hypoperfusion) and $</\geq 1.9$ ml/min/m^2 (cardiogenic shock versus no shock). Sensitivity was computed by the total of the correctly classified patients as positive (low, hypoperfusion or cardiogenic shock) divided by the sum of those correctly classified as positive (true positive) and those incorrectly classified as negative (false negative). Specificity was computed by the total of the correctly classified patients as negative (normal, no hypoperfusion or no shock) divided by the sum of those correctly classified as negative (true negative) and those incorrectly classified as positive (false positive).

Primary Aim 3 (Exploratory):

Unlike the other studies that have developed estimation equations for resting VO_2, this analysis included only patients with HFrEF, making it worthwhile to develop an

empirical equation. If the hypothesis for Aim 1a is supported, stepwise regression analysis was performed with a number of covariates (e.g., age, sex, etiology, LVEF, heart rate at time of data collection). Covariates were removed from the equation one at a time from lowest to greatest significance. Similar to LaFarge & Miettinen (LaFarge & Miettinen, 1970), the model was reduced until all remaining covariates were significant at $p \leq 0.05$.

CHAPTER IV

RESULTS

The purpose of this study was to measure the resting VO_2 in adult patients with HFrEF during right heart catheterization procedures, investigate the accuracy of three widely used equations for the estimation of resting VO_2 compared to the direct breath-by-breath measurement of expired air using a metabolic cart and determine to what extent clinically significant errors occur using estimation equations.

Patient Characteristics, Catheterization and Gas Exchange Results

Patient demographic data for the 44 patients for which gas exchange was completed are summarized in **Table 6**. The average age of the patients was 64.5 $\pm$ 10.7 years (range was 34 to 86 years), 65.9% of patients were male, 65.9% were Caucasian, 65.9% had non-ischemic cardiomyopathies and 47.7% had New York Heart Association Class III symptoms. The majority of patients were prescribed beta-blockers, ACE-I/ARB, and loop diuretics (**Table 7)**, suggesting the majority of patients was on guideline-recommended medical therapy. The summary of the pre-catheterization blood labs, right heart catheterization results and resting gas exchange results are listed in **Tables 8-10**.

Table 6. Summary of Patient Demographic Data.

	Variable Summary	Range
Gender		
Female	15 (34.1%)	
Male	29 (65.9%)	
Age (years)	64.5 $\pm$ 10.7	34 - 86
Race		
Asian	1 (2.3%)	
Black/African-American	14 (31.8%)	
White/Caucasian	29 (65.9%)	
Body Mass Index (kg/m^2)	28.2 $\pm$ 6.4	18.1 - 46.7
<25 kg/m^2	14 (31.8%)	
25-29.9 kg/m^2	10 (22.7%)	
≥ 30 kg/m^2	20 (45.5%)	
Body Surface Area (m^2)	1.96 $\pm$ 0.27	1.41 - 2.58
Heart Failure Etiology		
Ischemic Cardiomyopathy	15 (34.1%)	
Non-Ischemic Cardiomyopathy	29 (65.9%)	
Left Ventricular Ejection Fraction (%)	22.0 $\pm$ 6.4	10 - 37.5
New York Heart Association Class		
II	9 (20.0%)	
III	21 (47.7%)	
IIIb	9 (20.0%)	
IV	5 (11.4%)	
Diabetes		
No Diabetes	29 (65.9%)	
Insulin-Dependent	5 (11.4%)	
Non-Insulin Dependent	10 (22.7%)	
Smoking Habit		
Never Smoked	19 (43.2%)	
Current Smoker	10 (22.7%)	
Former Smoker	15 (34.1%)	
Cardiac Rhythm Management		
None	21 (47.7%)	
Cardiac Resynchronization Therapy	5 (11.4%)	
Implanted Cardioverting Device	16 (36.4%)	
Pacemaker	2 (4.5%)	

Continuous data presented as mean $\pm$ standard deviation. Categorical data presented as number of patients (percentage of total).

Table 7. Summary of Patient Prescribed Heart Failure Medications.

	Prescribed	Not Prescribed
Beta Blocker	34 (77%)	10 (23%)
Angiotensin Converting Enzyme Inhibitor	24 (55%)	20 (45%)
Angiotensin Receptor Blocker	12 (27%)	32 (73%)
Loop Diuretic	31 (70%)	13 (30%)
Aldosterone Antagonist	14 (32%)	30 (68%)
Digoxin	7 (16%)	37 (84%)
Hydralazine	6 (14%)	38 (86%)
Long-Acting Nitrate	7 (16%)	37 (84%)

Data presented as number of patients (percentage of total).

Table 8. Summary of Patient Pre-catheterization Blood Labs.

	Variable Summary	Range
Red Blood Cell (Mil/μL)	4.57 $\pm$ 0.75	2.97 - 7.37
Hemoglobin (g/dL)	13.2 $\pm$ 1.6	8.8 - 16.9
Hematocrit (%)	40.0 $\pm$ 4.7	27 - 51.6
Creatinine (mg/dL)	1.34 $\pm$ 0.81	0.39 - 5.54
Potassium (mEq/L)	4.2 $\pm$ 0.6	3.2 - 5.7
Sodium (mEq/L)	138 $\pm$ 2	133 - 142
Carbon Dioxide (mEq/L)	27 $\pm$ 3	21 - 40
Calcium (mg/dL)	9.4 $\pm$ 0.5	8.5 - 10.6
Blood Urea Nitrogen (mg/dL)	23 $\pm$ 11	10 - 50
Glucose (mg/dL)	130 $\pm$ 66	79 - 407

Data presented as mean $\pm$ standard deviation.

Table 9. Summary of Results from Right Heart Catheterization Procedure.

	Mean ± SD	Range
Systolic Pulmonary Artery Pressure (mm Hg)	45 ± 13	10 - 77
Diastolic Pulmonary Artery Pressure (mm Hg)	20 ± 7	7 - 38
Mean Pulmonary Artery Pressure (mm Hg)	31 ± 10	7 - 51
Pulmonary Capillary Wedge Pressure (mm Hg)*	19 ± 8	5 - 36
Systolic Right Ventricular Pressure (mm Hg)	46 ± 11	26 - 77
Diastolic Right Ventricular Pressure (mm Hg)	7 ± 3	-1 - 16
Systolic Right Atrial Pressure (mm Hg)*	12 ± 4	4 - 28
Diastolic Right Atrial Pressure (mm Hg)†	11 ± 5	3 - 28
Mean Right Atrial Pressure (mm Hg)	9 ± 5	1 - 24
Arterial Saturation (%)	94 ± 3	89 - 99
Venous Saturation (%)	59 ± 7	39 - 70
Arterial Oxygen Content (mL O_2/L)	170.1 ± 21.3	110.1 - 220.8
Venous Oxygen Content (mL O_2/L)	106.0 ± 18.5	59.9 - 152.8

*Data was not recorded for 2 patients. †Data was not recorded for 1 patient

Table 10. Summary of Gas Exchange Results.

	Mean ± SD	Range
Oxygen Consumption (ml/min)	229.7 ± 57.5	142 - 382
Oxygen Consumption (ml/kg/min)	2.80 ± 0.61	1.64 - 4.81
Respiratory Exchange Ratio	0.82 ± 0.07	0.64 - 1.07
Heart Rate (beats/min)	73 ± 12	54 - 105
Respiratory Rate (breaths/min)	16 ± 4	9 - 26
Tidal Volume (ml)	532 ± 224	307 -1620
Ventilation (L/min)	8.4 ± 2.9	4.6 - 17.5
Partial Pressure of End-Tidal Carbon Dioxide (mm Hg)	33 ± 5	22 – 45
Ventilatory Equivalent for Carbon Dioxide	44.2 ± 6.6	30.6 - 58.8

All ventilatory data was derived from breath-by-breath averaged over last 5 minutes of data collection. Heart rate was recorded every 15 seconds and averaged over the last 5 minutes of data collection.

Primary Aim 1

Figures 5-7 are the Bland-Altman plots of the difference between the estimated and the measured VO_2. The mean difference and the mean difference $\pm$ 1.96SD are highlighted on each figure. The mean difference is indicative of bias in the estimate and the mean difference $\pm$ 1.96SD provides the limits of agreement. Additionally, a best fit linear trend line was added to each plot in order to highlight the trend of overestimation of lower VO_2 and underestimation of higher VO_2.

Figure 5. Bland-Altman Plot of the Percent Error of the Resting Oxygen Consumption Estimated by the Lafarge & Miettinen Equation. (dashed gray line is 0 ml/min difference reference; gray solid line is best fit linear trend)

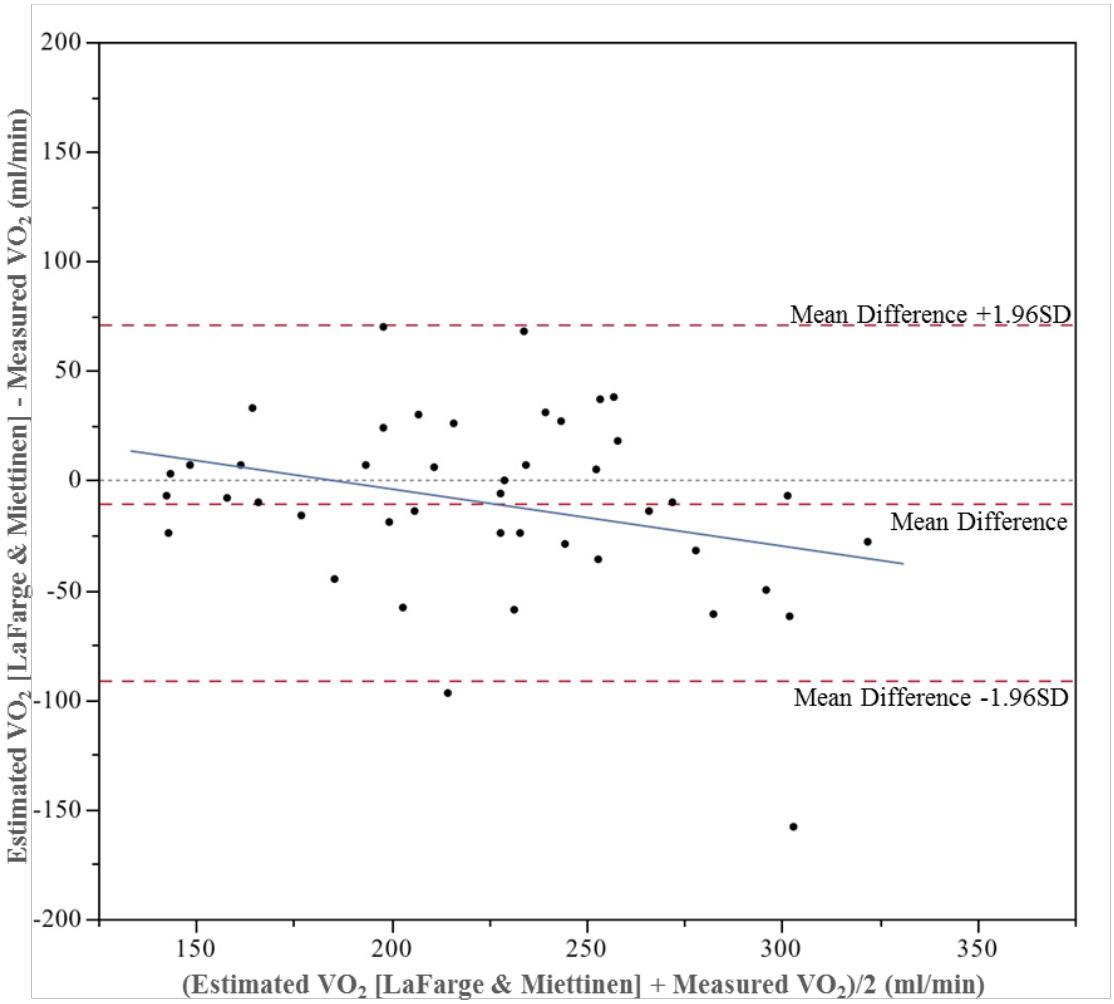


Figure 6. Bland-Altman Plot of the Percent Error of the Resting Oxygen Consumption Estimated by the Dehmer et al. Equation. (dashed gray line is 0 ml/min difference reference; gray solid line is best fit linear trend)

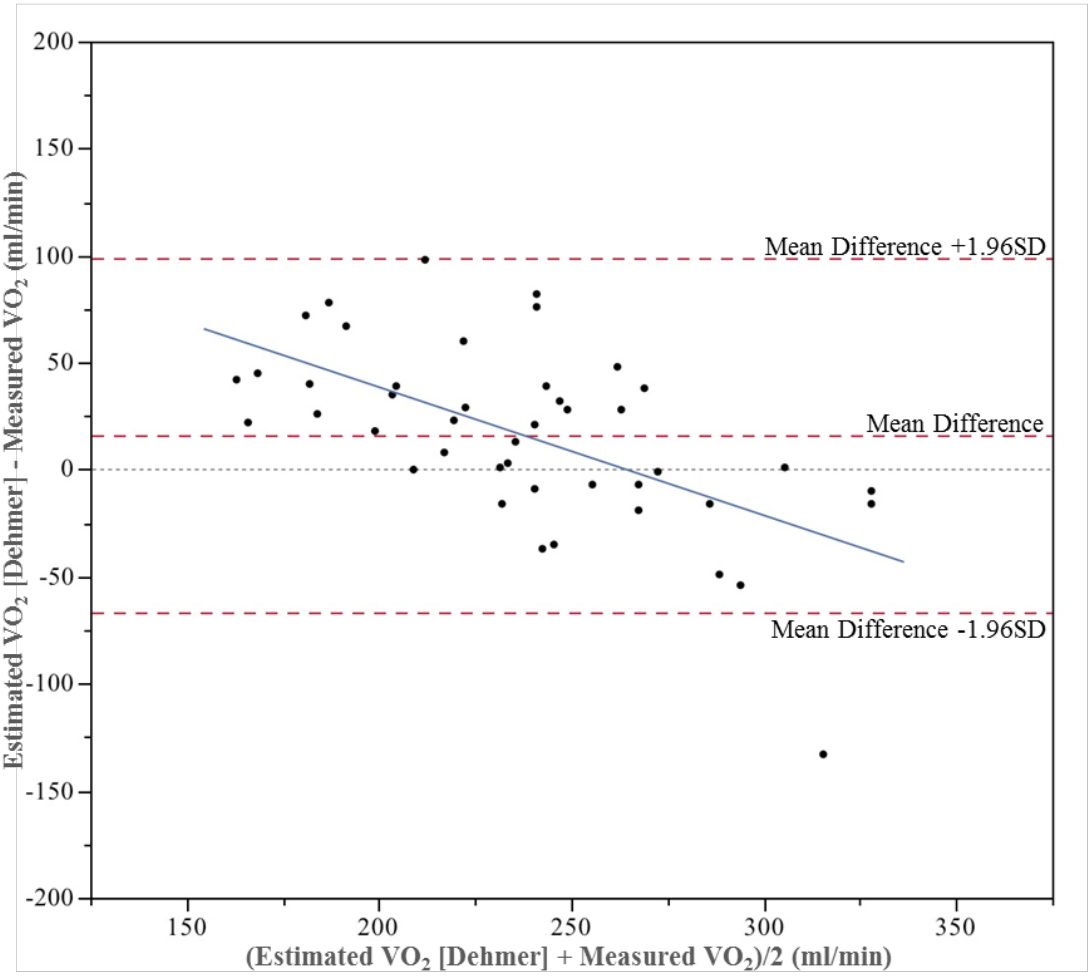
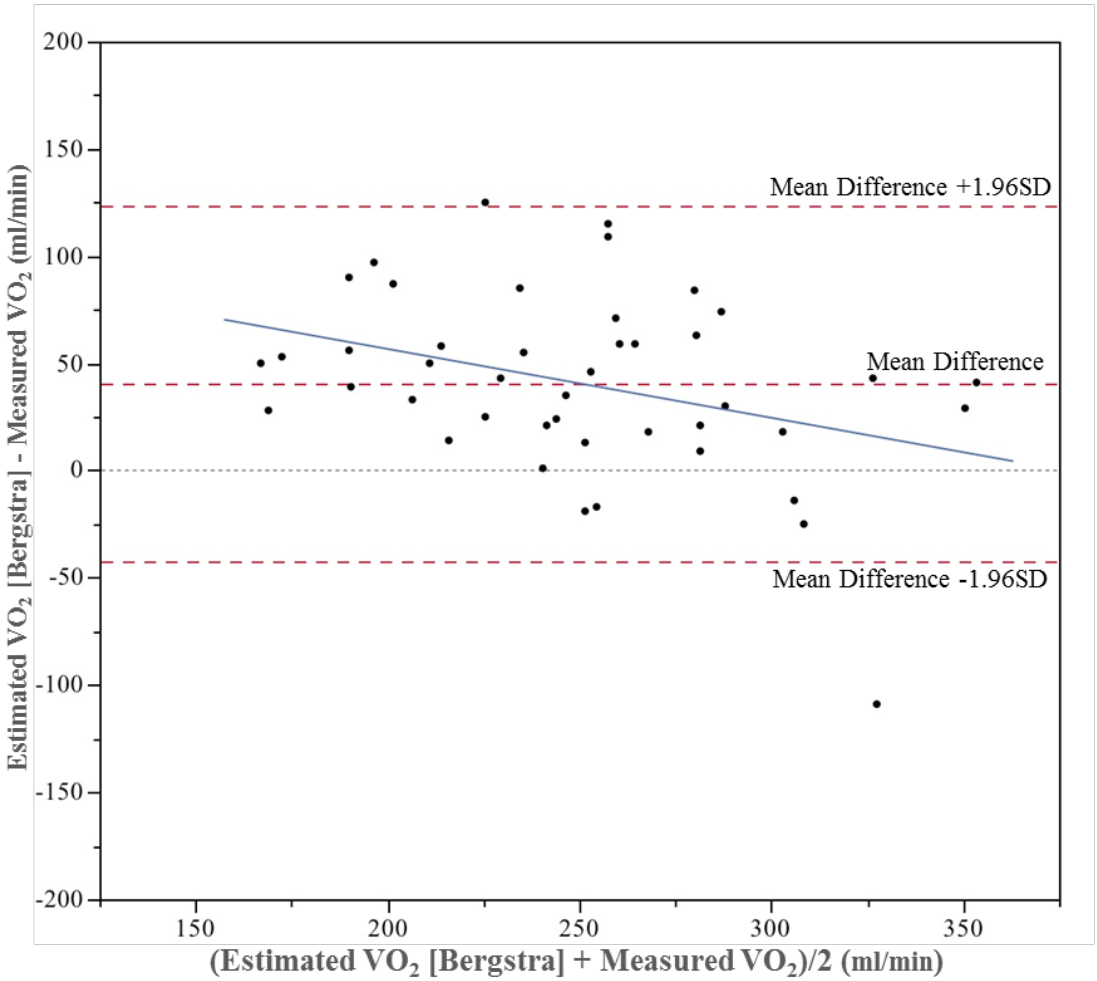


Figure 7. Bland-Altman Plot of the Percent Error of the Resting Oxygen Consumption Estimated by the Bergstra et al. Equation. (dashed gray line is 0 ml/min difference reference; gray solid line is best fit linear trend)



In addition to the above Bland-Altman plots, additional plots were created (**Figures 8-10**) converting the differences between the estimated and the measured VO_2 into percent error of the estimation [*(estimated – measured)/measured*]. These more clearly evaluate the limits of agreement by setting the acceptable limits to ±25% of the measured VO_2. Again, the mean error and limits of agreement are highlighted (red dashed lines) as well as the hypothetical mean of 0% error and the acceptable ±25%

range (black dashed lines). These plots suggest the limits of agreement for each estimation equation are too large, as the limits of agreement for the estimation exceed the ±25% limits. The effect of the overestimation in the measurement of the Dehmer et al. and Bergstra et al. estimations (**Figures 9** and **10**, respectively) becomes prominent in these plots.

Figure 8. Bland-Altman Plot of the Percent Error of the Resting Oxygen Consumption Estimated by the Lafarge & Miettinen Equation. (Black dashed lines are 0% error, +25% error and -25% error)

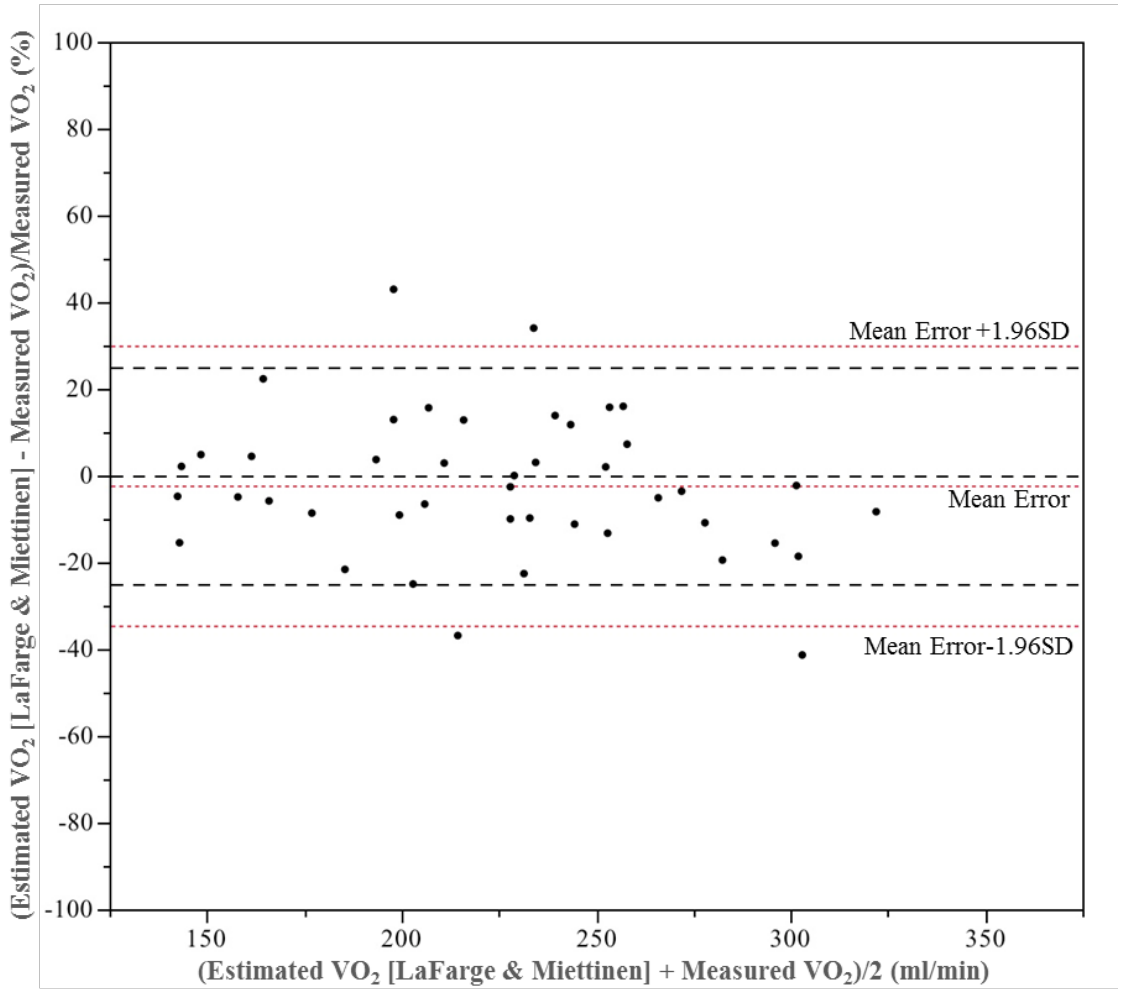


Figure 9. Bland-Altman Plot of the Percent Error of the Resting Oxygen Consumption Estimated by the Dehmer et al. Equation. (Black dashed lines are 0% error, +25% error and -25% error)

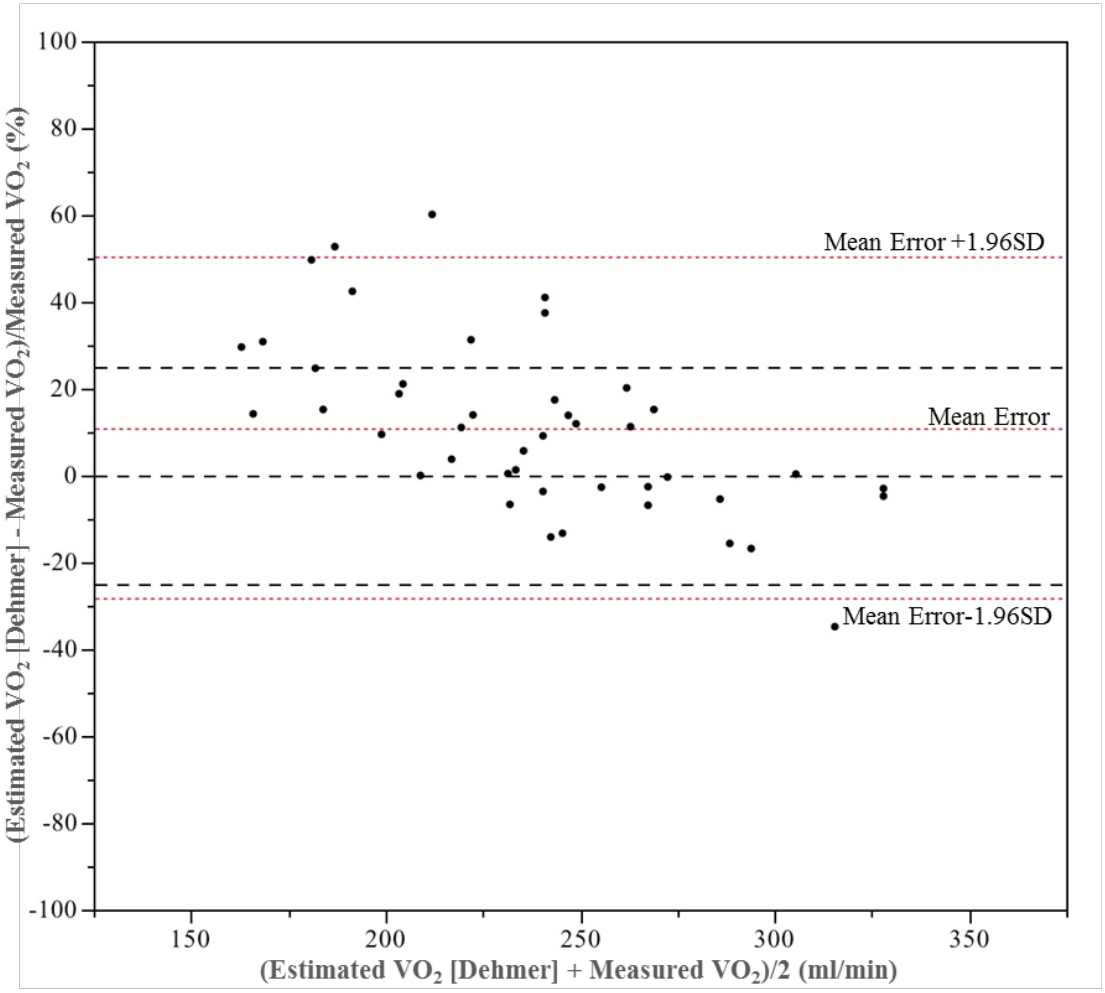
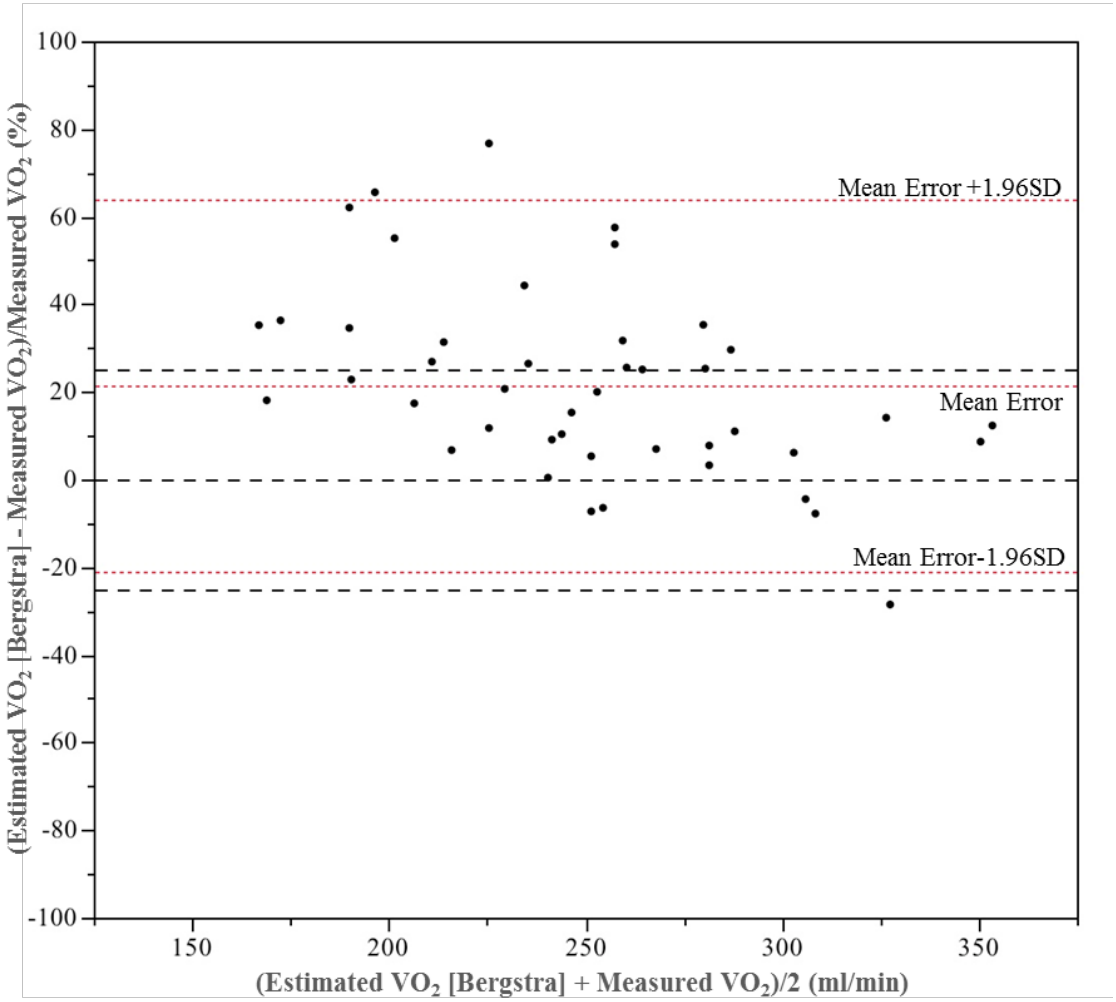


Figure 10. Bland-Altman Plot of the Percent Error of the Resting Oxygen Consumption Estimated by the Bergstra et al. Equation. (Black dashed lines are 0% error, +25% error and -25% error)



The results of the single-sample *t*-tests comparing the mean of differences against the hypothetical mean difference of zero can be found in **Table 11**. The estimation equations of Dehmer et al. and Bergstra et al. result in a significant overestimation of resting VO_2 ($p<0.05$). However, the estimation of LaFarge & Miettinen underestimated the resting VO_2, but did not reach significance.

Table 11. Overall and Sub-group Comparisons of the Estimation of Oxygen Consumption by Each of the Estimation Equations and the Measured Oxygen Consumption.

		LaFarge & Miettinen			Dehmer et al.			Bergstra et al.		
	Measured VO_2 ±SD (ml/min)	Estimated VO_2 ±SD (ml/min)	Difference ± SE (ml/min)	p-value	Estimated VO_2 ±SD (ml/min)	Difference ± SE (ml/min)	p-value	Estimated VO_2 ±SD (ml/min)	Difference ± SE (ml/min)	p-value
Overall group (n=44)	229.7 ± 57.5	219.4 ± 46.0	-10.3 ± 6.2	0.053	245.7 ± 34.1	16.0 ± 6.4	0.008*	270.3 ± 43.8	40.6 ± 6.4	<0.001*
Secondary Aim to Aim 1 Sub-Group Analyses										
Gender										
Male (n=29)	249.9 ± 49.1	242.7 ± 30.1	-7.2 ± 8.2	0.195	256.3 ± 27.4	6.4 ± 8.2	0.220	283.5 ± 35.4	33.6 ± 8.5	<0.001*
Female (n=15)	190.6 ± 53.3	174.3 ± 37.2	-16.3 ± 9.2	0.048*	225.1 ± 37.2	34.5 ± 8.3	<0.001*	244.8 ± 48.1	54.2 ± 8.3	<0.001*
Pulmonary Hypertension										
Yes (n=32)	238.1 ± 59.2	226.4 ± 43.8	-11.6 ± 7.2	0.058	247.7 ± 36.3	9.6 ± 7.4	0.900	272.9 ± 46.8	34.8 ± 7.3	<0.001*
No (n=12)	207.3 ± 48.0	200.5 ± 48.4	-6.8 ± 12.9	0.304	240.2 ± 28.2	32.8 ± 11.7	0.009*	263.4 ± 35.3	56.1 ± 12.1	<0.001*
Aldosterone Antagonist										
Prescribed (n=14)	261.4 ± 60.8	236.7 ± 35.0	-24.7 ± 14.5	0.056	256.6 ± 34.5	-4.8 ± 14.1	0.369	285.0 ± 44.7	23.6 ± 14.6	0.065
Not Prescribed (n=30)	214.9 ± 50.3	211.3 ± 48.8	-3.6 ± 6.0	0.276	240.5 ± 33.3	25.7 ± 6.1	<0.001*	263.1 ± 42.3	48.6 ± 6.1	<0.001*

Differences were determined by Estimated VO_2 - Measured VO_2.*significance considered when $p<0.05$.

LaFarge and Miettinen: (Male) $VO_2 = (138.1-(11.49*\ln(age)*0.378*HR))*body\ surface\ area$; (Female) $VO_2 = (138.1-(17.04*\ln(age)*0.378*HR))*body\ surface\ area$

Dehmer et al.: $VO_2 = 125*BSA$

Bergstra et al.: (Male) $VO_2 = (157.3*body\ surface\ area)+10-(10.5*\ln(age))+4.8$; (Female) $VO_2 = (157.3*body\ surface\ area)-(10.5*\ln(age))+4.8$

Secondary Aim to Aim 1

Patients were dichotomized based on several select characteristics from **Tables 6, 7** and **9**. The results of the unmatched pair *t*-tests of the mean measured VO_2 for each dichotomization (resulting in $\geq$10 patients in each group) can be found in **Table 12**. As can be seen males, patients with pulmonary hypertension, and those prescribed aldosterone inhibitors were found to have significantly higher resting VO_2 than their respective counterpart.

It was noted in the demographic data that BMI, race, New York Heart Association class, smoking habit, diabetes and cardiac rhythm management (presence of a pacemaker or ICD) could be stratified into more than two groupings. However, only BMI and smoking habit could be divided into sub-groups of at least 10 patients each (**Table 13**). Analysis of variation was performed with no significance found ($p>0.05$).

Table 12. Comparisons of Differences in Measured Oxygen Consumption among Dichotomous Groups.

	Measured VO_2 ±SD (ml/min)	Mean Difference ±SE (ml/min)	p-value
Gender			
Male (n=29)	249.9 ± 49.1		
Female (n=15)	190.6 ± 53.3	59.3 ± 16.1	<0.001*
Race			
White/Caucasian (n=29)	236.6 ± 50.6		
Non-White/Caucasain (n=15)	216.4 ± 68.9	20.2 ± 20.1	0.164
Body Mass Index			
≥ 30 kg/m^2	240.0 ± 58.4		
<30 kg/m^2	221.1 ± 56.5	18.9 ± 17.4	0.142
Heart Failure Etiology			
Ischemic (n=15)	239.7 ± 57.6		
Non-Ischemic (n=29)	224.5 ± 57.8	15.1 ± 18.3	0.208
New York Heart Association Class			
II-III (n=30)	228.3 ± 53.1		
IIIb-IV (n=14)	232.6 ± 68.0	-4.3 ± 20.6	0.418
Diabetes			
No (n=29)	236.3 ± 60.0		
Yes (n=15)	216.9 ± 51.8	19.4 ± 17.4	0.136
Smoking History			
Current/Former (n=25)	233.6 ± 63.0		
Never Smoked (n=19)	224.5 ± 50.6	9.2 ± 17.1	0.298
Cardiac Rhythm Management			
ICD/PPM/CRT (n=23)	239.0 ± 60.7		
No Device (n=21)	219.5 ± 53.3	19.5 ± 17.2	0.131
Pulmonary Hypertension			
Yes (n=32)	238.1 ± 59.2		
No (n=12)	207.3 ± 48.0	30.7 ± 17.4	0.045*
Beta-Blocker			
Prescribed (n=34)	227.4 ± 53.2		
Not Prescribed (n=10)	237.3 ± 72.9	-9.9 ± 24.8	0.651
Angiotensin Converting Enzyme Inhibitor			
Prescribed (n=24)	231.8 ± 54.4		
Not Prescribed (n=20)	227.2 ± 62.3	4.6 ± 17.8	0.400
Angiotensin Receptor Blocker			
Prescribed (n=12)	238.2 ± 71.6		
Not Prescribed (n=32)	226.5 ± 52.2	11.7 ± 22.6	0.307
Loop Diuretic			
Prescribed (n=31)	236.9 ± 62.7		
Not Prescribed (n=13)	212.5 ± 39.8	24.3 ± 15.8	0.066
Aldosterone Antagonist			
Prescribed (n=14)	261.4 ± 60.8		
Not Prescribed (n=30)	214.9 ± 50.3	46.6 ± 18.7	0.010*

Dichotmous groups consisting of at least 10 patients per sub-group were selected from Tables 6 & 7 (except pulmonary hypertension, which was dervied from individual catheterization results). *significance considered when $p<0.05$.

Table 13. Comparisons of Differences in Measured Oxygen Consumption among Grouping Variables with more than Two Sub-groups.

	Measured VO_2 $\pm$SD (ml/min)	Mean Square Difference	p-value
Body Mass Index			
<25 kg/m^2 (n=14)	218.8 $\pm$ 61.7		
25-29.9 kg/m^2 (n=10)	224.3 $\pm$ 51.3		
$\geq$30 kg/m^2 (n=20)	240.0 $\pm$ 58.4	2040.5	0.550
Smoking History			
Never (n=19)	224.5 $\pm$ 50.6		
Current (n=10)	232.9 $\pm$ 65.3		
Former (n=15)	234.1 $\pm$ 63.7	458.1	0.876

From Tables 6, variables were chosen based on having $\geq$10 patients in each sub-group and could be divided into >2 sub-groups. Significance was considered when $p<0.05$.

Table 11 also contains the individual sub-group results of the paired-sample *t*-tests of the differences between the measured VO_2 and the estimated VO_2 by each estimation equation for selected patient characteristics. Males have no significant mean difference between the estimated and measured for the LaFarge & Miettinen equation and the Dehmer et al. equation, whereas females were found to be significantly underestimated by the LaFarge & Miettinen equation ($p=0.048$) and overestimated by the Dehmer et al. equation ($p<0.001$). The Dehmer et al. equation resulted in a significant overestimation in those without pulmonary hypertension ($p=0.003$). The Dehmer et al. equation also resulted in a significant overestimation for those patients not prescribed aldosterone antagonist medications ($p<0.001$). The Bergstra et al. estimations resulted in significant mean differences (overestimations) at all levels of dichotomization, except for those patients that were prescribed aldosterone antagonist medications ($p=0.065$).

Figures 11-19 are the Bland-Altman plots of the error of each of the estimation equations for each dichotomized variable (sex, post-capillary pulmonary hypertension, and prescribed aldosterone antagonist). The points and limit of agreement lines are color-coded for each sub-group within each dichotomous variable. Color-matched range arrows were added to highlight the limits of agreement for each sub-group. As can easily be seen no sub-group within each variable have limits of agreement contained inside the acceptable limits of agreement (black dashed line) of $\pm$25% error.

Figure 11. Bland-Altman Plot (by Sex) of the Percent Error of the Resting Oxygen Consumption Estimated by the LaFarge & Miettinen Equation.

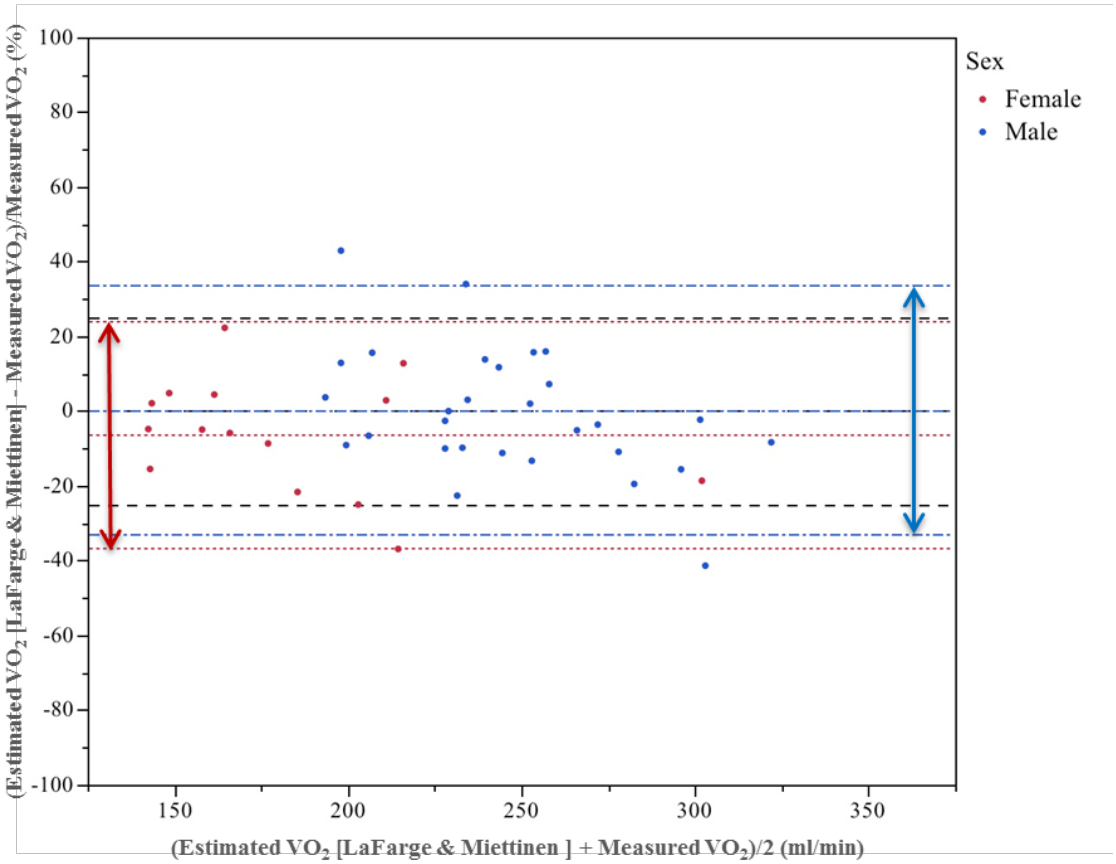


Figure 12. Bland-Altman Plot (by Sex) of the Percent Error of the Resting Oxygen Consumption Estimated by the Dehmer et al. Equation.

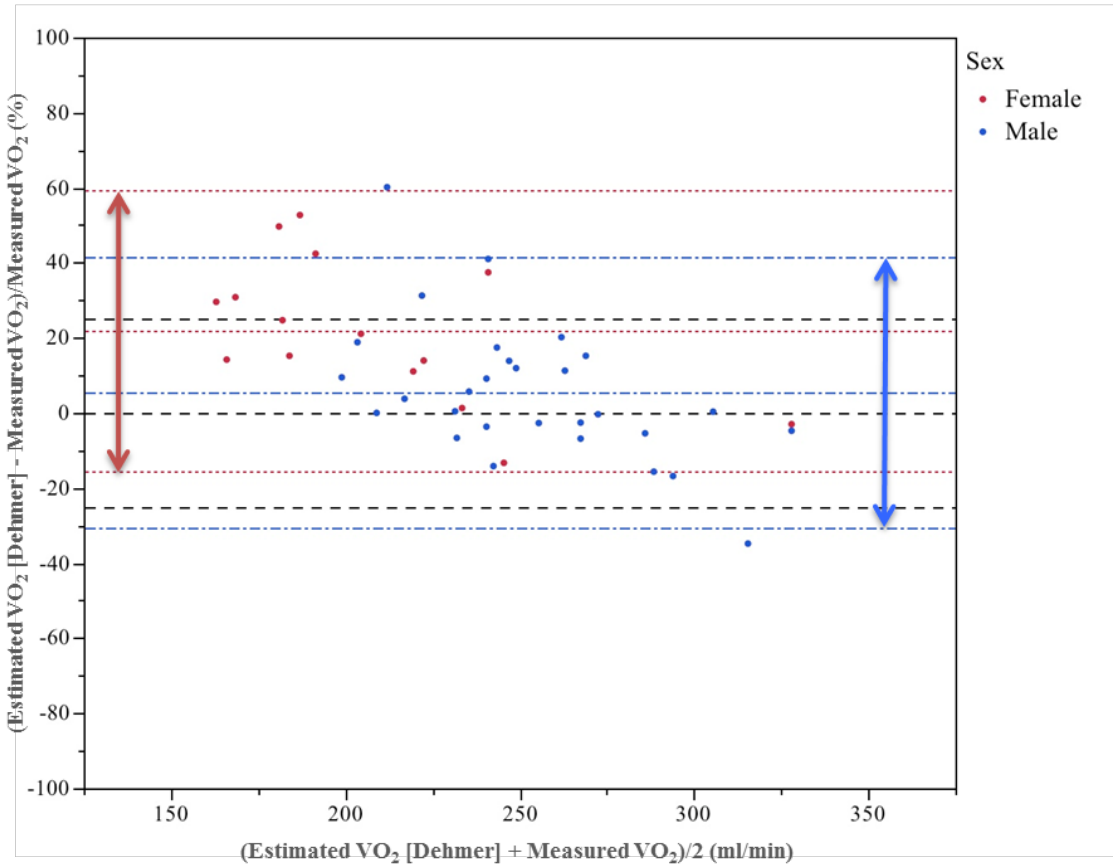


Figure 13. Bland-Altman Plot (by Sex) of the Percent Error of the Resting Oxygen Consumption Estimated by the Bergstra et al. Equation.

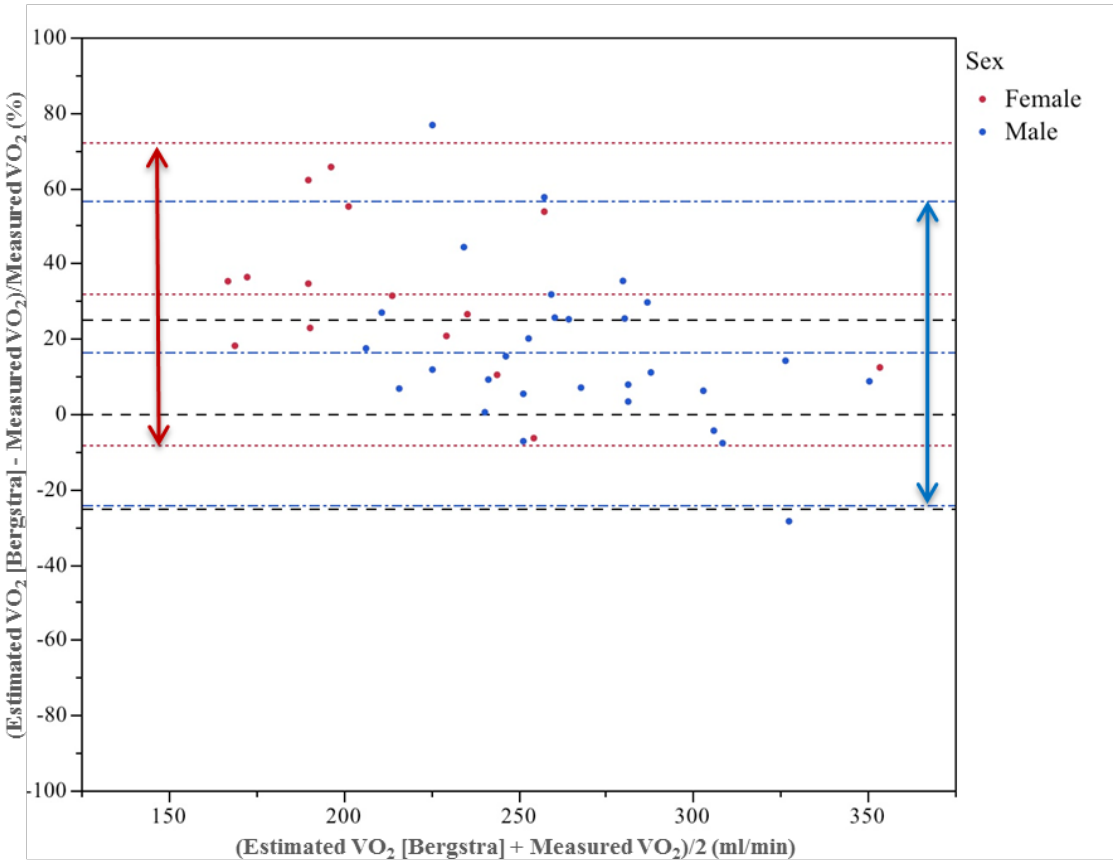


Figure 14. Bland-Altman Plot (by Pulmonary Hypertension) of the Percent Error of the Resting Oxygen Consumption Estimated by the LaFarge & Miettinen Equation.

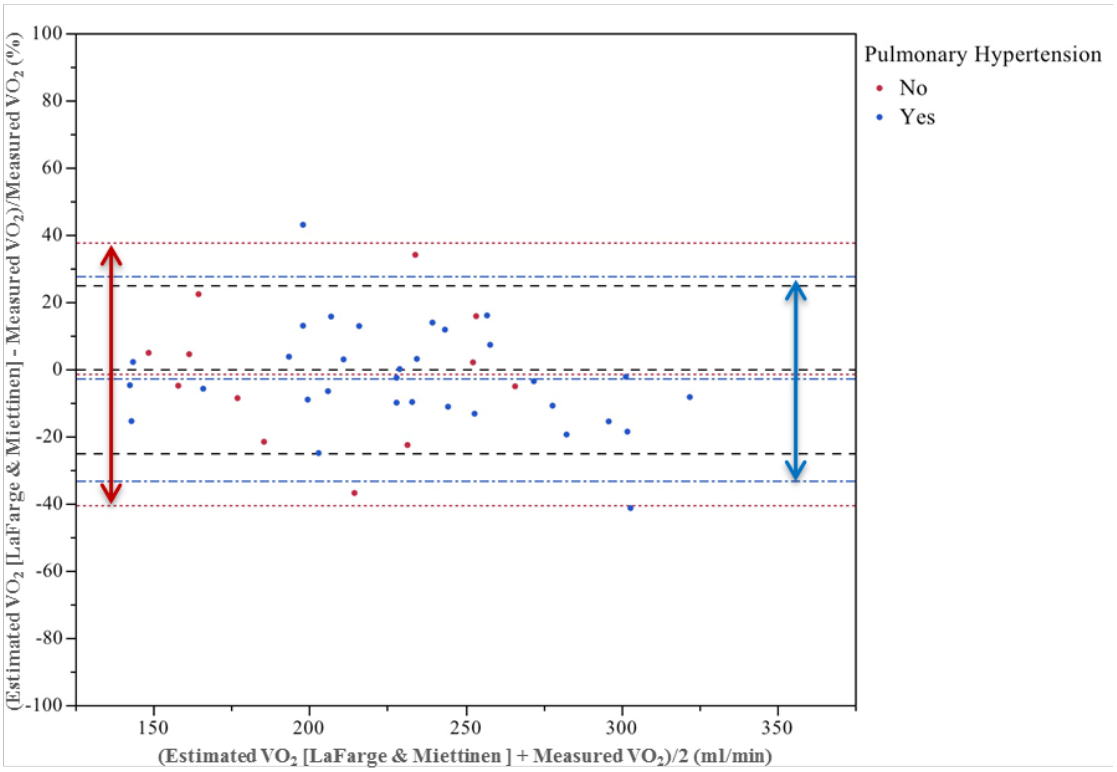


Figure 15. Bland-Altman Plot (by Pulmonary Hypertension) of the Percent Error of the Resting Oxygen Consumption Estimated by the Dehmer et al. Equation.

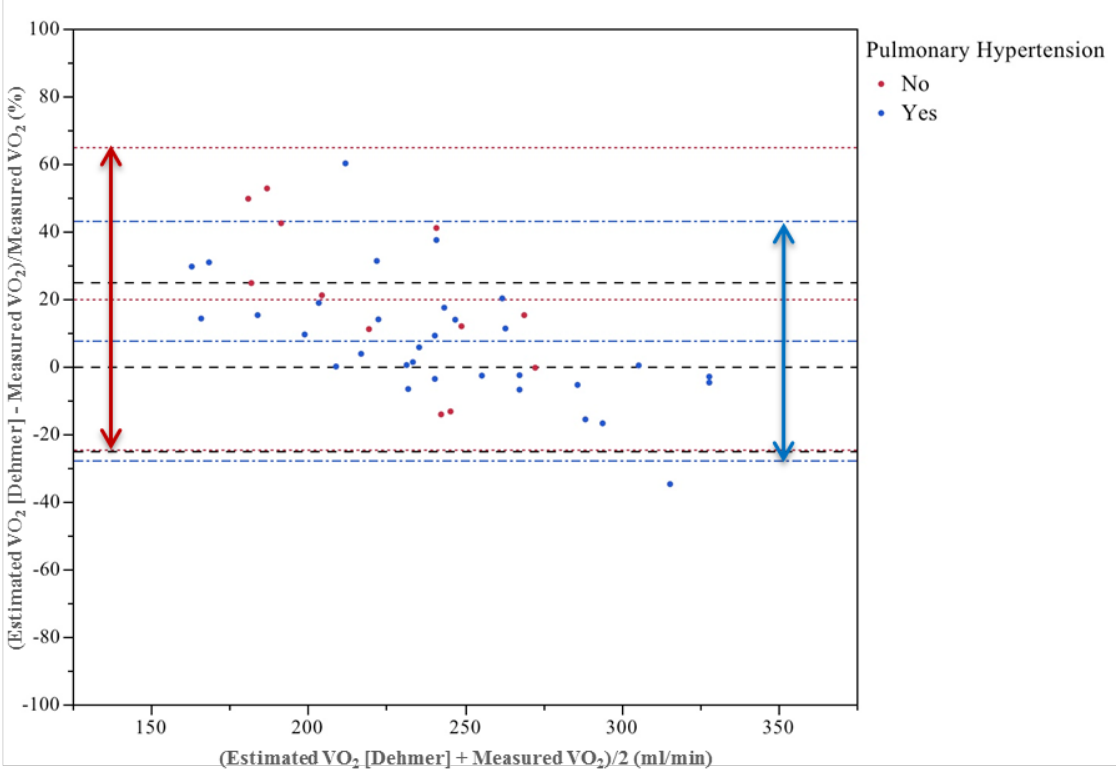


Figure 16. Bland-Altman Plot (by Pulmonary Hypertension) of the Percent Error of the Resting Oxygen Consumption Estimated by the Bergstra et al. Equation.

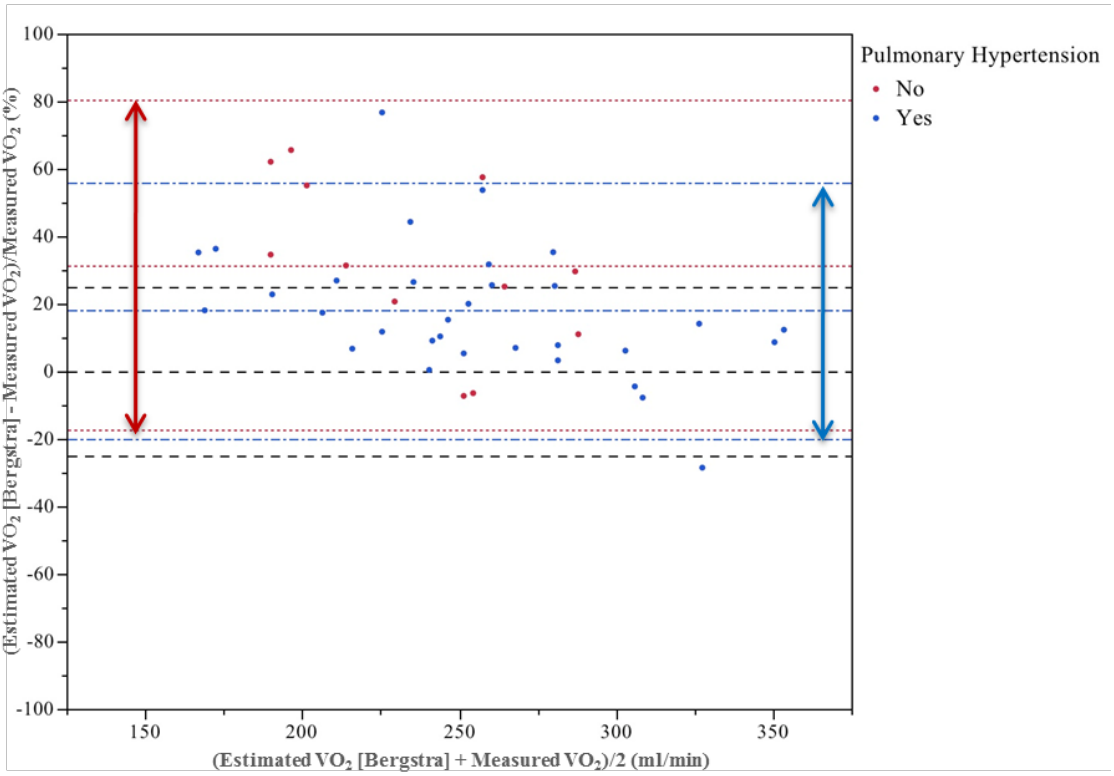


Figure 17. Bland-Altman Plot (by Aldosterone Antagonist) of the Percent Error of the Resting Oxygen Consumption Estimated by the LaFarge & Miettinen Equation.

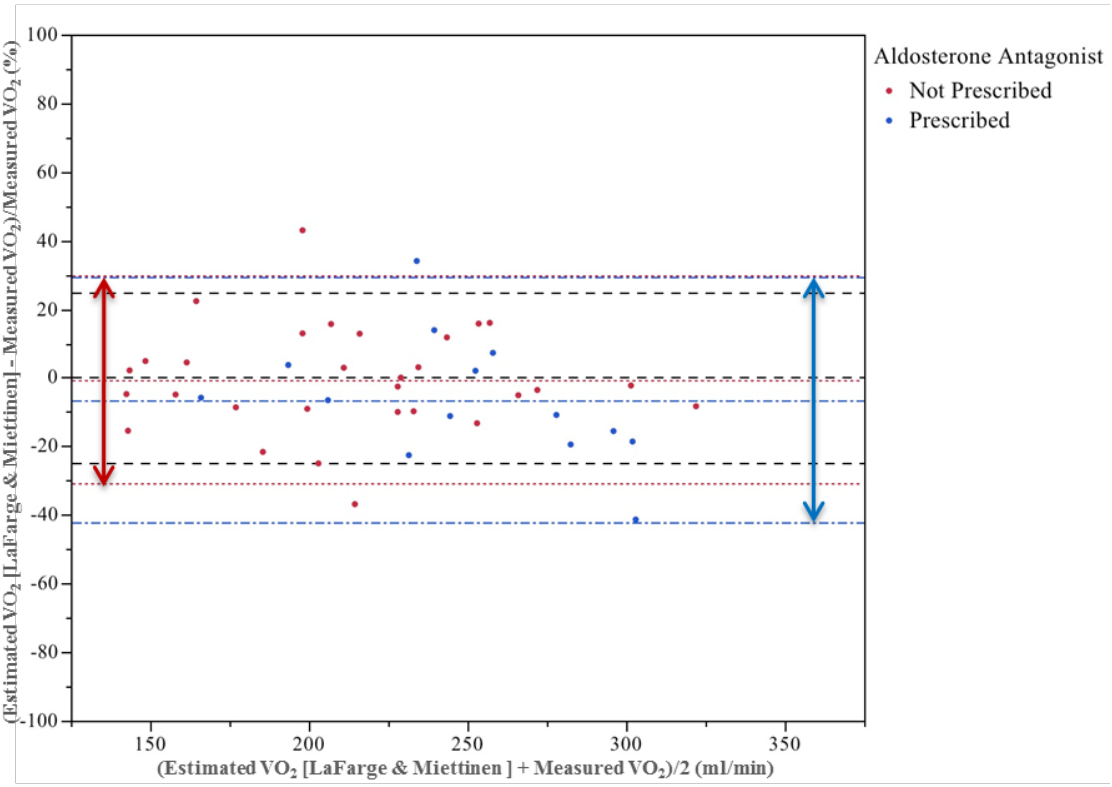


Figure 18. Bland-Altman Plot (by Aldosterone Antagonist) of the Percent Error of the Resting Oxygen Consumption Estimated by the Dehmer et al. Equation.

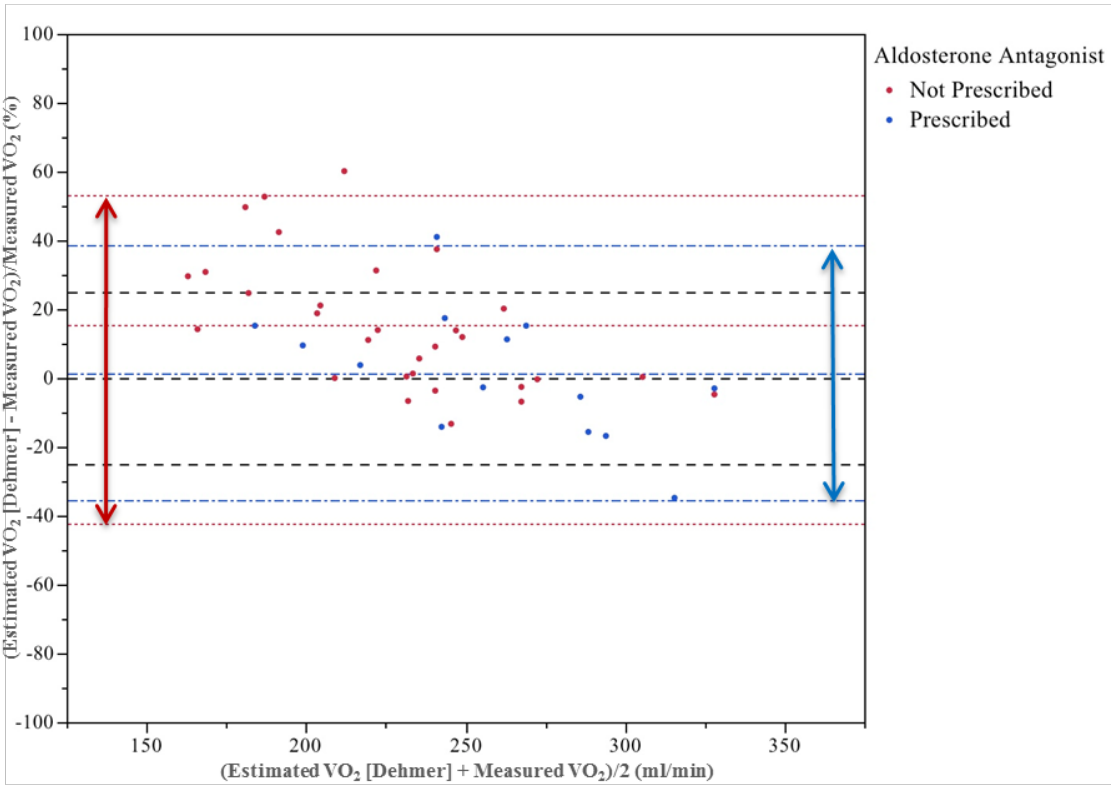
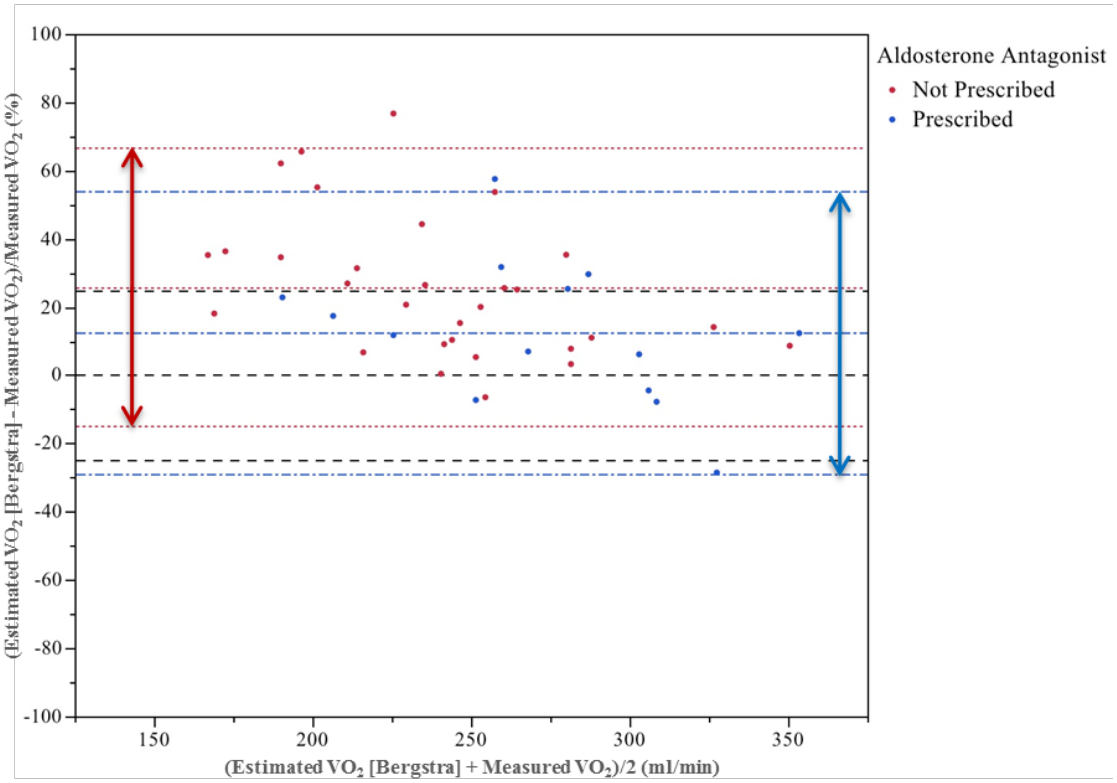


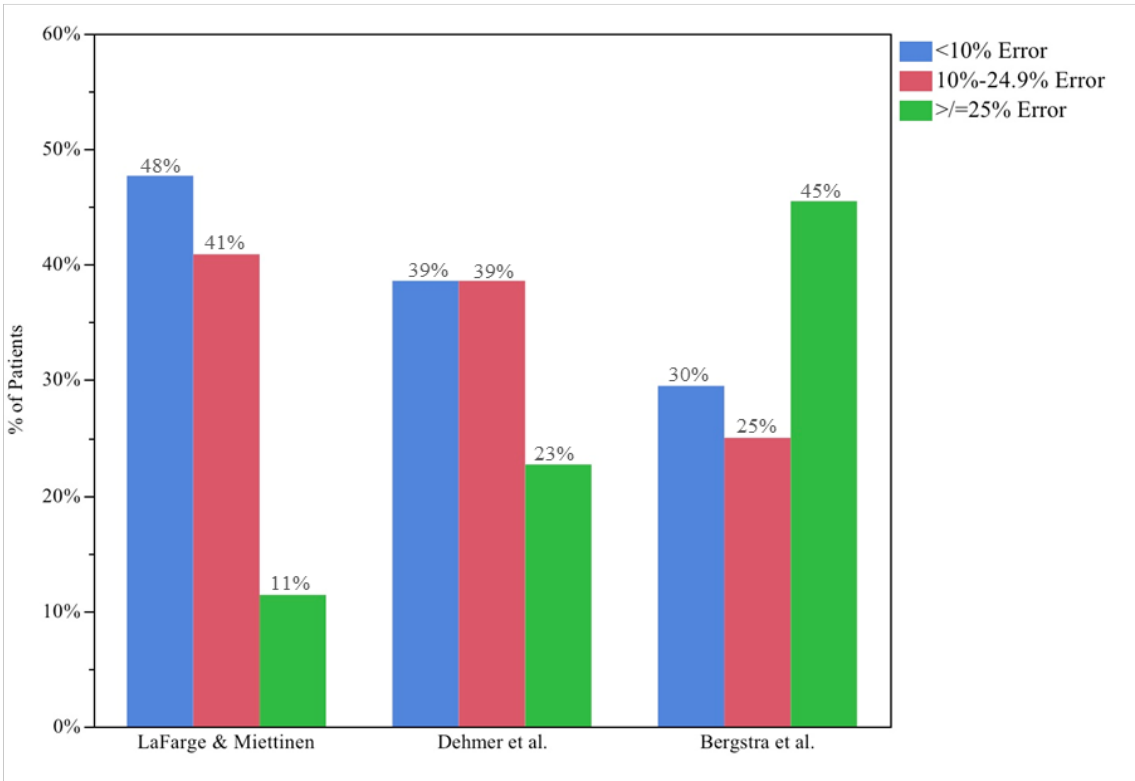
Figure 19. Bland-Altman Plot (by Aldosterone Antagonist) of the Percent Error of the Resting Oxygen Consumption Estimated by the Bergstra et al. Equation.



Primary Aim 2

For each of the estimation equations, **Figure 20** demonstrates the percentage of patients in each of three error categories (<10%, 10-24.9%, and ≥25%). Only 11.4% of patients fall into the ≥25% error category when using the estimation equation of LaFarge & Miettinen. However, the Bergstra et al. equation results in 45% of the patients with ≥25% absolute error in the resting VO_2.

Figure 20. Percentage of Patients with <10% Absolute Error, 10-24.9% Absolute Error and ≥25% Absolute Error for Each of the Three Estimation Equations.



Secondary Aim to Aim 2

The actual clinically significant errors in cardiac index for each of the estimation equations for various cut-offs can be found in **Figures 21-29**. All estimation equations have >15% of patients with clinically significant error at the cut-off for hypoperfusion (<2.2 L/min/m^2) and cardiogenic shock (<1.9 L/min/m^2). At the highest cut-off of low versus normal cardiac index (<2.6 L/min/m^2) only the estimation of Bergstra et al. had ≥15% of the patients with clinically significant error.

Figure 21. Clinically Significant Error in Determining Cardiogenic Shock by Cardiac Index Calculated by LaFarge & Miettinen Estimated versus by Measured Oxygen Consumption. (cardiac index <1.9 L/min/m^2)

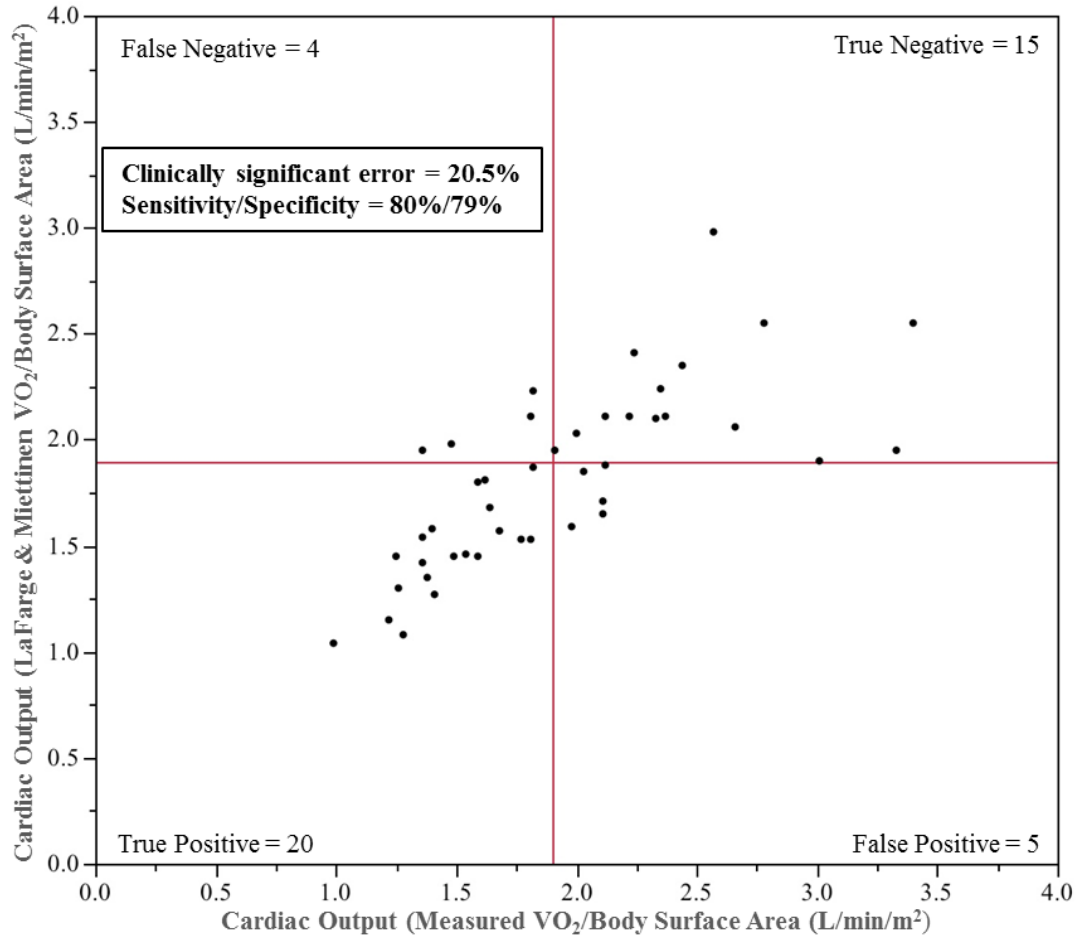


Figure 22. Clinically Significant Error in Determining Hypoperfusion by Cardiac Index Calculated by LaFarge & Miettinen Estimated versus by Measured Oxygen Consumption. (cardiac index <2.2 L/min/m^2)

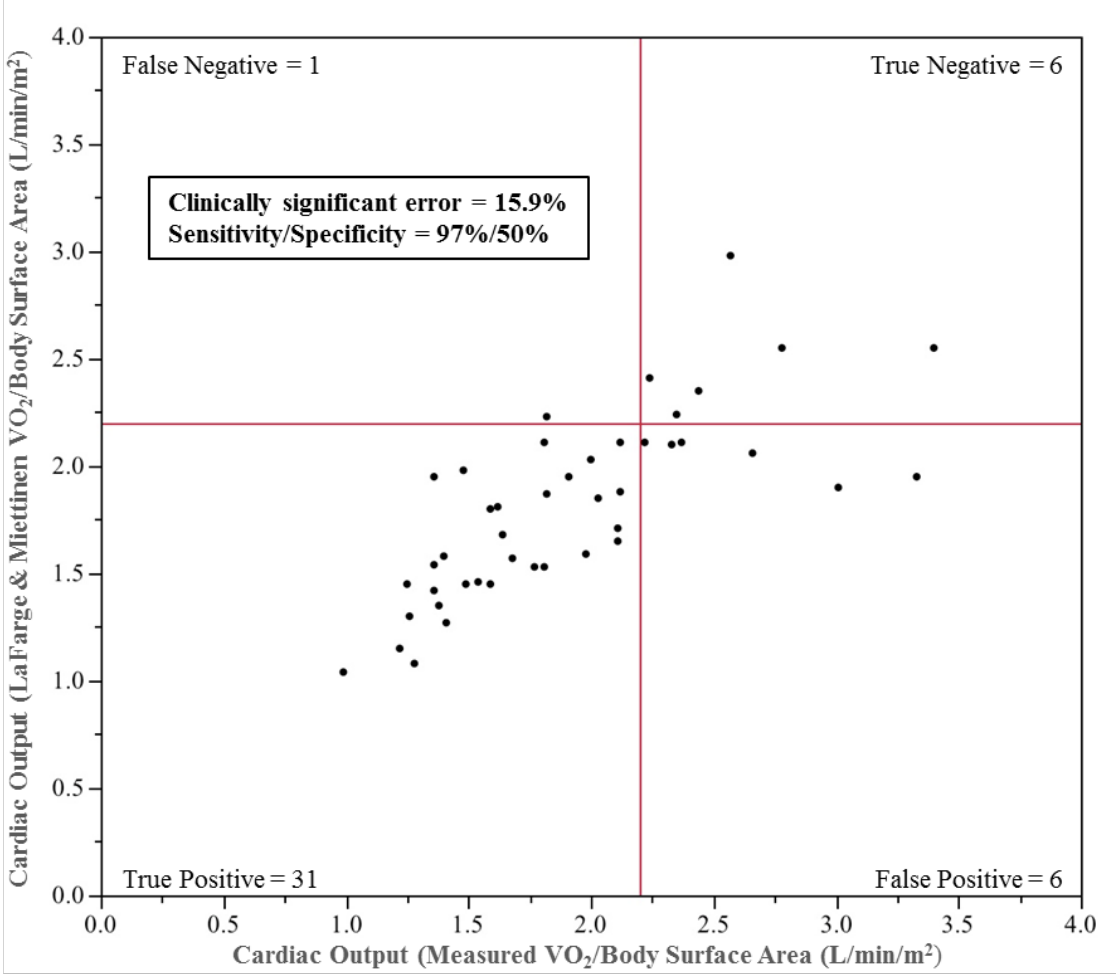


Figure 23. Clinically Significant Error in Determining Abnormal Cardiac Index Calculated by LaFarge & Miettinen Estimated versus by Measured Oxygen Consumption. (cardiac index <2.6 L/min/m^2)

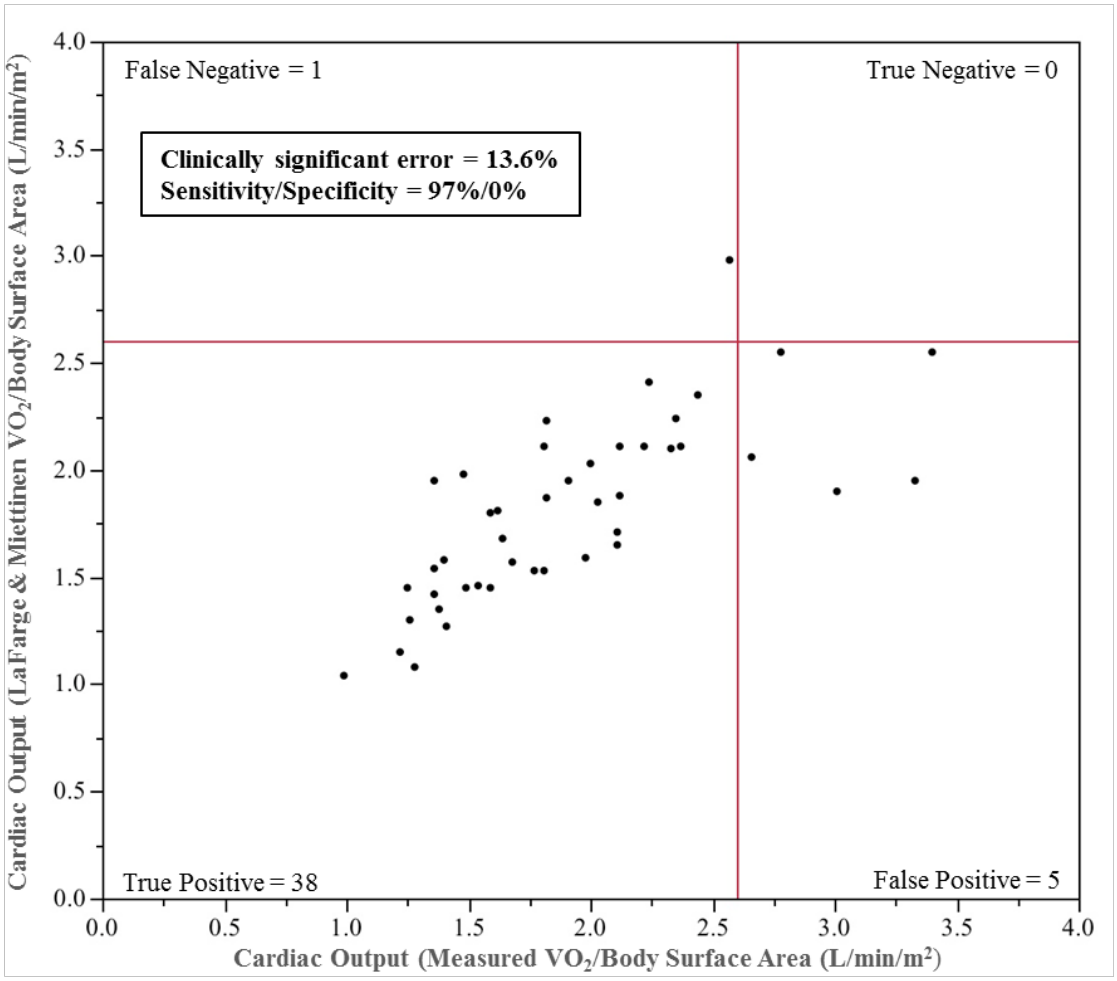


Figure 24. Clinically Significant Error in Determining Cardiogenic Shock by Cardiac Index Calculated by Dehmer et al. Estimated versus by Measured Oxygen Consumption. (cardiac index <1.9 L/min/m^2)

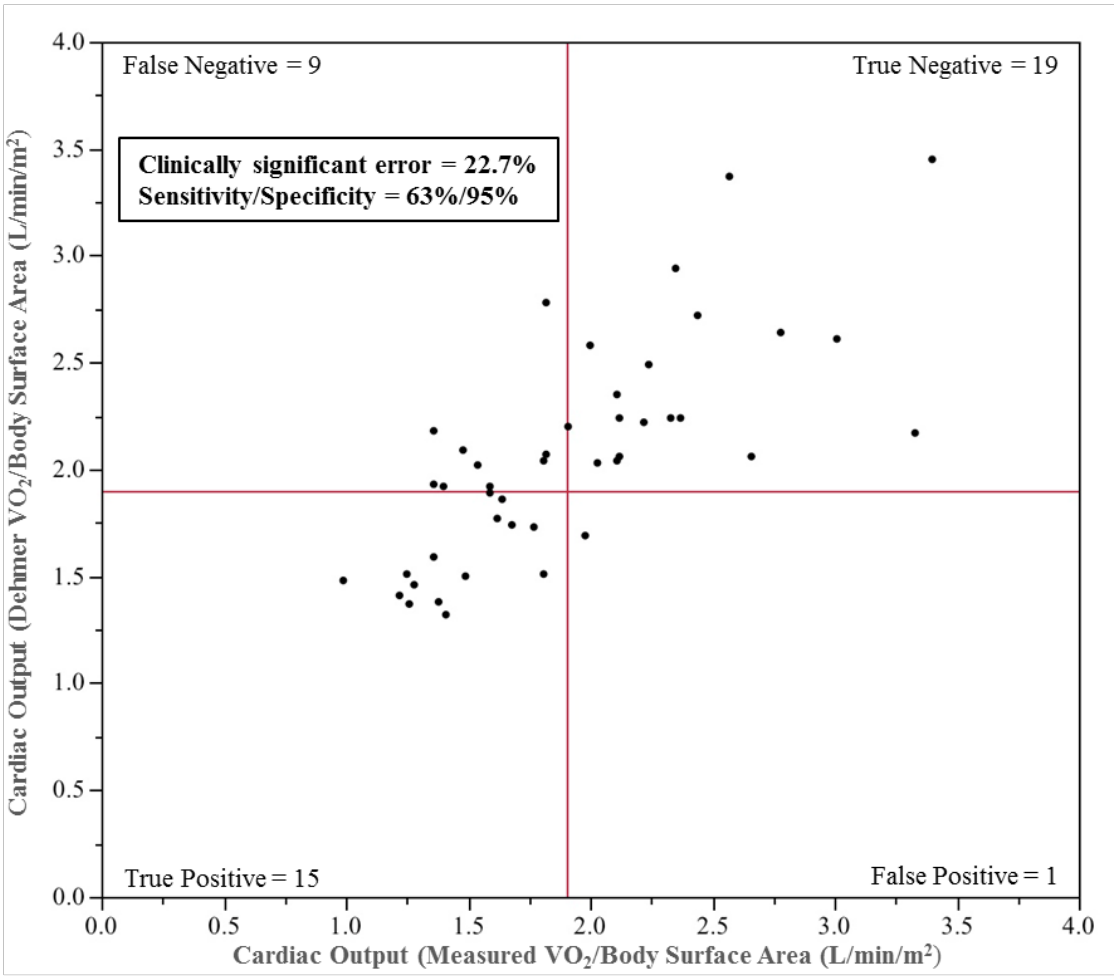


Figure 25. Clinically Significant Error in Determining Hypoperfusion by Cardiac Index Calculated by Dehmer et al. Estimated versus by Measured Oxygen Consumption. (cardiac index <2.2 L/min/m^2)

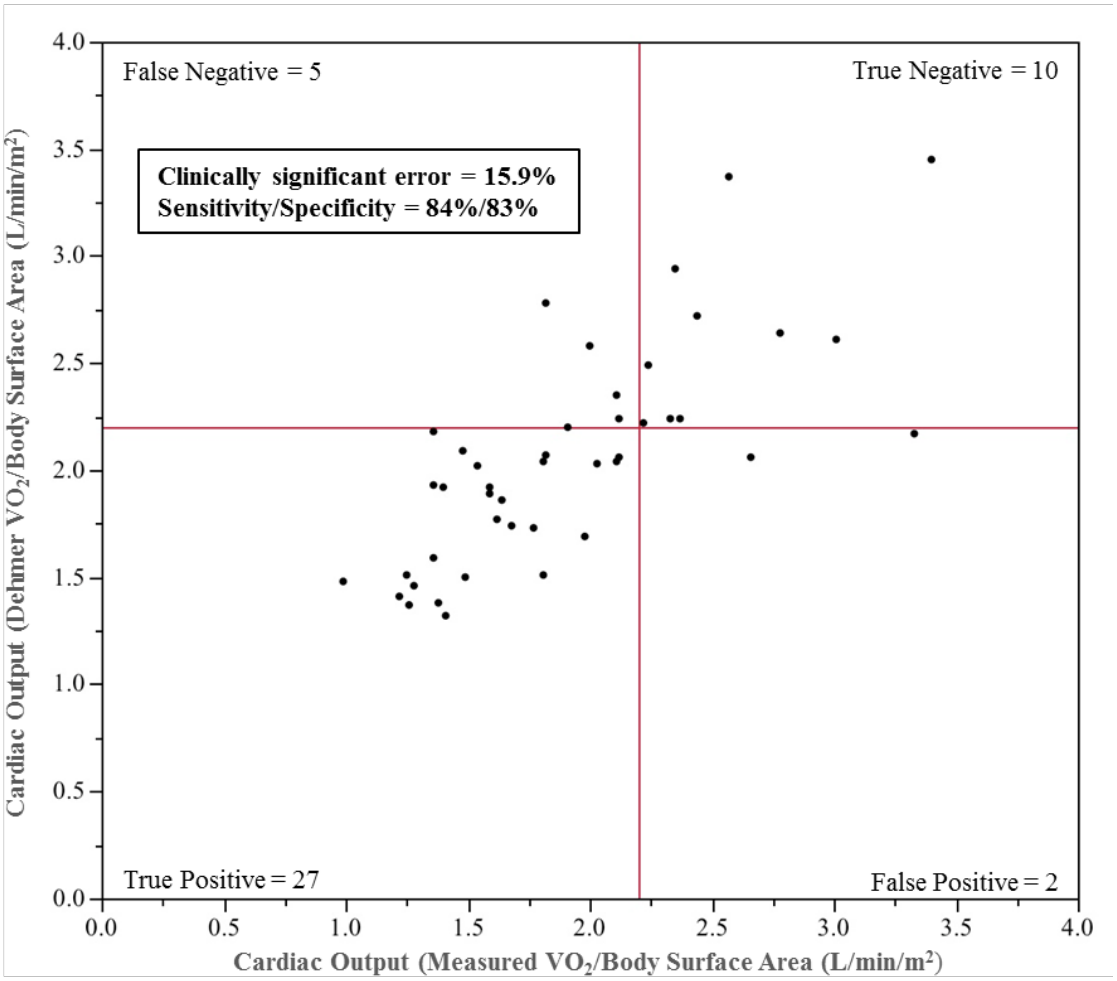


Figure 26. Clinically Significant Error in Determining Abnormal Cardiac Index Calculated by Dehmer et al. Estimated versus by Measured Oxygen Consumption. (cardiac index <2.6 L/min/m^2)

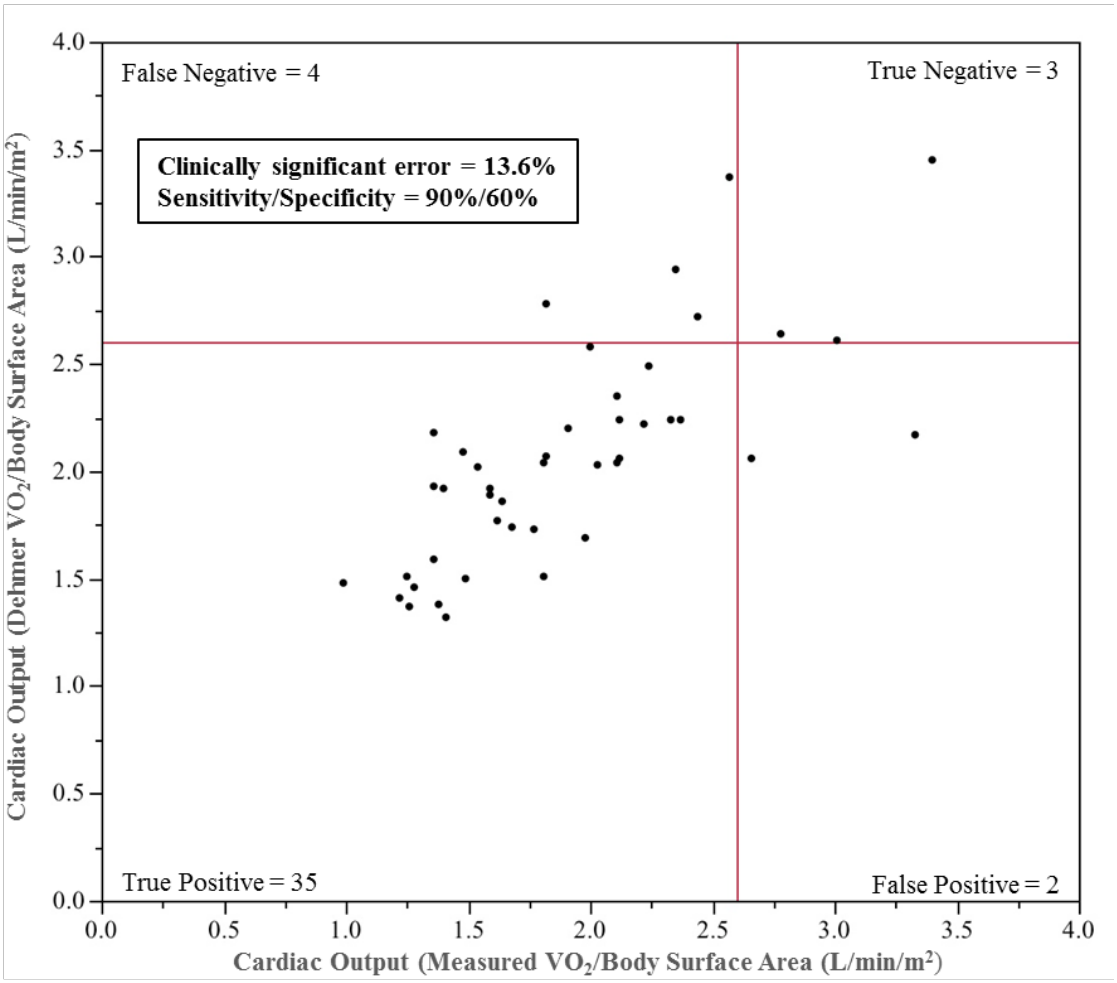


Figure 27. Clinically Significant Error in Determining Cardiogenic Shock by Cardiac Index Calculated by Bergstra et al. Estimated versus by Measured Oxygen Consumption. (cardiac index <1.9 L/min/m^2)

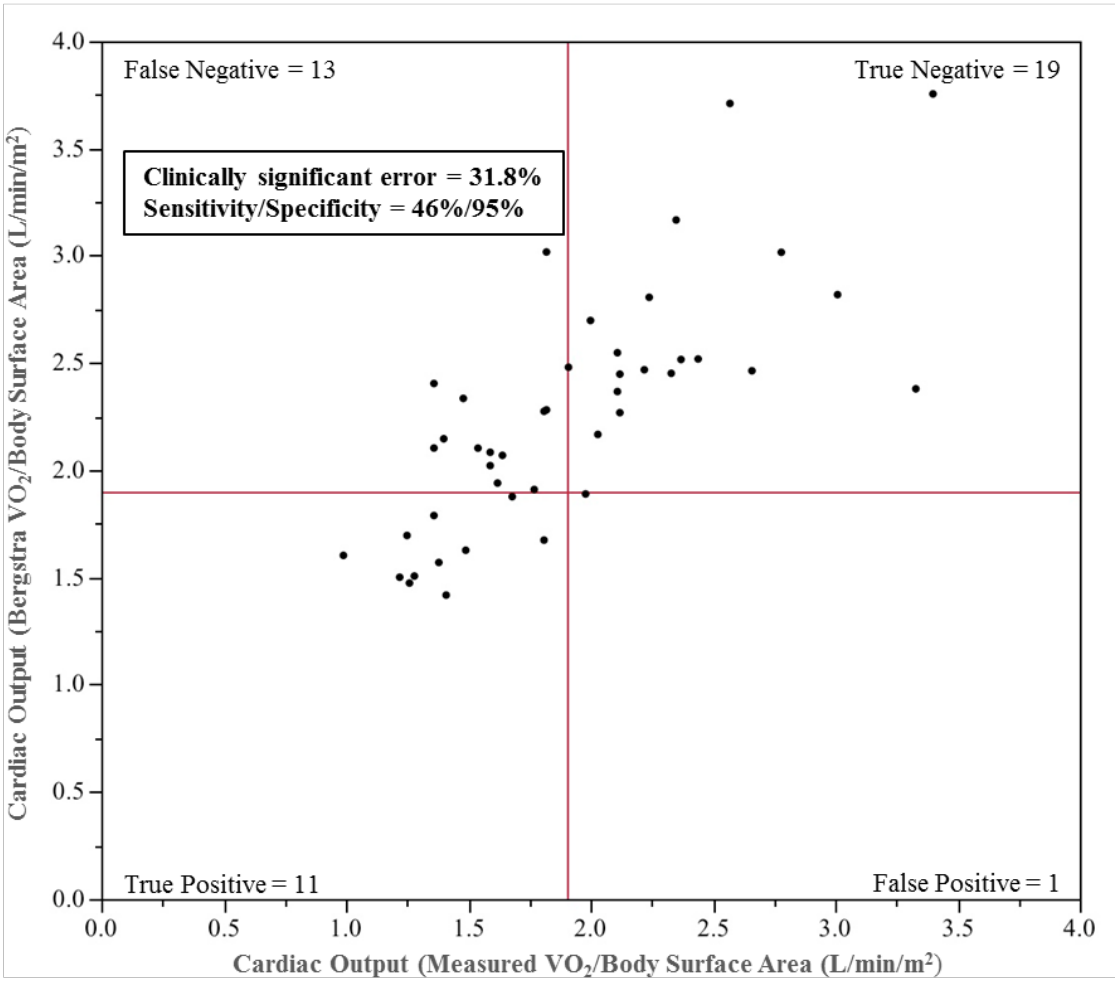


Figure 28. Clinically Significant Error in Determining Hypoperfusion by Cardiac Index Calculated by Bergstra et al. Estimated versus by Measured Oxygen Consumption. (cardiac index <2.2 L/min/m^2)

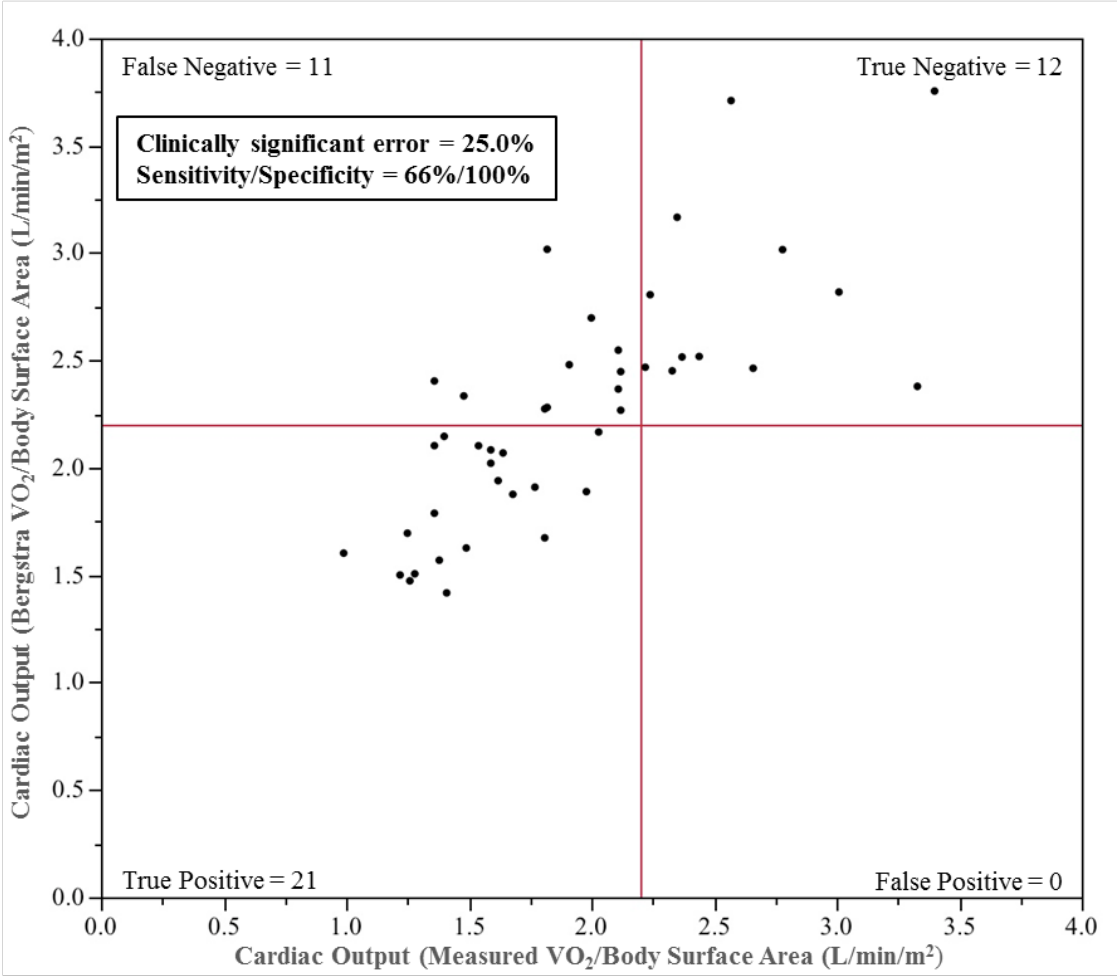
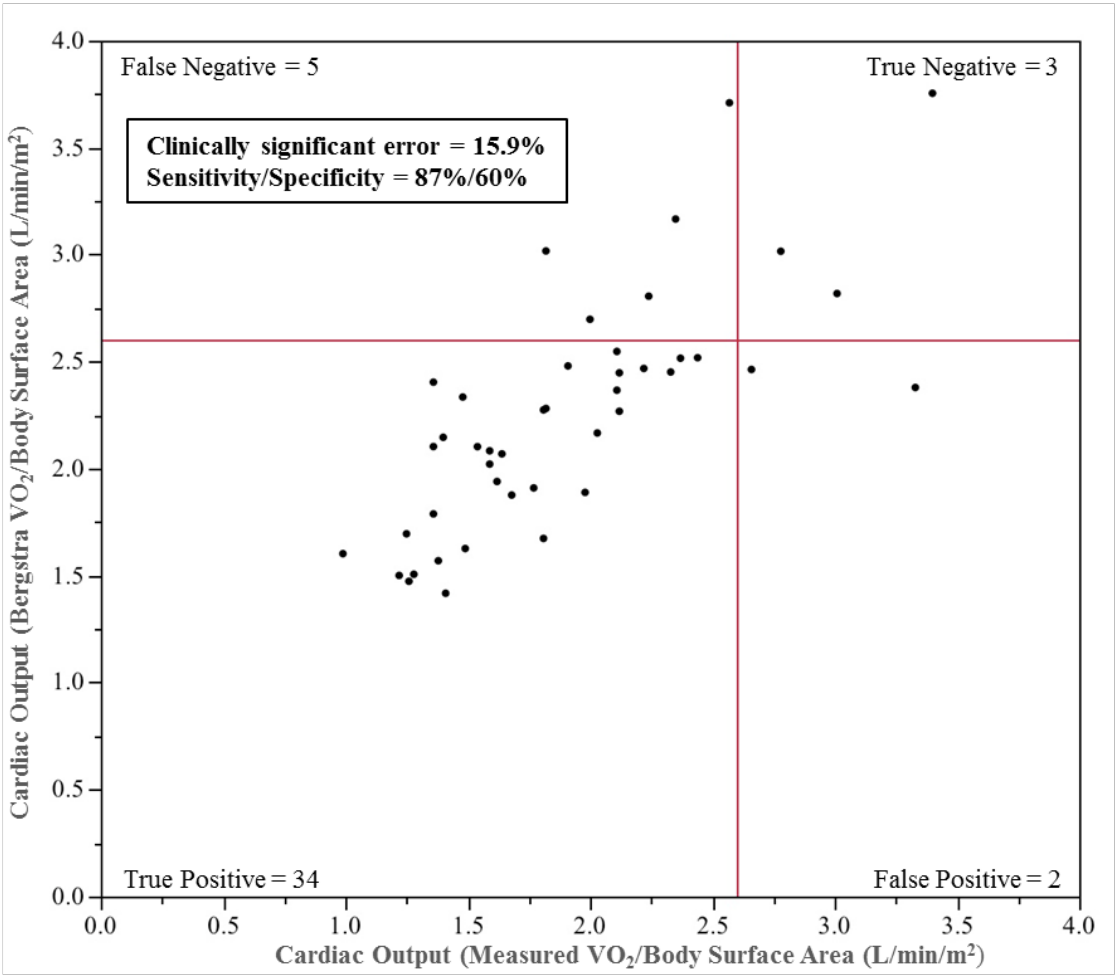


Figure 29. Clinically Significant Error in Determining Abnormal Cardiac Index Calculated by Bergstra et al. Estimated versus by Measured Oxygen Consumption. (cardiac index <2.6 L/min/m^2)



Aim 3

As described in the methods section, variables were included in the development of the estimation equation if they were found to have a significant influence on the resting VO_2. **Table 14** contains an extensive list of continuous variables and the result of linear regression analysis. Among these variables the natural log of age was included because of its use in both the LaFarge & Miettinen equations and the Bergstra et al. equations. From

this list, only BMI, BSA, red blood cell count, systolic RV pressure, mean RV pressure, and diastolic right atrial pressure were found to be significantly correlated with measured resting VO_2 (all $p<0.05$). Since BMI and BSA are estimations of body size that both include height and weight, it was decided to run the regression analysis two times with BMI included in one (BSA not entered) and BSA included in the other (BMI not entered) to avoid issues of colinearity. Since mean RV pressure includes the measurement of systolic RV pressure, and both variables had the same correlation and significance ($R^2=0.11$, $p=0.027$), only the systolic RV pressure was included in the analysis. The three dichotomous variables that were evaluated in the secondary aim to Aim 1 above were also entered into the analysis. Stepwise regression analysis was performed with these covariates utilizing a randomly selected sample of 34 patients. Each covariate was removed from the equation one at a time from lowest to greatest significance until the remaining covariates were significant at $p\leq0.05$. Results of the linear regression modeling can be found in **Table 15**, and the resulting empirical formulas are as follows:

1) Model 1 (root mean square error = 43.38, adjusted $R^2 = 0.52$, $p<0.001$):

   *VO_2 = -10.76+(127.74*BSA)+(aldosterone antagonist [prescribed=1, not prescribed=-1]*22.15)*

2) Model 2 (root mean square error = 49.35, adjusted $R^2 = 0.38$, $p<0.001$):

   *VO_2 = 149.4+(sex [male=1, female=-1]*25.41)+(aldosterone antagonist [prescribed=1, not prescribed=-1]*28.34)*

The remaining 10 patients were then used as a test group for each of the resultant equations. **Table 16** contains the results of the mean difference in the estimated and measured resting VO_2. Bland-Altman plots of the error in the estimate can be seen in **Figures 30** and **31**.

Table 14. Linear Regression Analysis of Continuous Patient Characteristics.

	Slope	R^2	adjusted-R^2	p-value
Age (years)	-1.4	0.06	0.04	0.099
Natural Log of Age	-85.3	0.07	0.05	0.074
Heart Rate (beats/min)	-0.68	0.02	0.00	0.356
Body Mass Index (kg/m^2)	3.1	0.12	0.10	0.022*
Body Surface Area (m^2)	144.4	0.47	0.46	<0.001*
Left Ventricular Ejection Fraction (%)	-0.02	0.00	-0.02	0.870
Red Blood Cell (Mil/μL)	23.2	0.09	0.07	0.047*
Hemoglobin (g/dL)	-0.9	0.00	-0.02	0.875
Hematocrit (%)	0.7	0.00	-0.02	0.703
Creatinine (mg/dL)	0.1	0.00	-0.02	0.992
Potassium (mEq/L)	-3.9	0.00	-0.02	0.807
Sodium (mEq/L)	-4.4	0.03	0.01	0.248
Carbon Dioxide (mEq/L)	-2.0	0.01	-0.01	0.461
Calcium (mg/dL)	-29.1	0.05	0.03	0.131
Blood Urea Nitrogen (mg/dL)	-0.1	0.00	-0.02	0.873
Glucose (mg/dL)	-0.1	0.02	-0.01	0.417
Systolic Pulmonary Artery Pressure (mm Hg)	0.9	0.04	0.02	0.166
Diastolic Pulmonary Artery Pressure (mm Hg)	2.3	0.08	0.06	0.059
Mean Pulmonary Artery Pressure (mm Hg)	1.4	0.05	0.03	0.130
Pulmonary Capillary Wedge Pressure (mm Hg)	2.2	0.08	0.06	0.060
Systolic Right Ventricular Pressure (mm Hg)	1.7	0.11	0.09	0.027*
Diastolic Right Ventricular Pressure (mm Hg)	2.9	0.03	0.01	0.255
Mean Right Ventricular Pressure (mm Hg)	3.9	0.11	0.09	0.027*
Systolic Right Atrial Pressure (mm Hg)	2.5	0.04	0.01	0.220
Diastolic Right Atrial Pressure (mm Hg)	3.3	0.10	0.07	0.043*
Mean Right Atrial Pressure (mm Hg)	3.3	0.07	0.05	0.081

Variables reaching significance ($p<0.05$) were included into estimation modeling

Table 15. Results from Linear Regression Modeling.

	Model 1			Model 2		
	B ± SE	β	p-value	B ± SE	β	p-value
Body Surface Area (m^2)	127.74 ± 28.93	0.56	<0.001	--	--	--
Not Prescribed Aldosterone Antagonist	22.15 ± 8.66	-0.33	0.016	-28.34 ± 9.57	-0.42	0.006
Female Gender	--	--	--	-25.41 ± 8.98	-0.40	0.008
Intercept (constant)	-10.76 ± 58.13	--	0.854	234.72 ± 9.78	--	<0.001

Model 1 variables entered: Body Surface Area, Pulmonary Hypertension, Gender, Aldosterone Antagonist, Diastolic Right Atrial Pressure, Systolic Right Ventricular Pressure, Red Blood Cell Count

Model 2 variables entered: Body Mass Index, Pulmonary Hypertension, Gender, Aldosterone Antagonist, Diastolic Right Atrial Pressure, Systolic Right Ventricular Pressure, Red Blood Cell Count

B = estimation coefficient, SE = standard error, β = beta coefficient, an indicator of the relative impact/importance on the resting oxygen consumption.

Table 16. Single-sample *t*-test Results of the Proposed Models.

	Measured VO_2 ±SD (ml/min)	Estimated VO_2 ±SD (ml/min)	Difference ± SE (ml/min)	p-value
Model 1	231.9 ± 37.6	242.9 ± 36.7	11.0 ± 10.7	0.165
Model 2		244.2 ± 42.8	12.4 ± 17.5	0.249

Model 1: *VO_2 = -10.76+(127.74*BSA)+(aldosterone antagonist [prescribed=1, not prescribed=-1]*20.33)*

Model 2: *VO_2 = 234.72+(sex[male=1,female=-1]*25.41)+(aldosterone antagonist [prescribed=1, not prescribed=-1]*28.34)*

Figure 30. Bland-Altman Plot of the Percent Error of the Resting Oxygen Consumption Estimated by Model 1. (Black dashed lines are 0% error, +25% error and -25% error)

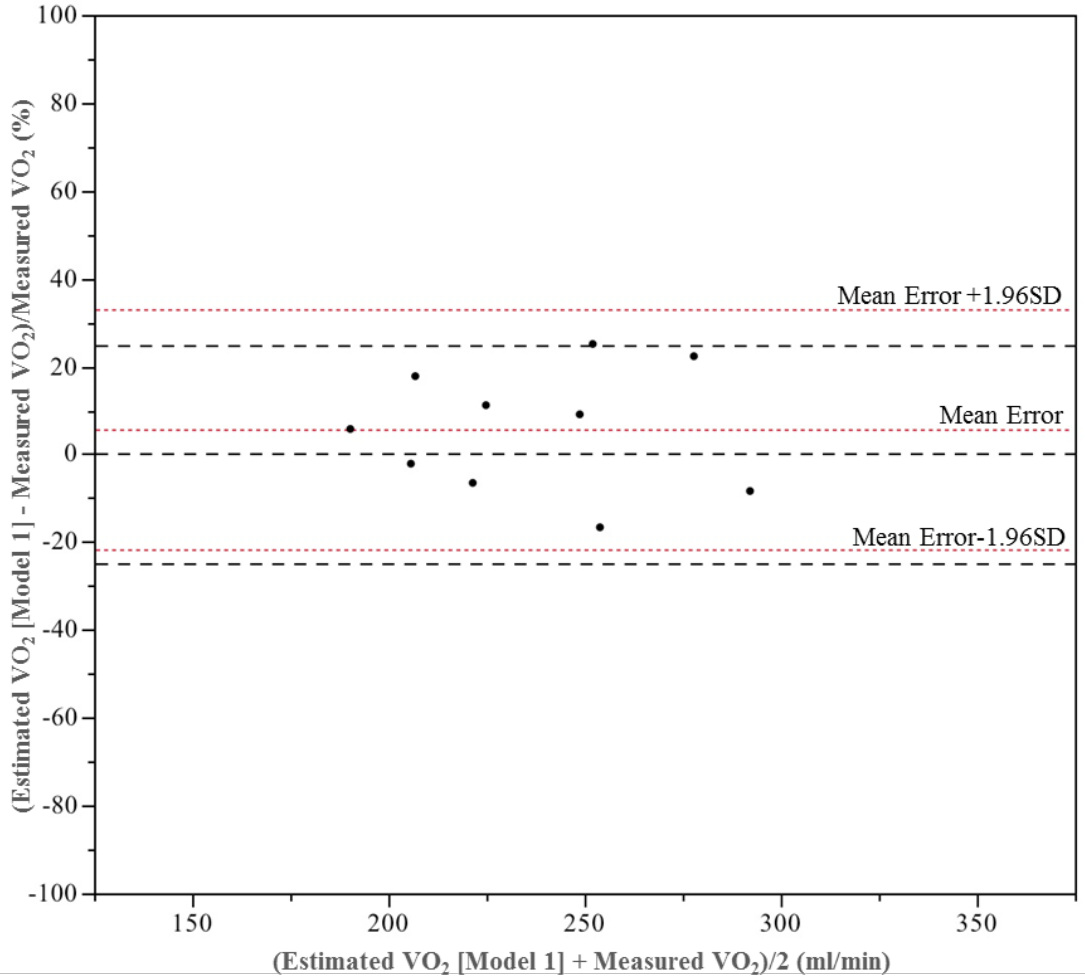
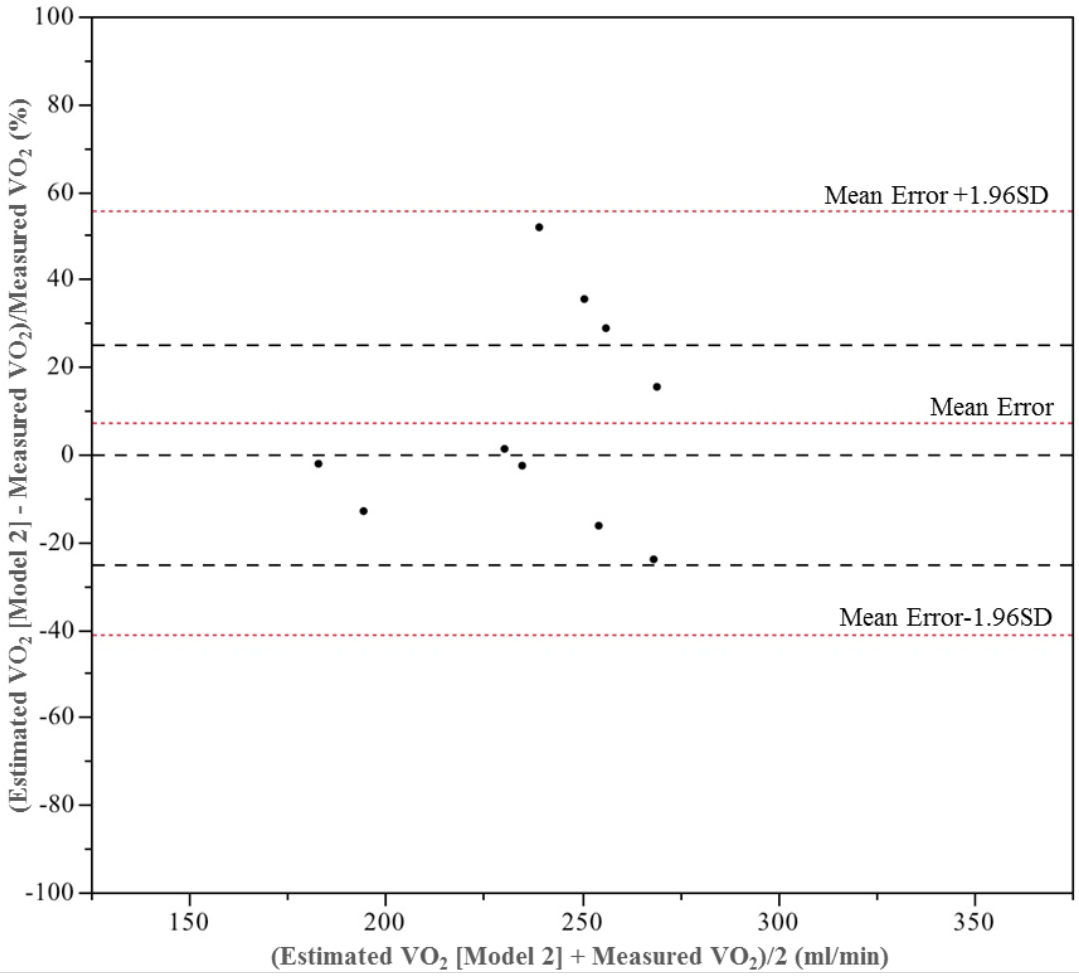


Figure 31. Bland-Altman Plot of the Percent Error of the Resting Oxygen Consumption Estimated by Model 2. (Black dashed lines are 0% error, +25% error and -25% error)



CHAPTER V

DISCUSSION

The purpose of this study was to investigate the accuracy of three widely used equations for the estimation of resting VO_2 compared to the direct breath-by-breath measurement of expired air using a metabolic cart in an adult population with HFrEF undergoing right heart catheterization.

Aim 1

This study was designed to accomplish primary and secondary aims. The first aim was to compare the differences between the measured resting VO_2 and the estimates from three commonly used prediction equations (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970). It was hypothesized that each of the estimations would result in statistically significant differences compared to the measured VO_2. The mean difference was found to be significantly different, with significant overestimation, with the Dehmer et al. equation (16.0 $\pm$ 6.4 ml/min, p=0.008) and the Bergstra et al. equations (40.6 $\pm$ 6.4 ml/min, p<0.001). However, the LaFarge & Miettinen equations resulted in a non-significant underestimation with a mean difference of -10.3 $\pm$ 6.2 ml/min (p=0.053). The mean difference is a measure of bias in the estimation towards over- or under-estimating the actually measured VO_2. Using a paired-sample *t*-test provides an objective evaluation of the significance the bias differs from 0, or has no bias. However,

mean difference is only part of fully understanding the differences between the measured and estimated VO_2.

Bland-Altman plots reveal information about the mean difference that is not apparent in *t*-tests, which is that all the estimation equations appear to trend towards overestimating at lower VO_2 and underestimating at higher VO_2. This has been a consistent finding in all the validation studies performed (Bergstra et al., 1995; Dehmer et al., 1982; Kendrick et al., 1988; Narang et al., 2012; Narang et al., 2014; Wolf et al., 1998). Additionally, it was suggested by Bland & Altman that although some variability around the mean difference of 0, the variability should be random without an apparent trend in differences across the range of measurements (Bland & Altman, 1986). So, this finding alone suggests that the estimation equations do not appropriately estimate resting VO_2. Furthermore, the plots reveal large ranges in the agreement between the measured and estimated VO_2. However, in order to better understand the impact of these large ranges in agreement, the Bland-Altman plots were reconfigured by dividing the difference between the estimated and measured VO_2 by the measured VO_2 in order to obtain percentage of error in the estimation. Aim 2 provided appropriate limits of agreement with clinically significant error most likely to occur when the error in the estimation reaches 25%. So, limits of agreement ranging from +25% to -25% errors were plotted. For the estimations to be truly acceptable, both the positive and negative ranges of the mean error $\pm$ 1.96 SD should be contained within the $\pm$25% limits of agreement. In all instances, the mean error $\pm$ 1.96 SD ranges were not contained within the $\pm$25%

limits. Although this additional analysis was not originally proposed, it was felt to be a more novel approach that would fully address the goal of Aim 1.

A secondary aim to Aim 1 was to begin to explore patient characteristics that may have influence on the reliability of the estimation equations. It was proposed to dichotomize patients in various sub-groups with a minimum of 10 patients in each group. From the demographic data, several appropriate sub-groups were identified and included sex, race (white/Caucasian vs. non-white/non-Caucasian), BMI (obese vs. non-obese), heart failure etiology (ischemic vs. non-ischemic), New York Heart Association class (II-III vs. IIIb-IV), diabetes (No diagnoses of diabetes vs. diagnosis of diabetes), smoking history (never smoked vs. current/former smoker), cardiac rhythm management (No ICD/pacemaker/CRT vs. having ICD/pacemaker/CRT) and whether patients were prescribed each beta-blockers, ACEI, angiotensin receptor blockade, loop diuretics, and aldosterone antagonists. Additionally, pulmonary hypertension was derived from the right heart catheterization data constructed two groups (with and without pulmonary hypertension).

Within these various subgroups, male sex ($p<0.001$), pulmonary hypertension ($p=0.045$), and being prescribed aldosterone antagonists ($p=0.010$) all resulted in significantly higher measured resting VO_2 than their respective counterparts. All previous studies that have considered differences between males and females have demonstrated higher resting VO_2 measurements in men (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970; Narang et al., 2014). The resulting cardiac output was compared between men and women to determine if the higher resting VO_2 resulted in a

higher value. In fact the mean difference and SE were 0.61 $\pm$ 0.43 L/min (p=0.084) was not significantly higher in men.

Pulmonary hypertension is a common finding among patients with HF, occurring in >60% of all (HFpEF and HFrEF) patients with HF (Guazzi & Borlaug, 2012). Despite a lack of solid epidemiological evidence, there is likely lower incidence of pulmonary hypertension in patients with HFrEF with reported rates of 16-60% demonstrated in clinical trials (Guazzi & Galiè, 2012). In addition, the rate was found to be dependent on patient selection (Guazzi & Galiè, 2012). The presence of pulmonary hypertension in patients with HFrEF indicates more advanced disease and is correlated with worse clinical outcomes (Guazzi & Borlaug, 2012; Guazzi & Galiè, 2012). The guidelines for determining pulmonary hypertension indicate that all patients with pulmonary hypertension have a mean PA pressure $\geq$25 mm Hg and those with post-capillary pulmonary hypertension (most common form of pulmonary hypertension in patients with HF) also have a PCWP $\geq$15 (Galiè et al., 2009). In the current study 32 (73%) patients were found to have pulmonary hypertension, and among these 28 (64%) patients were found to have post-capillary pulmonary hypertension. Again, this raised the question if the higher VO_2 in those with pulmonary hypertension portended to higher cardiac output. The mean differences and SE of 0.07 $\pm$ 0.39 L/min (p=0.430) clearly indicates there was not a benefit to cardiac output from the higher VO_2.

The relationship between aldosterone antagonist prescription and resting VO_2 (all were prescribed spironolactone) is certainly novel, as these medications were not used in the management of HF when any of the estimation equations were developed.

Aldosterone antagonist medications are prescribed to patients with severe HF signs and symptoms, LVEF <35% and without significant renal dysfunction (Lindenfeld et al., 2010). Analysis of patient characteristics found that patients prescribed aldosterone antagonists were younger (59.6 $\pm$ 11.8 years) than those not prescribed these medications (66.7 $\pm$ 9.4 years; mean difference 7.2 $\pm$ 3.6 SE, p=0.03), and there was a greater percentage of men in the prescribed group versus the non-prescribed group (86% vs. 57%, p=0.057). Although age, as a continuous variable, was not found to be significantly correlated with resting VO_2 in the current analysis, results from other studies of have suggested that resting VO_2 decreases with age (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970). In at least the limited age-range of the current study, this seems to be consistent. It has been suggested that similar to resting VO_2, the cardiac output decreases with age at ~1% per year (Brandfonbrener et al., 1955). However, the comparison of cardiac output between these two groups were not significantly different (mean difference 0.43 $\pm$ 0.42 L/min SE, p=0.160). Men have a significantly higher resting VO_2 than women, and most certainly the two women in the prescribed aldosterone antagonist group are likely having less influence on the mean VO_2 of the group than the 13 women in the non-prescribed group. It has been shown that older individuals tend to have a greater degree of renal dysfunction and older individuals and females are more prone to the side-effect of hyperkalemia associated with aldosterone antagonists (Ko et al., 2006), which may drive prescription practice toward younger individuals. Although not significant, indicators of renal function (creatinine mean difference -0.27 $\pm$ 0.19 mg/dL SE, p=0.086; blood urea nitrogen mean difference -4.60 $\pm$ 3.03 mg/dL SE,

p=0.070) suggesting a tendency of patients on aldosterone antagonists to have better renal function.

Within all these grouping variables, the higher resting VO_2 did not result in significantly higher cardiac outputs. This seems to suggest that within these groups the higher VO_2 represents a compensatory increase in metabolic work in order to preserve cardiac output. Considering the Fick equation of *cardiac output = VO_2/a-vO_2diff,* it was expected that a-vO_2diff would be higher in men vs. women, those with pulmonary hypertension versus those without and in those prescribed aldosterone antagonists versus not prescribed this medication. However, only patients with pulmonary hypertension were found to have significantly higher a-vO_2diff than their counterparts (mean difference 8.87 $\pm$ 4.22 mlO_2/L SE). Re-working the Fick equation, *VO_2=heart rate*stroke volume [cardiac output]*a-vO_2diff,* the VO_2 could be higher for males and those prescribed aldosterone antagonist due to higher heart rate or stroke volume. For males, there was no significant difference (males – females) in heart rate (-3.9 $\pm$ 4.0 bpm SE, p=0.170) and stroke volume tended to be higher in males (11.4 $\pm$ 6.8 ml/beat, p=0.053). In those prescribed aldosterone antagonist, heart rate was found to be significantly lower (-5.7 $\pm$ 3.3 bpm SE, p=0.045), but stroke volume was not significantly higher in the prescribed group (10.1 $\pm$ 7.2 ml/beat SE, p=0.085). Although there were more males and the patients were younger in the prescribed aldosterone antagonist group, further investigation into the results did not yield a clear explanation for the higher resting VO_2 in this group.

Each of the resulting six sub-groups were then subjected to the same analysis as performed in primary Aim 1, including paired-sample *t*-tests and Bland-Altman plots (plots utilizing the error were used). The hypothesis for this secondary aim was that all differences between the estimated and measured VO_2 would remain statistically significant. Unfortunately these results failed to support that hypothesis.

An important aspect of this secondary aim was to explore the sex-specific equations of LaFarge & Miettinen and of Bergstra et al. The findings of the current study suggest that the female-specific equation for LaFarge & Miettinen resulted in a significant difference of underestimating the resting VO_2 ($p=0.048$), where no significant difference was found for men ($p=0.195$). However, both sexes had significant overestimation of the VO_2 when the Bergstra et al. estimations were used (both $p<0.001$) and reflects the overall poor performance of Bergstra et al. equations. The Dehmer et al. estimation does not have sex-specific formulas. It was reported that men had higher resting VO_2 than women (Dehmer et al., 1982), which is what was found in the current study. However, these results suggest the significant mean difference found in the overall Dehmer et al. data are being primarily driven by female patients. That is, the mean difference between the estimated and measured VO_2 for men was 6.4 ml/min ($p=0.220$), where it was 34.5 ml/min ($p<0.001$) for women. Overall, the results from all three equations suggest that a greater number of female patients should be included in the development of estimation equations to improve the performance of the estimations. Clinically, if these formulas are used, greater consideration should be made of the results when used on female patients.

The two novel variables of pulmonary hypertension and aldosterone antagonist prescription have not been explored by previous research, including the research developing the estimation equations. Similar to sex, the estimations of Bergstra et al. resulted in significant overestimations regardless of the presence or absence of pulmonary hypertension. Where, the Dehmer et al. equation significantly overestimated resting VO_2 in those without pulmonary hypertension. For the Dehmer et al. and Bergstra et al. equations, not being prescribed aldosterone antagonists resulted in significant overestimation of the VO_2. Interestingly, with no significant differences found in the estimated and measured VO_2 for those with or without pulmonary hypertension, or for those prescribed or not prescribed aldosterone antagonists, the LaFarge & Miettinen equations appear to be resistant to these two variables. The LaFarge & Miettinen equation may be resistant to these variables because the equations were developed on a large cohort (still largest to date), which likely included patients with pulmonary hypertension and accounted for factors such as age (younger) and sex (male) that made up the aldosterone antagonist prescribed group.

Despite whether variables were found to have significant differences or not, the Bland-Altman plots of the error demonstrated large variability and poor agreement for both sub-groups of each variable. This result is consistent with findings of the primary aim that regardless of the significance of the bias of the mean difference, the range of error falls outside of the acceptable limits of agreement.

Aim 2

The second primary aim of the study was to investigate the rate at which each equation results in a clinically significant error in resting VO_2. This level was chosen based on what has been suggested in the literature as being the level at which clinically significant error would most likely occur (Kendrick et al., 1988; Wolf et al., 1998). It was hypothesized that each of the equations would result in ≥15% of the patients with ≥25% absolute error. These results do not support this hypothesis. Particularly, the LaFarge & Miettinen estimation resulted in 11.4% of patients falling in this category of absolute error. In the studies that have performed similar analysis, found that the LaFarge & Miettinen had the lowest rates of patients with ≥25% error (Kendrick et al., 1988; Narang et al., 2012; Narang et al., 2014; Wolf et al., 1998). In this sense these results are consistent with the literature. When reviewing the Bland-Altman plots of the differences or of the error, one can see the 5 patients (11.4%) that fall into this elevated error group. Further exploration into the dichotomized Bland-Altman plots there does not appear to be a consistent characteristic of these patients with regard to the variables that were found to have influence on the results (3 male/2 female, 2 with post-capillary pulmonary hypertension/3 without pulmonary hypertension, 2 prescribed aldosterone antagonist/3 not prescribed aldosterone antagonists). The estimation of Bergstra et al. resulted in 48% of the patients with ≥25% error, which seems to strongly support that these equations are inappropriate for use with patients with HFrEF. These results are consistent with previous research (Narang et al., 2014; Wolf et al., 1998), which found the highest rate of results with ≥25% error with the Bergstra et al. equations. Also both studies recommended that

the Bergstra et al. equations should not be used for any clinical population (Narang et al., 2014; Wolf et al., 1998). Certainly the findings in the current study support the idea that the Bergstra et al. estimation should be avoided. Although these are important, further exploration of the true resulting error in a variable derived from the VO_2 can provide better insight into the real occurrence of clinically significant error. That is, cardiac indexes of 1.0 L/min/m^2 and 1.26 L/min/m^2 (26% difference) would not be considered clinically different, yet cardiac indexes of 2.0 L/min/m^2 and 2.2 L/min/m^2 (10% difference) would be clinically different.

Of course cardiac output (VO_2/a-vO_2diff) is probably the most obvious variable to consider, but the cardiac index (cardiac output/BSA) is clinically more useful. Where cardiac output is the measure of the amount of blood that is being circulated every minute, the cardiac index of how well the cardiac output is perfusing the body's tissues. So, it may be a more sensitive indicator of cardiac function than the absolute cardiac output. In the context of HFrEF, cardiac index is particularly used to help guide treatment and determine appropriateness for advanced therapies, such as cardiac transplant or LVAD. The secondary aim to Aim 2 essentially plotted the cardiac index using the estimated VO_2 over the cardiac index derived by the measured VO_2. Narang et al. performed a similar analysis in a "hypothetical clinical context of aortic valve calculations" (Narang et al., 2014), in which the only variable that changed within the calculation of the aortic valve area was the individual measure or estimated VO_2 (Narang et al., 2012; Narang et al., 2014). In these studies, this approach makes sense. Specifically, in Narang et al. 2012, the analysis was done prior to exercise tests in

patients without heart disease and were absent of any results that would be obtained from the right heart catheterization. In Narang et al. 2014, the data were collected during clinically indicated right heart catheterizations, but with a broad range of clinical indications for undergoing the procedure. Therefore, creating a hypothetical scenario homogenized the data for easier analysis. In the current analysis, the patients all had HFrEF and the cardiac index was of particular interest in all these patients. So, understanding the real clinically significant error provides for more direct clinical relevance. At the level of the normal versus abnormal cardiac index ($</\geq 2.6$ L/min/m^2) only the estimations of Bergstra et al. had >15% of patients with clinically significant error, which further supports the idea of these equations should not be used in HFrEF population. Given the idea that majority of patients with HFrEF are found to have reduced cardiac index (Carlsson et al., 2012; Cotter et al., 2003), one would really expect little error at this level. However, all equations demonstrated >15% of patients with clinically significant error at the level of hypoperfusion (<2.2 L/min/m^2) and >20% of patients with clinically significant error at the level of cardiogenic shock (<1.9 L/min/m^2). Misclassifying patients at these two levels can have significant downstream effects. For example, patients that have a cardiac index by the estimation equations >1.9 L/min/m^2, but in reality have a cardiac index <1.9 L/min/m^2, may be moved toward LVAD implant. However, such patients may be too sick for this advanced therapy and would be at high risk for major complications from the procedure. On the other hand, if the true cardiac index was used, these patients may be given a round of intravenous (IV)

inotropic therapy which could improve the cardiac index and increase the safety of implanting the LVAD.

During the data collection of the study, it was observed that four patients were given IV inotrope challenges. During an IV inotrope challenge, patients that are found to have a cardiac index substantially <1.9 L/min/m^2 during the right heart catheterization are given IV infusion of milrinone or dobutamine (milrinone was used in all four instances). The infusion is usually staged to find dosing that will demonstrate improvement in cardiac index towards 1.9 L/min/m^2 or greater. Furthermore, the infusion of inotropic medication can also improve (particularly post-capillary) pulmonary hypertension by lowering systemic vascular resistance and PCWP (Loh et al., 2001). After each infusion dose, the cardiac output (subsequently cardiac index) is measured. Therefore, errors could be compounded due to the multiple measures of cardiac output, and (as has been shown in the current study) improvements in pulmonary hypertension.

Aim 3

The third aim of the study was certainly the most exploratory of the aims and was an attempt to develop an empirical formula that may be more specific to patients with HFrEF. Several factors were considered in the development of the equations that were used in other formulas. Both the LaFarge & Miettinen and the Bergstra et al. formulas involved the inclusion of the natural log of age (Bergstra et al., 1995; LaFarge & Miettinen, 1970). This variable did not prove to have predictive quality in the current analysis. Although the range of patients in the study ranged from 34 to 86 years old, the average age in the study was 64.5 years with relatively low standard deviation of $\pm$10.7

years. Therefore, low variability in this variable likely prevented it from being predictive. Bergstra et al. also included heart rate in the calculations, but it also did not predict VO_2 in the current study. Similar to age, heart rate did have a large range (54 to 105 bpm) but, again, there was not a great deal of variability (73 $\pm$12 bpm). It should be noted that LaFarge & Miettinen considered heart rate, and was excluded out of their final model as well (LaFarge & Miettinen, 1970).

As hypothesized, there were novel variables that were found to be significant predictors in the multivariate linear regression. These novel variables included BMI, pulmonary hypertension, aldosterone antagonist prescription, red blood cell count, systolic RV pressure and diastolic RA pressure. Of course, BSA was found to be the strongest overall predictor (adjusted R^2=0.46, $p<0.001$) and this is consistent with results from all three estimation equations (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970). Sex differences were also consistent findings from the three estimation equations as well (Bergstra et al., 1995; Dehmer et al., 1982; LaFarge & Miettinen, 1970). Although it is not considered in the Dehmer et al. equation, the intention of Dehmer et al. was not to produce an estimation equation, but rather to discount the use of estimation equations (particularly LaFarge & Miettinen's) to determine resting VO_2 (Dehmer et al., 1982).

Although not as strong as BSA, BMI was found to be predictive. However, this was not very surprising since both of these variables are indicators of body size and are significantly correlated (R^2=0.48, $p<0.001$). To avoid issues of colinearity, these were not entered in the regression modeling at the same time and are the reason two separate

models were calculated. For the model in which it was entered BMI was not retained, which is likely related to BMI's limitations. In comparing BSA and BMI further, BSA is the stronger predictor likely because it is a better measure of the total cross-sectional area metabolic mass, and BSA and BMI are positively correlated because of weight. That is, holding height the same, increasing weight increases both BSA and BMI (decreasing weight decreases both) and increases the resting VO_2 (ml/min). This relationship does not hold for height, where maintaining weight constant and increasing height will increase BSA, but decrease BMI. So, BMI helps to describe how weight is distributed across height, where BSA describes how much tissue there is to be perfused.

Pulmonary hypertension was another variable that has not surfaced in previous estimation equations. However, despite the fact that patients with pulmonary hypertension had a significantly higher resting VO_2, this dichotomization was not retained in either of the equations. This was somewhat surprising in that it had the most interesting results in the analyses for the exploratory aim for Aim 1. This variable would have set a potential equation apart by tying a marker of clinical severity to estimate resting VO_2.

The retention of the aldosterone antagonists into both of the resulting equations is certainly novel. As found with the exploration of this variable before, there were a greater number of men prescribed these aldosterone antagonists. This may, in part, be driving the elevated VO_2 in this group. Also, patient selection may have some influence. Within the context of the patients selected in the current study, those prescribed aldosterone antagonists were younger and absent of significant renal dysfunction. Aldosterone

antagonists reverse the action of having elevated circulating aldosterone including; reducing volume status, reducing inflammation, and decreasing sympathetic nervous system activation (Maron & Leopold, 2010). Although they had a higher average resting VO_2, there was evidence of decreased activation of the sympathetic nervous system with a significantly lower resting heart rate in those prescribed aldosterone antagonists (mean difference -5.7 $\pm$ 3.3 bpm SE, p=0.045). So, while the overall effect of the aldosterone antagonists on resting VO_2 may be related to the patients prescribed the medication, there may be other influences from the action of the medication itself. However, any definitive effects if aldosterone inhibition on resting VO_2 are unknown at this point.

The model 2 equations results in patients falling into one of four predicted VO_2 measures; males prescribed aldosterone antagonists = 288.5 ml/min; males not prescribed aldosterone antagonists = 231.8 ml/min; females prescribed aldosterone antagonists = 237.7 ml/min; and females not prescribed aldosterone antagonists = 181.0 ml/min. This almost categorical finding significantly limits the ability of the model to accurately estimate the VO_2 for an individual patient. After all, the range of measured VO_2 in the current study was 240 ml/min; more than twice 107 ml/min range from Model 2. Bland-Altman evaluation of the test group demonstrates a non-significant bias towards overestimating resting VO_2 and the upper limit of agreement is well above the upper 25% error line, which represents the upper limit of agreement.

Model 1 shares some commonalities with the LaFarge & Miettinen and the Bergstra et al. equations. All three of the equations attempt to account for individual variability in true resting VO_2 by accounting for sex and BSA. Additionally, however, the

intercept of the linear regression was included in this model. Without including the intercept the model greatly overestimates the resting VO_2. Again there does not appear to be a significant mean difference in the error with model 1 and the upper limit of agreement is just above the upper 25% error limit. Despite this, it may be worthwhile to further test this model in future research with a larger sample of patients.

Conclusion

This study was not without limitations. First, the sample size was too small to fully investigate the findings of the exploratory aim of Aim 1. Furthermore, the sample size was too small to adequately build an acceptable estimation equation in Aim 3. However, based on the results of previous studies, the study was sufficiently powered to compare the estimated and measured VO_2 to address the primary Aim 1 and Aim 2. Secondly, patients are generally not accustomed to having breathing monitored, particularly while breathing through a mouthpiece. This may inherently change the patient's breathing characteristics and influence resting VO_2 (Perez & Tobin, 1985). However, this is a common method for measuring ventilatory gas exchange and was the method utilized by LaFarge & Miettinen (LaFarge & Miettinen, 1970). However, compared to the Douglas bag collection of expired gas-exchange performed by LaFarge & Miettinen, the measurement of breath-by-breath ventilatory gas exchange by a computerized metabolic cart may limit this comparison. However, utilization of metabolic carts is more common in modern laboratories, making it more clinically applicable. Lastly, due to the limitations of the metabolic cart, gas exchange measurement was not possible if any patient was receiving supplemental O_2 and patients

receiving more than the standard dose of sedation. Therefore these patients were not included in the study making the generalization of these results to these patients difficult.

The purpose of this study was to measure the resting VO_2 in adult patients with HFrEF during right heart catheterization procedures, investigate the accuracy of three widely used equations for the estimation of resting VO_2 compared to the direct breath-by-breath measurement of expired air using a metabolic cart and determine to what extent clinically significant errors occur using estimation equations. Despite the fact that not all of the proposed hypotheses were supported by the findings, particularly for Aims 1 and 2, the overall conclusion for all three estimations equations argues against the routine use of VO_2 estimation equations in patients with HFrEF. This is consistent with findings of previous literature, particularly that of Narang et al. which evaluated the same three estimation equations on large cohorts of non-clinical (Narang et al., 2012) and clinical patients (Narang et al., 2014). The results of the secondary aim to Aim 1 suggest that certain patient characteristics influence the bias (mean difference) for each of the estimation equations, but despite the significance of bias Bland-Altman plots of the error indicate limits of agreement outside of what was proposed to be acceptable. Likewise, Aim 2 indicates that patients with $\geq$25% absolute error occurred at rates of 11%, 23% and 46% for the LaFarge & Miettinen equation, Dehmer et al. equation and Bergstra et al. equation, respectively. Further exploration of the clinically significant error, found that the cardiac index derived from the each of estimation equations resulted in >15% with clinically significant error at cardiac index thresholds that are most commonly encountered in patients with HFrEF.

Although this was not the first analysis to evaluate estimation equations in exclusively patients with HF, it is the first study to utilize exclusively patients with HFrEF during routine right heart catheterization. Therefore, it was important to explore the possibility of deriving an empirical equation specific to HFrEF patients. Dehmer et al. suggested the large range found in their analysis argues against any empirical formula that could reliably estimate resting VO_2 across the entire range (Dehmer et al., 1982). In fact the range of resting VO_2 measured in the current analysis was even larger than that found by Dehmer et al. Nonetheless, the use of this specific patient population made the endeavor of deriving an empirical formula worthwhile. Two models were developed, and immediately Model 2 was dismissed due to the fixed, categorical, nature of the results. Model 1, however shared similarities to the estimations of LaFarge & Miettinen and Bergstra et al., and initially appeared to provide reasonable results when applied to the 10 patient test-sample. However, despite insignificant mean differences, the limits of agreement fell just outside the acceptable limits. Since the limits were just outside of acceptable, it would be interesting to explore the estimation of Model 1 in a larger cohort. Furthermore, adding more patients (particularly females) into the development of the model may yield an improved, HFrEF-specific estimation.

In conclusion, the findings from the current study do not support the use of these empirical formulae to estimate the resting VO_2 in patients with HFrEF undergoing right heart catheterization. The direct measurement of the resting VO_2 should be the primary method applied to the Fick equation for cardiac output. However, if estimations are used,

clinicians need to be aware of the significant limitations of these estimations and should use caution and good clinical judgment considering administration of advanced therapies.

REFERENCES

Abraham, W. T., Young, J. B., Leon, A. R., Adler, S., Bank, A. J., Hall, S. A., . . . on behalf of the Multicenter InSync ICD II Study Group. (2004). Effects of Cardiac Resynchronization on Disease Progression in Patients With Left Ventricular Systolic Dysfunction, an Indication for an Implantable Cardioverter-Defibrillator, and Mildly Symptomatic Chronic Heart Failure. *Circulation, 110*(18), 2864-2868. doi: 10.1161/01.cir.0000146336.92331.d1

Alpert, J. S. (1989). The lessons of history as reflected in the pulmonary capillary wedge pressure. *J Am Coll Cardiol, 13*(4), 830-831. doi: 0735-1097(89)90224-6 [pii]

Armstrong, L. E., & Costill, D. L. (1985). Variability of respiration and metabolism: responses to submaximal cycling and running. *Research Quarterly for Exercise and Sport, 56*(2), 93-96.

Bahrami, H., Kronmal, R., Bluemke, D. A., Olson, J., Shea, S., Liu, K., . . . Lima, J. A. (2008). Differences in the incidence of congestive heart failure by ethnicity: the multi-ethnic study of atherosclerosis. *Arch Intern Med, 168*(19), 2138-2145. doi: 168/19/2138 [pii]10.1001/archinte.168.19.2138

Baim, D. S., & Grossman, W. (2006). G*rossman's cardiac catheterization, angiography, and intervention* (7th ed.). Philadelphia: Lippincott Williams & Wilkins.

Bashore, T. M., Bates, E. R., Berger, P. B., Clark, D. A., Cusma, J. T., Dehmer, G. J., . . . Documents, A. C. o. C. T. F. o. C. E. C. (2001). American College of Cardiology/Society for Cardiac Angiography and Interventions Clinical Expert Consensus Document on cardiac catheterization laboratory standards. A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J *Am Coll Cardiol, 37(*8), 2170-2214. doi: S0735109701013468 [pii]

Bergstra, A., van Dijk, R. B., Hillege, H. L., Lie, K. I., & Mook, G. A. (1995). Assumed oxygen consumption based on calculation from dye dilution cardiac output: an improved formula. E*ur Heart J, 16(*5), 698-703.

Berthelsen, P. G., Eldrup, N., Nilsson, L. B., & Rasmussen, J. P. (2002). Thermodilution cardiac output. A*cta Anaesthesiologica Scandinavica, 46(*9), 1103-1110. doi: 10.1034/j.1399-6576.2002.460908.x

Bibbins-Domingo, K., Pletcher, M. J., Lin, F., Vittinghoff, E., Gardin, J. M., Arynchyn, A., . . . Hulley, S. B. (2009). Racial differences in incident heart failure among young adults. N *Engl J Med, 360(*12), 1179-1190. doi: 360/12/1179 [pii]10.1056/NEJMoa0807265

Bland, J. M., & Altman, D. G. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. La*ncet, 1(8*476), 307-310.

Bleasdale, R. A., & Frenneaux, M. P. (2002). Prognostic importance of right ventricular dysfunction. He*art, 88(4*), 323-324.

Borlaug, B. A., & Redfield, M. M. (2011). Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Ci*rculation, 123(1*8), 2006-2013; discussion 2014. doi: 10.1161/CIRCULATIONAHA.110.954388

Brandfonbrener, M., Landowne, M., & Shock, N. W. (1955). Changes in cardiac output with age. Ci*rculation, 12(4*), 557-566.

Bristow, M. R., Saxon, L. A., Boehmer, J., Krueger, S., Kass, D. A., De Marco, T., . . . Feldman, A. M. (2004). Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N *Engl J Med, 350(2*1), 2140-2150. doi: 10.1056/NEJMoa032423350/21/2140 [pii]

Brooks, G. A., Fahey, T. D., & Baldwin, K. M. (2005). Ex*ercise physiology : human bioenergetics and its applications (*4th ed.). Boston: McGraw-Hill.

Bui, A. L., Horwich, T. B., & Fonarow, G. C. (2011). Epidemiology and risk profile of heart failure. Na*t Rev Cardiol, 8(1*), 30-41. doi: nrcardio.2010.165 [pii]10.1038/nrcardio.2010.165

Carlsson, M., Andersson, R., Bloch, K. M., Steding-Ehrenborg, K., Mosén, H., Stahlberg, F., . . . Arheden, H. (2012). Cardiac output and cardiac index measured with cardiovascular magnetic resonance in healthy subjects, elite athletes and patients

with congestive heart failure. J C*ardiovasc Magn Reson, 14,* 5*1*. doi: 10.1186/1532-429X-14-51

Clark, A. L., Goode, K., & Cleland, J. G. (2008). The prevalence and incidence of left bundle branch block in ambulant patients with chronic heart failure. Eur *J Heart Fail, 10(7),* 696-702. doi: 10.1016/j.ejheart.2008.05.001

Cotter, G., Moshkovitz, Y., Kaluski, E., Milo, O., Nobikov, Y., Schneeweiss, A., . . . Vered, Z. (2003). The role of cardiac power and systemic vascular resistance in the pathophysiology and diagnosis of patients with acute congestive heart failure. Eur *J Heart Fail, 5(4),* 443-451.

de Groote, P., Millaire, A., Foucher-Hossein, C., Nugue, O., Marchandise, X., Ducloux, G., & Lablanche, J. M. (1998). Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. J A*m Coll Cardiol, 32(4),* 948-954. doi: S0735-1097(98)00337-4 [pii]

Dehmer, G. J., Firth, B. G., & Hillis, L. D. (1982). Oxygen consumption in adult patients during cardiac catheterization. Cli*n Cardiol, 5(8),* 436-440.

Dickstein, K., Cohen-Solal, A., Filippatos, G., McMurray, J. J., Ponikowski, P., Poole-Wilson, P. A., . . . Reviewers, D. (2008). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur *Heart J, 29(19*), 2388-2442. doi: ehn309 [pii]10.1093/eurheartj/ehn309

Doughty, R. N., Whalley, G. A., Gamble, G., MacMahon, S., & Sharpe, N. (1997). Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. J Am *Coll Cardiol, 29(5),* 1060-1066.

Du Bois, D., & Du Bois, E. (1916). Clinical Calorimetry. A formula to estimate the approximate surface area if height and weight be known. Arch *Intern Med, 17, 86*3-871.

Fakler, U., Pauli, C., Hennig, M., Sebening, W., & Hess, J. (2005). Assumed oxygen consumption frequently results in large errors in the determination of cardiac output. J Th*orac Cardiovasc Surg, 130(2),* 272-276. doi: 10.1016/j.jtcvs.2005.02.048

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Beha*v Res Methods, 39(2),* 175-191.

Floras, J. S. (2009). Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. J Am *Coll Cardiol, 54(5),* 375-385. doi: 10.1016/j.jacc.2009.03.061

Galiè, N., Hoeper, M. M., Humbert, M., Torbicki, A., Vachiery, J. L., Barbera, J. A., . . . (CPG), E. C. f. P. G. (2009). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur *Heart J, 30(20),* 2493-2537. doi: 10.1093/eurheartj/ehp297

Ginsberg, F., & Parrillo, J. E. (2009). Cardiogenic shock: a historical perspective. Crit *Care Clin, 25(1),* 103-114, viii. doi: 10.1016/j.ccc.2008.12.005

Greger, R. (1997). Why do loop diuretics cause hypokalaemia? Neph*rol Dial Transplant, 12(9),* 1799-1801.

Guazzi, M., & Borlaug, B. A. (2012). Pulmonary hypertension due to left heart disease. Circ*ulation, 126(8),* 975-990. doi: 10.1161/CIRCULATIONAHA.111.085761

Guazzi, M., & Galiè, N. (2012). Pulmonary hypertension in left heart disease. Eur *Respir Rev, 21(126*), 338-346. doi: 10.1183/09059180.00004612

Haycock, G. B., Schwartz, G. J., & Wisotsky, D. H. (1978). Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. J Pe*diatr, 93(1),* 62-66.

He, J., Ogden, L. G., Bazzano, L. A., Vupputuri, S., Loria, C., & Whelton, P. K. (2001). Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch *Intern Med, 161(7),* 996-1002.

Heart Failure Society Of America. (2006). HFSA 2006 Comprehensive Heart Failure Practice Guideline. J Ca*rd Fail, 12(1),* e1-2. doi: S1071-9164(05)01361-8 [pii]10.1016/j.cardfail.2005.11.005

Hildick-Smith, D. J., Walsh, J. T., & Shapiro, L. M. (2000). Pulmonary capillary wedge pressure in mitral stenosis accurately reflects mean left atrial pressure but overestimates transmitral gradient. Am J *Cardiol, 85(4),* 512-515, A511. doi: S0002-9149(99)00785-7 [pii]

Hjalmarson, A., & Fagerberg, B. (2000). MERIT-HF mortality and morbidity data. Basic *Res Cardiol, 95 Suppl 1, I98*-103.

Huffman, M. D., Berry, J. D., Ning, H., Dyer, A. R., Garside, D. B., Cai, X., . . . Lloyd-Jones, D. M. (2013). Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. J Am *Coll Cardiol, 61(14),* 1510-1517. doi: 10.1016/j.jacc.2013.01.022

Hunt, S. A., Abraham, W. T., Chin, M. H., Feldman, A. M., Francis, G. S., Ganiats, T. G., . . . Yancy, C. W. (2009). 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circu*lation, 119(14),* e391-479. doi: CIRCULATIONAHA.109.192065 [pii]10.1161/CIRCULATIONAHA.109.192065

Just, H. (1996). Pathophysiological targets for beta-blocker therapy in congestive heart failure. Eur H*eart J, 17 Suppl B, 2-7.*

Kendrick, A. H., West, J., Papouchado, M., & Rozkovec, A. (1988). Direct Fick cardiac output: are assumed values of oxygen consumption acceptable? Eur H*eart J, 9(3),* 337-342.

Kirklin, J. K., Naftel, D. C., Kormos, R. L., Stevenson, L. W., Pagani, F. D., Miller, M. A., . . . Young, J. B. (2010). Second INTERMACS annual report: more than 1,000 primary left ventricular assist device implants. J Hea*rt Lung Transplant, 29(1),* 1-10. doi: 10.1016/j.healun.2009.10.009

Ko, D. T., Juurlink, D. N., Mamdani, M. M., You, J. J., Wang, J. T., Donovan, L. R., & Tu, J. V. (2006). Appropriateness of spironolactone prescribing in heart failure patients: a population-based study. J Car*d Fail, 12(3),* 205-210. doi: 10.1016/j.cardfail.2006.01.003

LaFarge, C. G., & Miettinen, O. S. (1970). The estimation of oxygen consumption. Cardi*ovasc Res, 4(1),* 23-30.

Lange, R. A., Moore, D. M., Cigarroa, R. G., & Hillis, L. D. (1989). Use of pulmonary capillary wedge pressure to assess severity of mitral stenosis: is true left atrial pressure needed in this condition? J Am *Coll Cardiol, 13(4),* 825-831.

Lechat, P., Packer, M., Chalon, S., Cucherat, M., Arab, T., & Boissel, J. P. (1998). Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. Circu*lation, 98(12),* 1184-1191.

Lehmann, K. G., & Platt, M. S. (1999). Improved accuracy and precision of thermodilution cardiac output measurement using a dual thermistor catheter system. J Am *Coll Cardiol, 33(3),* 883-891. doi: S0735-1097(98)00639-1 [pii]

Levy, D., Kenchaiah, S., Larson, M. G., Benjamin, E. J., Kupka, M. J., Ho, K. K., . . . Vasan, R. S. (2002). Long-term trends in the incidence of and survival with heart failure. N Eng*l J Med, 347(18),* 1397-1402. doi: 347/18/1397 [pii]10.1056/NEJMoa020265

Lindenfeld, J., Albert, N. M., Boehmer, J. P., Collins, S. P., Ezekowitz, J. A., Givertz, M. M., . . . America, H. F. S. o. (2010). HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Car*d Fail, 16(6),* e1-194. doi: S1071-9164(10)00173-9 [pii]10.1016/j.cardfail.2010.04.004

Lloyd-Jones, D., Adams, R. J., Brown, T. M., Carnethon, M., Dai, S., De Simone, G., . . . Stroke Statistics Subcommittee. (2010). Heart Disease and Stroke Statistics--2010 Update: A Report From the American Heart Association. Circul*ation, 121(7), e*46-215. doi: 10.1161/circulationaha.109.192667

Loh, E., Elkayam, U., Cody, R., Bristow, M., Jaski, B., & Colucci, W. S. (2001). A randomized multicenter study comparing the efficacy and safety of intravenous milrinone and intravenous nitroglycerin in patients with advanced heart failure. J Card *Fail, 7(2), 1*14-121. doi: 10.1054/jcaf.2001.24136

Maron, B. A., & Leopold, J. A. (2010). Aldosterone receptor antagonists: effective but often forgotten. Circul*ation, 121(7), 9*34-939. doi: 10.1161/CIRCULATIONAHA.109.895235

Mehra, M. R., Kobashigawa, J., Starling, R., Russell, S., Uber, P. A., Parameshwar, J., . . . Barr, M. (2006). Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates--2006. J Hear*t Lung Transplant, 25(9), 1*024-1042. doi: 10.1016/j.healun.2006.06.008

Mensah, G. A., & Brown, D. W. (2007). An overview of cardiovascular disease burden in the United States. Health *Aff (Millwood), 26(1), 3*8-48. doi: 26/1/38 [pii]10.1377/hlthaff.26.1.38

Mohrman, D. E., & Heller, L. J. (2010). Cardiov*ascular physiology (7th e*d.). New York: McGraw-Hill, Health Professions Division.

Morris, N. R., Snyder, E. M., Beck, K. C., Haseler, L. J., Olson, L. J., & Johnson, B. D. (2007). The relationship between resting lung-to-lung circulation time and peak exercise capacity in chronic heart failure patients. J Card *Fail, 13(5), 38*9-394. doi: 10.1016/j.cardfail.2007.02.002

Moss, A. J. (2003). MADIT-I and MADIT-II. J Cardi*ovasc Electrophysiol, 14(9 Supp*l), S96-98.

Moss, A. J., Hall, W. J., Cannom, D. S., Klein, H., Brown, M. W., Daubert, J. P., . . . Investigators, M.-C. T. (2009). Cardiac-resynchronization therapy for the

prevention of heart-failure events. N Engl *J Med, 361(14), 1*329-1338. doi: 10.1056/NEJMoa0906431

Narang, N., Gore, M. O., Snell, P. G., Ayers, C. R., Lorenzo, S., Carrick-Ranson, G., . . . McGuire, D. K. (2012). Accuracy of estimating resting oxygen uptake and implications for hemodynamic assessment. Am J Ca*rdiol, 109(4), 5*94-598. doi: 10.1016/j.amjcard.2011.10.010

Narang, N., Thibodeau, J. T., Levine, B. D., Gore, M. O., Ayers, C. R., Lange, R. A., . . . McGuire, D. K. (2014). Inaccuracy of estimated resting oxygen uptake in the clinical setting. Circula*tion, 129(2), 20*3-210. doi: 10.1161/CIRCULATIONAHA.113.003334

Nilsson, L. B., Nilsson, J. C., Skovgaard, L. T., & Berthelsen, P. G. (2004). Thermodilution cardiac output – are three injections enough? Acta An*aesthesiologica Scandinavica, 48(10), 1*322-1327. doi: 10.1111/j.1399-6576.2004.00514.x

Nishimura, R. A., Rihal, C. S., Tajik, A. J., & Holmes, D. R. (1994). Accurate measurement of the transmitral gradient in patients with mitral stenosis: a simultaneous catheterization and Doppler echocardiographic study. J Am Co*ll Cardiol, 24(1), 15*2-158. doi: 0735-1097(94)90556-8 [pii]

Novitsky, S., Segal, K. R., Chatr-Aryamontri, B., Guvakov, D., & Katch, V. L. (1995). Validity of a new portable indirect calorimeter: the AeroSport TEEM 100. Eur J A*ppl Physiol Occup Physiol, 70(5), 46*2-467.

O'Connell, J. B., & Bristow, M. R. (1994). Economic impact of heart failure in the United States: time for a different approach. J Heart *Lung Transplant, 13(4), S1*07-112.

Organ Procurement and Transplantation Network, & Scientific Registry of Transplant Recipients. (2012). OPTN/SR*TR 2011 Annual Data Report. Rock*ville, MD: Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation.

Ormiston, T. M., & Salpeter, S. R. (2003). Beta-blocker use in patients with congestive heart failure and concomitant obstructive airway disease: moving from myth to evidence-based practice. Heart F*ail Monit, 4(2), 45*-54.

Packer, M., Fowler, M. B., Roecker, E. B., Coats, A. J., Katus, H. A., Krum, H., . . . Group, C. P. R. C. S. C. S. (2002). Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circula*tion, 106(17), 2*194-2199.

Perez, W., & Tobin, M. J. (1985). Separation of factors responsible for change in breathing pattern induced by instrumentation. J Appl *Physiol, 59(5), 15*15-1520.

Pritchett, A. M., & Redfield, M. M. (2002). Beta-blockers: new standard therapy for heart failure. Mayo Cl*in Proc, 77(8), 83*9-845; quiz 845-836.

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Benjamin, E. J., Berry, J. D., Borden, W. B., . . . Turner, M. B. (2012). Heart Disease and Stroke Statistics—2012 Update. Circula*tion, 125(1), e2*-e220. doi: 10.1161/CIR.0b013e31823ac046

Ross, J. S., Bernheim, S. M., & Drye, E. D. (2011). Expanding the frontier of outcomes measurement for public reporting. Circ C*ardiovasc Qual Outcomes, 4(1), 11*-13. doi: 10.1161/CIRCOUTCOMES.110.959908

Rudolph, A. M., & Cayler, G. G. (1958). Cardiac catheterization in infants and children. Pediatr *Clin North Am, 5(4), 90*7-943.

Selzer, A., & Sudrann, R. B. (1958). Reliability of the determination of cardiac output in man by means of the Fick principle. Circ Re*s, 6(4), 48*5-490.

Shenkman, H. J., Pampati, V., Khandelwal, A. K., McKinnon, J., Nori, D., Kaatz, S., . . . McCullough, P. A. (2002). Congestive heart failure and QRS duration: establishing prognosis study. Chest, *122(2), 52*8-534.

Slaughter, M. S., Pagani, F. D., Rogers, J. G., Miller, L. W., Sun, B., Russell, S. D., . . . Investigators, H. I. C. (2010). Clinical management of continuous-flow left

ventricular assist devices in advanced heart failure. J Heart *Lung Transplant, 29(4 Supp*l), S1-39. doi: 10.1016/j.healun.2010.01.011

Summerhill, E. M., & Baram, M. (2005). Principles of pulmonary artery catheterization in the critically ill. Lung, 1*83(3), 20*9-219. doi: 10.1007/s00408-004-2537-9

Taylor, A. L., Ziesche, S., Yancy, C., Carson, P., D'Agostino, R., Ferdinand, K., . . . Investigators, A.-A. H. F. T. (2004). Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl *J Med, 351(20), 2*049-2057. doi: 10.1056/NEJMoa042934

Thompson, D. (2010, 9/16/2010). FDA approves devices for heart failure patients. News & *Events. Retri*eved 11/10/2010, 2010, from http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm226123.htm

Towbin, J. A., Lowe, A. M., Colan, S. D., Sleeper, L. A., Orav, E. J., Clunie, S., . . . Lipshultz, S. E. (2006). Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA, 2*96(15), 1*867-1876. doi: 296/15/1867 [pii]10.1001/jama.296.15.1867

van Grondelle, A., Ditchey, R. V., Groves, B. M., Wagner, W. W., & Reeves, J. T. (1983). Thermodilution method overestimates low cardiac output in humans. American *Journal of Physiology - Heart and Circulatory Physiology, 245(4), H69*0-H692.

Verbraecken, J., Van de Heyning, P., De Backer, W., & Van Gaal, L. (2006). Body surface area in normal-weight, overweight, and obese adults. A comparison study. Metaboli*sm, 55(4), 515*-524. doi: 10.1016/j.metabol.2005.11.004

Voelkel, N. F., Quaife, R. A., Leinwand, L. A., Barst, R. J., McGoon, M. D., Meldrum, D. R., . . . National Heart, L. n., and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. (2006). Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. Circulat*ion, 114(17), 18*83-1891. doi: 114/17/1883 [pii]10.1161/CIRCULATIONAHA.106.632208

Wang, Y., Moss, J., & Thisted, R. (1992). Predictors of body surface area. J Clin An*esth, 4(1), 4-10*. doi: 0952-8180(92)90111-D [pii]

Wolf, A., Pollman, M. J., Trindade, P. T., Fowler, M. B., & Alderman, E. L. (1998). Use of assumed versus measured oxygen consumption for the determination of cardiac output using the Fick principle. Cathet Ca*rdiovasc Diagn, 43(4), 372*-380. doi: 10.1002/(SICI)1097-0304(199804)43:4<372::AID-CCD3>3.0.CO;2-5 [pii]

Yancy, C. W. (2004). The prevention of heart failure in minority communities and discrepancies in health care delivery systems. Med Clin *North Am, 88(5), 1347*-1368, xii-xiii. doi: S0025712504000653 [pii]10.1016/j.mcna.2004.04.015

Østergaard, M., Nilsson, L. B., Nilsson, J. C., Rasmussen, J. P., & Berthelsen, P. G. (2005). Precision of bolus thermodilution cardiac output measurements in patients with atrial fibrillation. Acta Anaes*thesiologica Scandinavica, 49(3), 366-37*2. doi: 10.1111/j.1399-6576.2005.00613.x