ENERGY EXPENDITURE AND SUBSTRATE UTILIZATION IN OBESE INDIVIDUALS WITH HEART FAILURE

By

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Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

NURSING SCIENCE

December, 2012

Nashville, Tennessee

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To my wife, Amanda N. Squiers for without your infinite patience and support, this would not have been possible.

ACKNOWLEDGEMENT

I would personally like to dedicate this dissertation to the memory of Dr. Walter C. Randall, friend and mentor, who taught me too “anxiously and enthusiastically look forward to each day in the laboratory.” It was a great honor to be your final student.

I would like to express my thanks and appreciation to each of my committee members for their constant support and encouragement throughout this process. In particular, I would like to thank my advisor Dr. Michael Vollman for his continued mentorship and patience during my doctoral work. Dr. Mary Dietrich for her statistical guidance, and continued patience with my many questions. Dr. Lorraine Mion, for her guidance during the writing process. Dr. Terry Lennie, for continually challenging my thinking on metabolic matters and HF. Dr. Maciej Buchowski, who welcomed me into his lab, and provided continued guidance and education on calorimetry techniques. Dr. Henry Ooi, the heart failure cardiologist on this study, for his clinical guidance and willingness to challenge my thinking on HF modeling. Special thanks go to the Vanderbilt Clinical Research Center staff who provided clinical support throughout my study and created a wonderful atmosphere for a scientist in training.

This work would not have been possible without the financial support of the Vanderbilt Institute of Clinical and Translational Research, through a Clinical and Translational Award, which financially supported this work in part by Vanderbilt CTSA, grant UL1 RR024975 from NCRR/NIH.

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CHAPTER I

INTRODUCTION

Statement of Problem

Heart failure (HF) is a severely limiting terminal condition characterized by a progressive chronic disease state with intermittent acute exacerbations. Classic HF symptoms include progressive dyspnea, fatigue, and edema that increase in intensity during periods of acute exacerbations. These symptoms are usually progressive in severity over the course of the syndrome and eventually result in the patient's death. HF can be caused by any myocardial injury and its resulting myopathy (Hunt, 2005).

In modern countries, such as the United States, coronary artery disease, along with subsequent myocardial infarction, is the most common etiology of HF (Hunt, 2005). Although clinicians who monitor the treatment of patients with HF are aware of a variety of systemic metabolic derangements related to changing body composition over the course of HF, they lack appropriate evidence-based interventions, such as basic nutritional guidelines (Lennie, 2008). In the current neurohormonal model of HF, a number of short-term and long-term compensatory mechanisms for reduced cardiac output are described, such as the sympathetic nervous system (SNS), that result in compensatory effects (Packer, 1992). Because these compensatory mechanisms have previously been determined to be energy dependent systems, their chronic up-regulation suggests an increasing systemic energy demand. Therefore, one could reasonably hypothesize that these systems increase energy expenditure over time and potentially affect macronutrient substrate utilization rates during the course of HF.

Little evidence exists to guide the understanding of the metabolic demands associated with HF. Researchers conducted several studies in their attempts to determine the increase in metabolic rate associated with the disease, but these studies were plagued with poor measurement systems and a lack of participant inclusion controls (Roberto Aquilani et al., 2003; Obisesan et al., 1996; Obisesan, Toth, & Poehlman, 1997; Pasini, Opasich, Pastoris, & Aquilani, 2004; Toth, Gottlieb, Fisher, & Poehlman, 1997; Toth, Gottlieb, Goran, Fisher, & Poehlman, 1997). For these reasons, these studies yielded confounding results, making the determination of the clinical utility of measuring metabolic function in patients living with HF difficult. Although direct measurement of metabolic function did not yield specific evidence regarding potential energy demands of patients with HF, secondary analyses of data from randomized, controlled clinical trials and cohort studies revealed a clear survival benefit associated with obesity in patients with HF (Curtis et al., 2005; Fonarow, Srikanthan, Costanzo, Cintron, & Lopatin, 2007; Hall et al., 2005; Kalantar-Zadeh, Abbott, Salahudeen, Kilpatrick, & Horwich, 2005; Oreopoulos et al., 2008).

Purpose of Study

A variety of physiologic compensatory systems are up-regulated to preserve organ perfusion in response to HF, including the SNS, the rennin-angiotensin-aldosterone system (RAAS), endothelin production, and cardiac tissue remodeling. Although each of these systems acts to provide perfusion support early in the development of HF, their chronic up-regulation leads to rapid progression of HF. Pharmacologic therapies that chronically suppress these systems, such as beta-adrenergic blockade and angiotensin

converting enzyme inhibitors, have been found to reduce symptoms, such as shortness of breath, and decrease morbidity and mortality. Previous physiologic research indicated that these systems are energy dependent and that chronic up-regulation increases physiologic energy demands. For example, increased SNS stimulation results in increased heart rate and cardiac inotropy, both of which are energy dependent effects (Goodwin, Taylor, & Taegtmeyer, 1998). These systems are up-regulated chronically during the course of HF. Thus, one could reasonably expect that they result in chronic increased energy utilization. As HF symptoms increase, particularly during the late stages, these energy utilization effects should become more pronounced, potentially resulting in physiologic harm and more rapid disease progression. Unfortunately, this hypothesized increased energy utilization during the course of HF has not yet been fully described.

Although the chronic effects of these compensatory systems were not fully explored, evidence suggested that energy balance may play a unique and important role in HF. As discussed previously, recent evidence indicated that patients with HF who are obese appear to have significant survival benefits over normal weight patients (Oreopoulos et al., 2008). Because of this suggestion, the development of nutritional guidelines for both normal weight and obese patients living with HF has been difficult. Of particular interest were the results of several recent studies that suggest the natriuretic peptide system, which is up-regulated during the course of HF, may be responsible for lipolysis and subsequently for the shifting of systemic substrate utilization through the liberation of free fatty acids (the primary substrate utilized in myocardial energy production; (Kalra & Tigas, 2002; Sengenès, Zakaroff-Girard, & Moulin, 2002).

A more robust physiological model of HF was needed to account for the metabolic demands, both energetic and substrate, associated with the disease process and its progression. With systemic energetic measurement, one could measure total energy expenditure and its sub-components with great accuracy. What was unclear was the feasibility of taking these measures in the HF population and the development of an appropriate sampling strategy to account for metabolic variations found in the HF.

The primary problem addressed in this dissertation study was the lack of any feasibility data on whole room indirect calorimetry in the HF population, along with an accurate description of systemic energy expenditure and substrate utilization in individuals with HF. The purpose of this dissertation research study, therefore, was to assess the feasibility of whole room calorimetry in patients with HF by assessing for potential differences in systemic energy expenditure and substrate utilization between normal weight and obese individuals with HF.

Significance

The significance of studying systemic metabolism in patients with HF could be broadly viewed in terms of its significance to society, to the nursing profession, and to healthcare.

Significance to Society

HF represents a significant burden to society through increased morbidity, mortality, and healthcare costs. As of 2004, cardiovascular disease was present in over 80 million U.S. citizens and resulted in approximately 869,000 deaths per year, of which

284,000 were related to HF (Rosamond et al., 2008). This disease has been the number one killer of Americans since 1900, with the singular exception of 1918 when the influenza epidemic occurred.

Treatment aimed at avoiding mortality and improving quality of life during HF had an expected cost, both direct and indirect, of $34.8 billion in the United States in 2008 (Rosamond et al., 2008). Following initial hospital admission for HF, patients were likely to have repeat hospitalizations: 2% within 2 days of discharge, 20% within 30 days, and 50% within 6 months (Aghababian, 2002). Patients hospitalized for initial acute exacerbations of HF had 1-year mortality rates of 33.1% (Jong, Vowinckel, Liu, Gong, & Tu, 2002) and 5-year mortality rates of 50% (Aghababian, 2002). These mortality rates suggested that patients with HF may have mortality rates worse than patients with some cancers, including cancers of the breast, bowel, and ovary (Stewart, MacIntyre, Hole, Capewell, & McMurray, 2001). Therapy in HF has been focused on slowing the loss of the patient's functional limitations and on decreasing mortality. Therefore, because of the mortality rates and the substantial costs associated with treatment, HF has become a significant healthcare issue to society.

The incidence of HF has also been steadily rising since the 1980s, currently accounting for more than 1 million hospital admissions annually in the United States (Rosamond et al., 2008). Internationally, the World Health Organization reported that one third of global deaths were attributed to cardiovascular disease, including HF ("Strategic priorities of the WHO Cardiovascular Disease programme.," 2008). This increasing rate could have a massive economic impact in many countries. For example, over the 10-year period 2006–2015, China could lose an estimated $558 billion in national income related

to cardiovascular disease morbidity and mortality ("Strategic priorities of the WHO Cardiovascular Disease programme.," 2008). One of the current goals of the World Health Organization Task Force on Cardiovascular Disease, a program aimed at the prevention, management, and monitoring of cardiovascular diseases, has been the development of cost effective healthcare innovations for the treatment of cardiovascular disease, including HF.

Significance to the Nursing Profession

As discussed previously, cardiovascular disease has been rapidly increasing throughout the world. The majority of these cases will ultimately result in cardiomyopathies, initiating the clinical syndrome of HF, a symptomatic, progressive condition that ultimately results in the patient's death. HF will also be the cause of a significant amount of suffering among patients and families. As a profession whose primary goal is intervention for the reduction of human suffering, nurses will find cardiac disease and subsequent HF to be the primary focus of future clinical interventions.

Identifying specific clinical interventions to reduce or halt the progression of HF could be extremely difficult. Because HF is a complex syndrome that has yet to be fully described in a physiologic model adequate for predicting disease progression, identification of pathways to slow progression has been difficult. Expansion of the physiologic model to include factors such as metabolic dysfunction in HF might result in identification of new clinical interventions. In particular, nutritional therapy, a distinguishing feature of the nursing profession since the time of Nightingale

(Nightingale, 1992), might be a low-cost, efficacious target for HF intervention development.

Cardiovascular nurses (in particular, advanced practice nurses) are in a unique position to affect the outcomes of HF patients. Over the past decade, the management of complex chronic diseases, including HF, has been increasingly shifted to nurse-led clinics (Grady et al., 2000). Although a combination of pharmaceutical management and individualized symptom management is helpful in slowing HF disease progression, nurses have been limited by the lack of evidenced-based nutritional interventions for this population (Lennie, 2008).

Significance to Healthcare

An improved understanding of the metabolic changes associated with HF might yield a variety of potential clinical interventions for HF patients. Potential areas for advances based on an improved understanding of systemic metabolic changes in HF include (a) the development of nutritional guidelines for HF patients, (b) an improved clinical definition of cardiac cachexia, and (c) a method to measure systemic compensatory efforts during HF. At this time, no comprehensive nutritional guidelines for the care of patients with HF have been found (Lennie, 2008)

Studies indicated variations in body composition during HF are strongly related to long-term survival. Cardiac cachexia, the wasting state often associated with late stage HF, was associated with a marked increase in mortality of 50% in 18 months Conversely, overweight or obese patients had a significant survival improvement over normal weight HF patients (Oreopoulos et al., 2008). Although these body composition classifications

were associated with survival in HF, little information was found about the specific macro- and micro-nutrient requirements for individuals with HF. With information regarding the specific energetic needs and nutrient needs during the course of HF, nutritional guidelines could be developed with the potential to optimize body composition-related survival.

During the course of chronic HF, changes in systemic metabolism often result in a state of chronic catabolism and generalized tissue wasting. This wasting process is currently defined as cardiac cachexia, referring to the cachexia found specifically in the chronic HF. Cardiac cachexia has been linked to the rapid progression of symptoms found in late-stage HF, with a subsequent increase in mortality to 50% in 18 months (S. Anker et al., 1997). According to the suggested definition of cachexia, one must sustain a non-edematous weight loss of at least 6% over the course of 6 months (Anker et al., 2003). However, basing the diagnosis of cardiac cachexia on anthropometric changes, which require a significant amount of time to occur, often resulted in finding this systemic metabolic derangement late in its course. A better diagnostic definition might eventually be possible by using energy expenditure measurement and measurement of specific macronutrient utilization rates.

The individual compensatory systems found during the course of HF have been previously described as including (a) the SNS; (b) the RAAS; (c) inflammatory/immune activation; and (d) the production of vasoactive proteins, such as endothelin. These systems act acutely to compensate for loss of perfusion in HF, but their chronic up-regulation results in detrimental effects that negatively affect morbidity and mortality in late-stage HF. Although aspects of these compensatory actions can be measured, their

energetics have not yet been described. Because these compensatory systems are energy dependent, one approach to describe the cumulative compensatory effects of these systems during HF could be longitudinal assessments of energy expenditure and substrate utilization rates. This approach might result in a more robust description of the systemic metabolic stress placed on individuals with HF over time and in valuable evidence for the use of medications to suppress the chronic pathologic effects of these compensatory systems.

Overall, a more robust understanding of the metabolic changes associated with HF could result in a variety of potential clinical benefits. Thus, by including evidence of systemic metabolic changes over time in the current neurohormonal model of HF, improved clinical interventions could be developed.

CHAPTER II

LITERATURE REVIEW

Theoretical Framework

Physiologic models of HF have evolved over the past 60 years. Early models were focused on fluid volume overload to explain the patient's symptoms, such as fatigue, shortness of breath, edema, and general malaise. With one of the first modern models, the cardio-renal model, excessive sodium and fluid retention resulting from decreased renal blood flow and increased aldosterone, secondary to loss of cardiac contractility, were the primary causes of symptoms (Packer, 1992). Consequently, diuretic therapy was used to reduce fluid volume overload and related symptoms. Although this model explained some of the relationships between volume overload and symptoms, it could not be used to explain the continued progression of HF with diuretic treatment.

With the advent of right heart catheterization and echocardiography, an increasing interest in the hemodynamic alterations of HF resulted in the expansion of this model into the cardiocirculatory model of HF. This model served to augment earlier frameworks by including reduced cardiac output and peripheral vasoconstriction as central elements of the physiologic processes associated with HF symptoms. Several pharmacological treatment strategies suspected of improving symptoms and reducing mortality were tested under this model, including cardiac inotropes and vasodilators. Of particular interest was the development of various inotropic support agents, including milrinone, enoximone, imadzodan, vesnarinone, xamoterol, and ibopamine. Many of these agents were found to

significantly improve HF symptoms, although progressive testing revealed unexpectedly that all the agents resulted in increased mortality (J. N. Cohn et al., 1998; J. N. Cohn & Johnson, 1990; CONSENUS:Investigators, 1987; DiBianco et al., 1989; 1990; Hampton et al., 1997; O'Connor et al., 1999; Packer et al., 1991; Pfeffer et al., 1992; Uretsky et al., 1990; Yusuf, 1991; Yusuf et al., 1992).

A variety of other agents were tested for their potential benefits in HF, including beta-adrenergic blockade, suppressors of the RAAS, and diuretic therapies. Angiotensin converting enzyme inhibitors and beta- adrenergic blockers were found to improve symptoms and to dramatically reduce HF-associated mortality (CIBIS-II:Investigators, 1999; Colucci, 2004; CONSENUS:Investigators, 1987; Fowler, 2004; Packer et al., 1996; Pfeffer et al., 1992; Yusuf et al., 1992). Although these agents appeared to be beneficial in lowering mortality rates, the cardiocirculatory model was insufficient to explain the benefits of these agents.

Currently, the study of the HF pathophysiology has been focused on the neurohormonal model (Francis, 2001; Packer, 1992). In this model, the heart is viewed as having two distinct but interrelated functions. First, as conceptualized in the cardiocirculatory model, the heart is a muscular pump used to distribute blood. Second, the heart is an endocrine organ with specific homeostatic functions that interact with other physiologic systems to compensate for short-term depressed cardiac function. Discoveries in the early 1980s indicated that the heart also functioned to mediate a variety of physiologic functions by producing neurohormones that have physiologic effects at sites outside of the heart. Essentially, in this model, the heart is viewed as having a key role in hormone production and homeostatic regulation.

The Neurohormonal Model of Heart Failure

In the neurohormonal model, HF is conceptualized as a syndrome of activated neurohormonal systems following an initial myocardial injury (Anker & Al-Nasser, 2000; Packer, 1992; Tziakas, Chalikias, & Xateras, 2003). Although this model is inclusive of the known hemodynamic alterations of HF, it has been expanded to include the neurohormonal changes associated with both acute and chronic HF. These neurohormonal alterations are part of normal physiologic compensatory mechanisms. However, when activated during HF, these physiologic compensation mechanisms adversely affect the progression of HF.

These competing compensatory mechanisms are up-regulated by decreased cardiac output and tissue perfusion resulting from the cardiac injury. When these mechanisms activate, they result in preservation of blood flow and organ perfusion. Nonreversible myocardial damage results in chronic up-regulation of these neurohormonal mechanisms, leading to further progression of the disease. The primary neurohormonal compensatory mechanisms include the following (Tziakas et al., 2003): (a) SNS activation, (b) RAAS activation, (c) inflammatory/immune activation, (d) endothelin production, and (e) natriuretic peptide secretion.

These systems are up-regulated during periods of low cardiac output and low tissue perfusion to provide short-term compensation to increase cardiac output and organ perfusion. In cases of nonreversible chronic decreases in cardiac output, these systems are activated over long periods of time and adversely affect hemodynamics and myocardial

function. For further clarity, each of these systems has been discussed within the context of the neurohormonal model of HF.

Sympathetic nervous system activation. As discussed previously, the SNS is chronically stimulated in patients with HF with long-term detrimental effects (Hasking et al., 1986; Kaye et al., 1995). Studies from the 1960s revealed that urinary and serum norepinephrine (i.e., measures of SNS activation) are increased in individuals with HF and are positively associated with symptom severity (Chidsey, 1962; J. N. Cohn et al., 1984). Early in states of decreased cardiac output, the increased level of circulating norepinephrine is compensatory, resulting in increased cardiac output through chronotropic and inotropic responses while shunting blood from the periphery to the central circulation for increased organ perfusion. As the HF syndrome progresses, the RAAS is activated by the increased sympathetic stimulation, resulting in sodium and water retention that effects increased intravascular volume. Long-term sympathetic stimulation also results in cardiac myocyte hypertrophy, apoptosis, and necrosis (Gerdes & Capasso, 1995; McGavock, Victor, Unger, & Szczepaniak, 2006; Pfeffer & Braunwald, 1990). This long-term stimulation paradoxically results in down-regulating the beta-adrenergic receptors, in particular the beta-1 receptors, which can result in myocardial electrical and mechanical dysfunction. These processes effect further increases in sympathetic stimulation over time (Anversa, Olivetti, & Capasso, 1991; Pfeffer & Braunwald, 1990).

Renin-angiotensin-aldosterone system activation. Activation of the RAAS results in fluid retention and altered systemic hemodynamics when renal perfusion is low. Specifically, intravascular fluid volume is increased through aldosterone-dependent water

retention; and renal perfusion is increased through arterial vasoconstriction and sympathetic stimulation. A long-term reduction in renal perfusion results in (a) increased progressive fluid retention and (b) increased systemic vascular resistance. The effect of continued increased intravascular fluid volume is increased intravascular hydrostatic pressure with resultant pulmonary and peripheral edema. The effect of increased systemic vascular resistance is an increased left ventricular workload.

RAAS activation results in the production of angiotensin II, a potent systemic vasoconstrictor and efferent renal arteriole constrictor. The effect of this vasoconstriction is increased cardiac preload and afterload. At the renal efferent arteriole, the effect is an increased glomerular filtration rate and increased sodium reabsorption in the renal tubules. This vasoconstriction results in increased systemic blood pressure and increased vital organ perfusion, while increasing glomerular filtration. Increased levels of circulating angiotensin II present over long periods of time yield deleterious effects on the heart through increased filling pressure and increased workload. Along with cardiac effects, prolonged exposure to elevated levels of angiotensin II also results in afferent renal arteriole constriction, which effects a marked reduction in glomerular filtration rates over time and ultimately in renal failure (Ferrari, Ceconi, Curello, & Visioli, 1998; Schrier & Abraham, 1999).

Further prolonged RAAS activation, with subsequent angiotensin II production, results in considerable cardiac consequences, including cardiac remodeling. Chronically elevated levels of angiotensin II have been linked to cardiac myocyte hypertrophy, apoptosis, necrosis, and stimulation of cardiac fibroblasts. The cumulative effects of these pathways is progressive myocardial remodeling that furthers the progressive dysfunction

of HF (Anversa, Olivetti, & Capobasso, 1991; Gerdes & Capasso, 1995; Pfeffer & Braunwald, 1990; Schrier & Abraham, 1999).

Inflammatory/immune activation. HF is a state during which significant immune and inflammatory activation occurs (S. D. Anker & S. von Haehling, 2004; Mann, 2002; Torre-Amione, 2005). Much of this activation is subsequent to the initial myocardial injury that eventually results in HF symptoms. Previous research studies were focused on a variety of pro-inflammatory cytokines and their soluble receptors. Cytokines are a class of proteins used for intercellular communications in the cellular immune response. In particular, cytokines are produced by activated macrophages and mediate the systemic inflammatory response.

Currently, three competing hypotheses have been formulated to explain the source of potential antigens that initiate the immune response during HF (S. Anker & S. Von Haehling, 2004). According to the first hypothesis, tissue injury secondary to loss of cardiac output occurring at both the myocardium and peripheral tissue is responsible for immune activation. According to the second hypothesis, because of the significant bowel wall edema found in HF, lipopolysaccharides cross this barrier, translocating into the intravascular compartment where an immune response is initiated. Lipopolysaccharides are a strong endotoxin naturally produced in the cell wall of gram-negative bacteria. According to the third hypothesis, the myocardium may actively produce cytokines in response to prolonged sympathetic stimulation without a specific antigen present. Although several potential explanations exist for the potential activation of the immune/inflammatory response via antigen introduction or physiologically, no clear

identification of the source of this activation has yet been found. Each of these hypotheses might have a role, or some undiscovered phenomenon could be responsible.

Several key cytokines have been found to have roles in the pro- and anti-inflammatory responses associated with HF. The pro-inflammatory cytokines include tumor necrosis factor-alpha, interleukin-1, interleukin-6, and interferon-γ; the anti-inflammatory cytokine is interleukin-10 (Sharma, Coats, & Anker, 2000; Zhao & Zeng, 1997). The pro-inflammatory cytokines have been found capable of exerting a deleterious effect on the myocardium through inducing myocardial hypertrophy, apoptosis, and loss of inotropy via disarrangement of the myocardial extracellular space (Yokoyama et al., 1993). However, although the outcomes for cytokine production occurring in HF are identified, much of the specific pathophysiology has remained unknown.

Endothelin production. Endothelins are a family of peptides produced by the vascular endothelium that have potent vasoconstrictor and mitogenic properties. Circulating plasma endothelin concentrations have been shown to be elevated in HF and to be associated with symptom severity (Cody, Haas, Binkley, Capers, & Kelley, 1992; Pacher et al., 1996). Endothelins are produced primarily by the vascular endothelium and are the cause of peripheral vasoconstriction, which results in increased preload and afterload. At the renal arteriole bed, endothelins are the cause of renal constriction, resulting in sodium and water retention. Along with peripheral vasoconstriction, endothelins have been shown to cause severe pulmonary vasoconstriction, which results in increased right ventricular afterload and pulmonary hydrostatic pressure (Cody et al., 1992; Tsutamoto et al., 1999). Besides these hemodynamic effects, long-term endothelin production has been found to have direct deleterious effects on the myocardium,

including cardiac myocyte hypertrophy, myocardial fibrosis, and extracellular matrix disarrangement (Schrier & Abraham, 1999).

Natriuretic peptide release. In 1981, DeBold et al. were able to potentiate natriuresis and hypotension when the supernatants of Sprague-Dawley rats' atrial and ventricular cardiac tissues were administered intravenously in other Sprague-Dawley rats. This initial discovery resulted in the formation of the neurohormonal model of HF because it showed that cardiac tissues contained hormones capable of producing systemic and local biological activity.

Three natriuretic peptides have been identified in humans: atrial natriuretic peptides (produced in the atrial myocardium), brain-type natriuretic peptides (produced in the ventricular myocardium), and C-type natriuretic peptides. These neurohormones have several specific mechanisms, including (a) an increased glomuler filtration rate from efferent renal arteriole constriction and afferent renal arteriole dilation; (b) reduced sodium reabsorption with resultant natriuresis; (c) inhibition of the RAAS secondary to inhibition of renin secretion; (d) inhibition of aldosterone secretion, thereby increasing natriuresis; (e) inhibition of endothelin-1, resulting in pulmonary artery dilation; and (f) systemic vasodilatation. The effects of these actions are decreased systemic vascular resistance, reduced preload, reduced afterload, reduced cardiac workload, and increased cardiac output.

In addition to these systemic neurohormonal effects, the cardiac natriuretic peptides appear to have direct effects on the myocardium. These agents appear to have anti-mitogenic properties that counteract myocyte hypertrophy and inhibit fibrosis through reducing the number of fibroblasts in the myocardium (Calderone, Thaik,

Takahashi, Chang, & Colucci, 1998; Cao & Gardner, 1995; Pfeffer & Braunwald, 1990). These effects result in anti-remodeling of the injured ventricular myocardium.

The discovery that cardiac hormones appear to have a role in the metabolic processes of adipose tissue (Sengene, Berlan, Glisezinski, LaFontan, & Galitzky, 2000) has been of particular interest, suggesting that the heart may have a role in modulating systemic metabolic processes. Overall, the natriuretic peptide system appears to down-regulate many of the compensating systems, such as the SNS, the RAAS, and inflammatory markers, for periods of reduced cardiac output under normal conditions.

Systemic Bio-Energetics of Heart Failure

The neurohormonal model of HF contains several compensatory systems that interact over the course of HF. As described previously, many of these systems affect short-term compensation for decreased cardiac output and organ perfusion. However, when activated over long periods of reduced cardiac output, these systems result in direct end-organ damage. Of benefit is the ability of this model to explain patients' continued progression of HF independent of therapies that are inhibitors specific neurohormonal systems, such as beta-adrenergic blockers and agents that suppress the RAAS.

One of the interesting implications of this model is its potential to affect a variety of local and systemic metabolic pathways. For example, the compensatory systems discussed previously are all energy dependent in that significant energy expenditure is required in their activation and subsequent response. However, this energy dependence is secondary to the work achieved by each of the compensatory systems. Although the work

accomplished by these physiologic systems is described very well, the quantification of the energy utilized in this process has not yet been fully described.

Previous studies indicated increase body temperature, a surrogate marker of increased metabolism, throughout the course of HF (A. E. Cohn & Steele, 1934; Kinsey & White, 1940; Steele, 1934). These studies revealed the clearest evidence for increased energy production rates, possibly related to the increase in energy expenditure associated with these multiple compensatory systems. Although this is indicative of an energy production increase, the net energy expenditure has not yet been fully described and quantified. Therefore, one might reasonably assume that chronic activation of these systems, as indicated in the neurohormonal model of HF, will result in increased energy requirements both at the local tissue and systemic levels.

Although systemic energy expenditure appears to be increased in HF, consideration should be made for the increased energy expenditure of each of the activated physiologic compensatory systems. For example, in a study from 1922, researchers attempted to determine the energetic impact of immune activation (Barr, Russell, Cecil, & Du Boise, 1922). The results indicated that an increase of one degree centigrade in body temperature, initiated with the injection of protease or typhoid vaccine, was equal to an increase in basal energy expenditure of 7%–13%. This study was the last human study conducted to attempt to quantify the energetic impact of immune activation. However, although humans were understudied, the results of studies using animal models indicated that immune activation is clearly an energy dependent process (Bonneaud et al., 2003; Demas, Chefer, Talan, & Nelson, 1997; Sheldon & Verhulst, 1996).

The SNS has a role in maintenance and regulation of exchanges of energy, both internally and externally (Recordati, 2003). In compensating for the reduced perfusion in HF, cardiac chronotropic and inotropic effects increase substantially. These effects result in an increased energy demand secondary to an increased myocardial workload (Suga, 1990). Overall, the net effect is an increase in cardiac energy expenditure that, when paired with a lack of available substrate, results in worsening cardiac function (Ashrafian, Frenneaux, & Opie, 2007). Clinically, this might explain the association of beta-adrenergic blockade with substantial reductions in resting metabolic rate and some of the morbidity and mortality benefits of the drug in HF (Podbregar & Voga, 2002).

The SNS, RAAS, and ET endothelin all result in the constriction of vascular smooth muscle, ultimately to regulate blood flow and pressure. Vascular smooth muscle has a substantial metabolic demand because continued augmentation of muscular tone is necessary to deal with moment-to-moment variations in blood pressure and flow (Barron, Kopp, Tow, & Parrillo, 1996; Butler & Siegman, 1985). Thus, one might reasonably suspect that the chronic up-regulation of these systems results in chronic elevations in systemic energy demands.

One might also reasonably view the natriuretic peptide system not only as the cardiac regulatory system handling alterations in systemic hemodynamics but also as the system to provide needed substrate and energetic control during myocardial stress. This could be accomplished through free fatty acid liberation directly via lipolysis (Birkenfeld et al., 2005) or through down-regulating the workload of these systems, as previously discussed. When the heart is under acute stress, a shift occurs resulting in free fatty acid being used as the primary energy substrate, followed by carbohydrates (Goodwin et al.,

1998). However, little has been learned about cardiac metabolism during chronic long-term cardiac stress. Hypothetically, a substrate utilization shift to utilization of fat might be a way to compensate for the long-term increased metabolic demands of these compensatory systems.

Thus, the neurohormonal model of HF could be expanded to include a number of predicted pathways for increased EE and reduced energy intake. In this expanded model, a bio-energetic model of HF (Figure), the potential relationships between energy expenditure and the activated compensatory systems as previously discussed have been clarified. Previous work showed that later-stage HF results in decreased nutritional intake from psychosocial conditions and increased gut edema (Lennie, 2008; Pirlich, Norman, Lochs, & Bauditz, 2006; Stephan von Haehling, Doehner, & Anker, 2007; Witte & Clark, 2002). Ultimately, this model could be used to predict elevated expended energy and reduced nutrient intake in HF patients that result in massive systemic energy deficiencies. Such deficiencies could be the reason for the rapid progression of HF in later stages and could have implications in the development of cardiac cachexia (S. D. Anker et al., 1997). Accurate systemic level measurement could also be of assistance in the identification of these pathways and in the development of a HF model capable of predicting a patient's substrate and energetic needs.

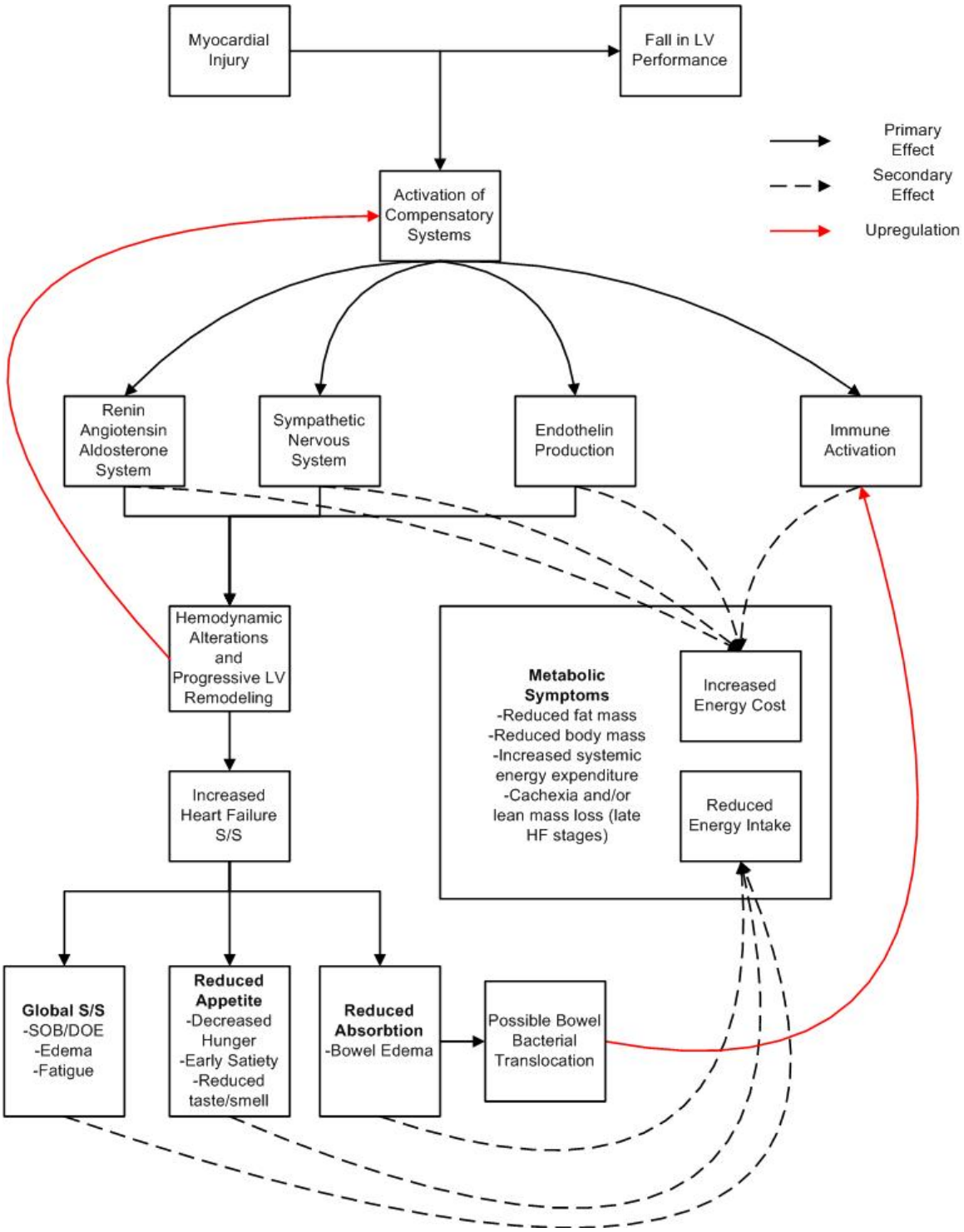

Figure. A bio-energetic model of heart failure.

Critical Analysis of Relevant Literature

Most current understandings of systemic metabolic processes occurring during HF have come from a variety of research studies focused on the measurement of systemic energy expenditure. Hood-based indirect calorimetry was first used in 1994 to study the differences in energy expenditure in patients with HF versus healthy subjects. Measured resting energy expenditure, calculated from a 45-minute period of gas exchange, was found to be 18% higher in patients with HF than in healthy subjects (1828+/- 275 kcals/d vs. 1543+/- 219 kcals/d), although no significant difference in caloric intake was noted between groups on a 3-day nutritional intake record (Poehlman, Scheffers, Gottlieb, Fisher, & Vaitekevicius, 1994). Differences in energy expenditure were more pronounced when energy expenditure was indexed against fat-free mass from dual x-ray absorptiometry. As fat-free mass increased, a strong, positive, linear correlation with energy expenditure was shown. This finding suggested that although fat mass has a role as an energy store, an increased basal metabolic rate is required to maintain an increased fat mass.

In 1997, Toth, Gottlieb, Fischer et al., attempted to use dually labeled water to measure energy expenditure in comparing cardiac cachexia patients to non-cachexic patients and healthy controls. Initial resting energy expenditure (REE; via hood-indirect calorimetry measured via gas exchange over 45 minutes) and dual energy x-ray absorptiometry (DEXA) for body composition also were completed. The study indicated no statistically significant short-term differences in REE between patients with HF and those without HF, including those patients with cachexia (Toth, Gottlieb, Goran, et al., 1997). These findings differed from those in previous studies that suggested increased

energy expenditure in HF. Because this study was cross-sectional and was based on a small sample size (N = 75), drawing conclusions regarding energy expenditure throughout HF progression was difficult. However, the findings appeared be in contrast to previous energy expenditure evaluations within HF.

Calorimetry based research was expanded with the use of a free fatty acid assessment in 1998. In a small study of patients with HF (N = 7) and healthy controls (N = 7), Lommi, Kupari, and Yki-Jarvinen (1998) attempted to quantify the differences in energy expenditure and free fatty acid concentration. The results revealed corroboration for the results of previous studies, confirming the increase in energy expenditure associated with HF. In this study, free fatty acid concentrations were found to be significantly higher in patients with HF, along with N-terminal-pro-B-natriuretic peptide levels. Although unknown at the time of publication, the findings were confirmation of the role of NPs in up-regulating fat metabolism (increasing free fatty acid).

In 2003, Acquilani et al. looked at the energy and nitrogen balance between non-obese subjects with HF and normal weight controls. By estimating total energy expenditure from REE (measured by metabolic cart) and comparing it to subjects' dietary records, they found a lack of appropriate caloric and protein intake to match daily needs. When direct measures of REE were assessed, although the methodology of this measurement was not described, significant differences were found between HF and control subjects matched by age, body mass index (BMI), and sedentary lifestyle (1499±228 kcals vs. 1309±315 kcals [$p < 0.05$], respectively; (R. Aquilani et al., 2003). Although the results from this study suggested increased protein and energy needs in patients with HF, they were limited by the accuracy of the metabolic measurement

techniques. In particular, metabolic measurements were averaged over a 60-minute period using metabolic carts and were transformed into total energy expenditure rates for a 24-hour period. Regardless, the results of this study still suggested that many HF subjects may be calorie and protein deficient.

More recently, a small study of eight patients with ischemic HF versus controls indicated that patients with HF had decreased rates of glucose oxidation and increased fat oxidation. However, no differences in resting energy expenditure were revealed over a 25-minute period (Norrelund et al., 2006). Although this study was limited by its sample size, it did show some apparent differences in substrate utilization between patients with HF and healthy individuals that warrant further study.

A variety of information in the literature suggested significant metabolic and inflammatory derangements are associated with HF and cardiac cachexia. These derangements have not been well described, primarily because of the accuracy and timing of instrumentation and lack of sufficient samples. Norrelund et al.'s (2006) and Acquilani et al.'s (2003) works, although limited by sample size and instrumentation, suggested potential differences in systemic substrate utilization and energy expenditure in patients with HF. The specific components of total energy expenditure used to identify basal energy expenditure, such as sleep energy expenditure and REE, have not yet been measured.

Recent suggestions that obesity improving survival in HF has resulted in scientific interest in the study of metabolic changes associated with obesity and HF (Curtis et al., 2005; Fonarow et al., 2007; Kalantar-Zadeh, Anker, Coats, Horwich, & Fonarow, 2005; Lavie, Osman, Milani, & Mehra, 2003). In 2001, Horwich, Fonarow, Hamilton,

MacLellan, Woo, and Tillisch described an unusual relationship between obesity and HF mortality, now referred to as the *obesity paradox*. Prior to this study, the presence of obesity as an independent risk factor for the development of cardiac disease, including HF, was well documented (Hubert, Feinleib, McNamara, & Castelli, 1983). Horwich et al. (1983) divided 1,203 patients enrolled in a comprehensive HF treatment program into four subsets based on BMI: underweight subjects (< 20.7), normal weight subjects (20.7 to 27.7), overweight subjects (27.8 to 31), and obese subjects (> 31). Subjects also were matched within baseline characteristics so that patient weight was the primary difference between groups. The follow-up time for subjects in the study was 60 months. At the end of the follow-up period, data were analyzed and mortality rates determined for each group. Subsequent analysis revealed that subjects with high BMIs (i.e., the overweight or obese categories) did not display increased mortality. Instead, they showed a trend toward improved 5-year survival (Horwich et al., 2001). Surprisingly, these investigators concluded that following a diagnosis of HF, obesity was not associated with increased mortality but appeared to improve survival rates. The authors speculated that this association might be related to obesity-associated alterations in a number of physiologic systems, including cytokine activation, global substrate utilization, and neuroendocrine alterations.

Horwich et al.'s (2001) study was followed by a subset analysis of the Digitalis Investigation Group (DIG) trial in which researchers looked at survival differences associated with BMI (Curtis et al., 2005). In the DIG study, the sample size was increased to 7,767 patients, more than 6 times larger than the sample in Horiwich et al.'s (2001) study. Also notable was that although the BMI categories in the DIG study were

similar to those in the earlier work, slightly different cutoffs for the subset groups were used. The DIG assigned patients to the following four groups: underweight (< 18.5), healthy weight (18.5 to 24.9), overweight (25.0 to 29.9), and obese (> 30). Subjects were followed for 37 months, and hazard ratios (*HR*) were calculated for the final time point. Subjects who were overweight or obese had significantly less risk of death during follow-up (*HR* = 0.88 [*CI* = 95%, 0.80–0.96] and *HR* = 0.81 [*CI* = 95%, 0.72–0.92], respectively) when compared to normal weight individuals (Curtis et al., 2005). This was consistent with an absolute risk reduction of almost 20% over 37 months.

A third study to examine obesity and HF was conducted in a European medical community. In 2003, Davos et al. reported results from their study designed to compare mortality rates between patients with cachexia (defined as "a state of incremental weight loss" [p. 29] associated with HF) and non-cachexic patients. The non-cachectic patients were divided into quintiles based on BMI. A total of 589 patients were followed prospectively for a total of 108 months. At the end of the follow-up, patients with BMIs in the 4th and 5th quintiles (20.7–26.9) appeared to have better survival rates. In fact, the 4th quintile group had the better survival rates at both 1 year (relative risk of 0.91 [0.85-0.96]) and 3 years (0.73-0.89) than those who were of normal weight. This prospective study appeared to confirm the results of previous retrospective studies that from a survival perspective, the "ideal" body weight for patients with HF is higher than that of the average population.

In 2005, a large multi-site cohort study was published in which 2,707 U.S. patients identified as having a primary admitting diagnosis of HF were followed for 3 years (Hall et al., 2005). Ejection fraction and admitting BMI were confirmed on the

initial hospital admissions. Patients were separated into four BMI quartiles: < 24.3, 24.4–28.5, 28.6–34.1, and ≥ 34.2. At the 3-year time point, cohort quartiles were analyzed for mortality while controlling for age, gender, and disease severity. The analysis showed an approximately 18% absolute reduction in mortality for patients with BMI ≥ 34.2 compared to the normal weight group.

The relationship between obesity and reduced HF mortality was suggested in all of these studies. Even though this relationship appeared to be well established, the underlying mechanisms associated with this phenomenon remained unidentified. However, researchers suspected systemic metabolism and inflammation were influenced by the role of adipose tissue in regulating and producing hormones (Bulcao, Ferreira, Giuffrida, & Ribeiro-Filho, 2006; Gualillo, Gonzalez-Juanatey, & Lago, 2007).

The studies (Curtis et al., 2005; Davos et al., 2003; Hall et al., 2005; Horwich et al., 2001) linking obesity and improved survival in HF suggested that by further understanding the metabolic processes that occur during HF, potential avenues may be revealed for the development of interventions to reduce mortality in patients with HF. Currently, no comprehensive guidelines exist for the nutritional support of patients with chronic HF. From a clinical perspective, determining what the appropriate nutritional recommendations for patients with HF should be has been difficult, especially in light of the apparent risk of developing HF once obese versus the survival benefit of obesity after developing HF. Clarification of the mechanisms driving this survival benefit could be useful in determining the appropriate interventions for patients with HF.

Indirect Calorimetry and Its Assumptions/Limitations

There are two potential measurement strategies for the measurement of human macronutrient oxidation reactions, such as those comprising human macronutrient oxidation reactions, direct or indirect calorimetry. With direct calorimetry, one measures the heat of combustion during a particular reaction, a technique that is well suited for the basic science assessment of the caloric values of specific chemical reactions. Although direct calorimetry of human subjects is possible (ie… thermography) via direct measure of heat production over time, these measurements are technically difficult to obtain and are prone to error. Thus, indirect calorimetry is currently the accepted method for the measurement of biologic oxidation and free energy production in clinical research subjects (Akohoue et al., 2007; Buchowski, Chen, Byrne, & Wang, 2002; Denne, 2001; Greco et al., 1998; Neyra et al., 2003; Treuth, Hunter, Weinsier, & Kell, 1995). Although Lavoisier's discovery that oxygen and carbon dioxide have major roles in respiration, Weir (1949) demonstrated it was possible to calculate energy production by measuring oxygen and carbon dioxide quantities in the difference between inhaled and exhaled air. Used in a number of clinical populations, this whole-room technique has not yet been used in HF.

Direct calorimeters were used early in the development of calorimetry techniques to provide measures of heat production over time. With these devices, either a heat sink method or direct thermography is employed. However, neither application is well suited for clinical application. The construction and adequate temperature controls necessary for a large scale heat sink (i.e., submersion of chamber in water) for human calorimetry are difficult to accomplish, and thermography is overly complex because multiple internal

(i.e., typically esophageal and rectal catheters) and external temperature probes are needed over time to calculate energy expenditure. Therefore, although changes in temperature can be measured, the response time of direct systems can be slow (Seale, Rumpler, Conway, & Miles, 1990; Walsberg & Hoffman, 2005).

Indirect calorimeters are now available in two configurations: metabolic carts, which are small, portable systems; and whole room indirect calorimeters, which are large chambers contained within a hospital-type room. These large indirect calorimeters can be validated and calibrated with the combustion (oxidation) reaction of a substance with a known caloric value, or mixed gas infusion technique. They are currently the most accurate systems for measuring energy expenditure

A variety of limitations and assumptions must be considered when using indirect calorimetry and its necessary stoichemetric calculations of substrate utilization and energy production (Ferrannini, 1988; Swyer, 1991). The first assumption is that the quantities of oxygen consumed and carbon dioxide produced can be measured accurately and reliably over a given period of time. Indirect calorimeters are often validated and calibrated for accuracy and reliability using these two primary techniques. In the first, the oxidation of a given amount of a particular substance with a known specific heat is recorded in the calorimeter and compared to known values. This technique, originally described by Barrett and Robertson in 1937, can be used to test the calorimeter against a substance with a known oxygen consumption and carbon dioxide production rate. In the second, a gas infusion technique can be used to evaluate response time and gas analyzer accuracy (Moon, Vohra, Jimenez, Puyau, & Butte, 1995). This technique involves the infusion of N_2 and CO_2 gas. Currently, these techniques are used for the calibration of

metabolic chambers and to assess the accuracy of a particular chamber prior to metabolic assessment.

The second assumption is that the stoichiometry of each of the substrate equations remains fixed. In other words, the ratio of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) remains the same for each of the substrates during the entire period of measurement. This is of particular concern for protein oxidation because some variations in protein waste and protein energy production may occur during periods of catabolism. In this system of equations, the ratio of protein used in energy production versus that wasted is assumed to remain constant.

The third assumption is that no anaerobic metabolism occurs. Because complete anaerobic metabolism is not compatible with human life, this assumption is of little concern. Although some anaerobic metabolism does occur in the gut, with the subsequent production of methane, it is assumed to be negligible in this system of metabolic measurement.

The final assumption is that no unusual metabolic substrates exist in the system at the time of measurement. Specifically, alcohol and ketones can be metabolized, if available, and have different free energy production values than the substrates noted previously, resulting in inaccurate substrate utilization rates and energy expenditure. Alcohol is excluded as a metabolite by controlling the subject's intake. Ketone metabolism can be excluded by excluding subjects with insulin resistance and diabetes.

As with many physiologic measurements systems, indirect chamber calorimeters have the advantage of being tested against a known substance for the purposes of calibration. These systems are calibrated by combusting a known weight of ethanol

($\Delta G_E^{\circ} = -7.064 \frac{kcal}{g}$) and measuring the VO_2 and VCO_2. Then the non-protein corrected Weir equation is used to determine the energy released in the combustive reaction. Because the actual free energy released from a gram of ethanol is known, a comparison between an actual energy released value and the calculated energy released can be made via the Weir equations. Although this is the basic procedure for testing and calibrating all indirect calorimeters, the combustive substance is not restricted to ethanol. Any substance that fully combusts and has a known free energy value can be used.

Although a variety of pragmatic issues surrounding indirect chamber calorimetry exist, it has remained the gold standard for measurement of systemic substrate utilization and subsequent energy production (Ferrannini, 1988; Sun, Reed, & Hill, 1994). Because of this gold standard of accuracy and the ability to measure metabolism over periods of several hours to several days, whole-room indirect calorimetry is the ideal instrument for the initial physiologic measurement of systemic energy utilization during a disease state.

Specific Aims and Hypotheses

Based on a synthesis and understanding of the extant literature on systemic metabolic factors in HF, the following specific aims and hypotheses were examined in this dissertation research study:

Specific Aim 1: To determine the feasibility of 24-hour indirect calorimetry measurement in the HF population, including the assessment of obese and non-obese patients with HF.

Specific Aim 2: To assess energy expenditure and substrate utilization in obese and non-obese HF patients.

Research Hypothesis 1: There will be a difference in 24-hour daily average resting energy expenditure (REE; kcal/min/kg of lean mass) between obese and normal weight patients with ischemic HF.

Research Hypothesis 2: There will be a difference in average 24-hour resting respiratory quotient (RQ) between obese and normal weight patients with ischemic HF.

CHAPTER III

METHODS

Design

In this study, a descriptive, quasi-experimental, nonequivalent groups design was used to examine the feasbaility of whole-room indriect calorimtery and to asssess potential energy expenditure and substrate utilization differences between obese patients with HF and those without HF.

Rationale and Specific Aims

Despite advances in the medical treatment of HF, little has been learned about the systemic metabolic factors associated with the disease. Failure to understand mechanisms linking altered systemic metabolism with poor HF outcomes has been the major reason metabolic interventions have not been developed and tested. The purpose of this dissertation research study, therefore, was to test the feasibility of using whole-room, indirect calorimetry to measure systemic metabolic function in patients with HF. Examining systemic metabolic function and energy substrate utilization in patients with HF might result in further clarification of the energy-dependent processes associated with disease progression in this population and, thus, should be rigorously examined using highly precise instrumentation.

The original specific aims in this study were to describe potential differences between obese and normal weight patients with HF with respect to both energy

expenditure and macronutrient utilization. Evidence from previous research suggested a potential survival benefit for obese patients with HF compared to patients of normal weight. Although fatty acid oxidation is known to be an important source of energy for the myocardium, understanding the differences in the number of calories burned and substrates (i.e., fat, protein, or carbohydrate) being used could reveal the reason obese HF patients appear to have better survival. However, modifications to the protocol and to the specific aims were made due to circumstances encountered once the study was begun.

Protocol Modification

Over a 10-month recruitment period, while the entire obese HF arm of the study was successfully recruited, only one subject was identified for enrollment in the non-obese HF arm of this study. Based on an interim meeting with faculty advisors, the study was closed for further recruitment. A total of seven subjects consented to the study, with six subjects (five obese, one non-obese) completing the approved protocol. A single subject withdrew from the study due to inability to schedule the required Vanderbilt University General Clinical Research Center (GCRC) in-patient visit.

In lieu of using the planned non-obese HF group for comparison, historical control data collected from healthy obese subjects were accessed, identified, and analyzed. These de-identified control subjects had data maintained in the Vanderbilt University Energy Balance Laboratories database and were collected from healthy obese patients who had participated as control subjects in previous clinical research studies. These control data were obtained from studies in which measures identical to those used in this protocol were employed, including assessment of demographic factors, 24-hour calorimetry measures, anthropometrics, and Dual-energy X-ray absorptiometry

(DEXA). The control subjects were healthy individuals, free from disease, who could perform activities of daily living independently and had no diet control prior to their whole-room indirect calorimeter measurement. Five control subjects were matched to the five obese HF subjects on age range, gender, race and obesity class. The matched individuals from the control database met all exclusion criteria set for the obese arm of the study. Because of this matching process, comparisons between healthy obese subjects and obese subjects with HF could be performed. Thus, the total sample size for this study was 10 participants.

Aim and Hypotheses Modifications

Modifications were also required for Specific Aim 2 and both research hypotheses:

Modified Specific Aim 2: To assess energy expenditure and substrate utilization between healthy obese individuals and obese patients with ischemic HF.

Research Hypothesis1: There will be a difference in resting energy expenditure (REE; kcal/min/kg of lean mass) between healthy obese individuals and obese patients with ischemic HF.

Research Hypothesis 2. There will be a difference in resting respiratory quotient (RQ) between healthy obese individuals and obese patients with ischemic HF.

The purpose of these new hypotheses was to determine the potential effects of HF on REE and RQ in obese patients.

Protocol

Obese patients with HF were admitted to the Vanderbilt University GCRC for a 24-hour period. Prior to their stay, subjects filled out a 3-day dietary log (Appendix A). This log was evaluated for patterns of unusual substrate intake prior to the indirect calorimetry assessment. To develop the inpatient diet, the Mifflin-St. Jeor equation was used to calculate caloric needs of each subject (Mifflin et al., 1990). A standardized diet was then prepared using U.S. Department of Agriculture (Guidelines Advisory Committee, 2010) recommendations, which included a calorie distribution of 60% carbohydrates, 20% fat, and 20% protein. The diet also contained less than 3 grams of sodium per day per the sodium restriction guidelines of the Heart Failure Society of America (Lindenfeld J et al., 2010). Study subjects received a total of four meals, three during the 24-hour chamber stay and one the following morning prior to discharge. All meals were weighed before and after consumption to determine caloric and substrate intake during the chamber stay. Study subjects were asked to eat this specific diet but were not restricted if they requested other nourishment. During their GCRC stay, subjects were asked to bring their home medications, which they self-administered while in the calorimeter.

On arrival at the GCRC, subjects' physical measurements, including height, weight, and abdominal girth, were obtained and DEXA scans were completed to determine each subject's total amount of fat, protein, and bone. Subjects were then placed in the whole-room indirect calorimeter for 24 hours, where the oxygen used and carbon dioxide produced from the participant's respirations were measured. Physical activity was measured during the indirect calorimeter stay using two GT3X ActiGraph tri-axial

accelerometers. The GT3X ActiGraph is an instrument designed to measure accelerations from 0.5 to 2.5 G, with each acceleration defined as a “count” with corresponding G amplitude. In earlier studies, ActiGraph accelerometers were validated against measures of energy expenditure, primarily through doubly-labeled water techniques with *R* ranging from 0.51 to 0.96 (Laporte et al., 1979; Melanson & Freedson, 1996; Plasqui & Westerterp, 2007). Of the commercially available accelerometry-based activity monitors, ActiGraphs have shown the best reliability (G coefficient = 0.64, *SEM* = 348; (Welk, Schaben, & Morrow, 2004)

For this study, acceleration counts were used to measure the subjects’ physical activities. One GT3X ActiGraph was placed on the wrist of the subject’s dominant side and one on the hip of that side to allow for differentiation between whole body movements via the hip sensor and small, upper extremity movements via the wrist sensor. During their stay, subjects were asked to do some basic physical activities to assess physical activity energy expenditure (see Study Procedures).

Inclusion/Exclusion Criteria

The inclusion/exclusion criteria for this study were designed to be as inclusive of subjects diagnosed with ischemic HF as possible yet realistic within the context of a limited feasibility study. The following inclusion criteria were developed for the HF arm of the study: (a) 40–65 years of age at time of consent; (b) diagnosed with ischemic HF; (c) New York Heart Association Functional Classification (NYHA) Class II or III; (d) a history of HF for more than 6 months; (e) ejection fraction on previous echocardiogram of less than 40%; (f) current therapy with angiotensin converting enzyme inhibitor (or

angiotensin receptor blocker) and beta adrenergic receptor blocker; and (g) a BMI of 18.5 to 24.9 kg/m^{2}for the normal weight group or 30.1 to 40 kg/m^2 for the Class 1 and Class 2 obese group. The following exclusion criteria were used: (a) female gender; (b) identified cardiac cachexia, defined as more than 6.0% euvolemic weight loss over a period of less than 6 months; (c) patients currently experiencing acute decompensated HF exacerbation per Heart Failure Society of America guidelines; (d) known diabetes mellitus; (e) known hypothyroidism, requiring thyroid replacement therapy; (f) current diagnosis of cancer; (g) alcohol intake 24-hours prior to entry to the metabolic chamber; (h) requiring assistance with activities of daily living; (i) inability to complete a dietary log prior to calorimetry measures; and (j) inability to lay supine for completion of DEXA scanning.

Rationale

A variety of metabolic factors have been found to influence energy expenditure and substrate utilization (e.g., age, gender, and concurrent medical conditions). Because current epidemiologic trends indicated the age range of individuals diagnosed with ischemic HF is 40–65 years (Rosamond et al., 2008), this age group was selected for participation in this research study. Only obsese patients with HF and healthy obsese control subjects were included because the modified Specific Aim 2 in this study concerned assessment of the differences between these two groups. NYHA classification II or III was selected to exclude the actively decompensating patients within Class IV and the asymptomatic patients within Class I. Ejection fraction was selected to ensure all patients had systolic HF, with an ejection fractionless than 40%. A history of HF for more than 6 months was selected to ensure that chronic HF patients were enrolled, and

that they did not meet the definition of cachexia. Subjects were only enrolled if they had been prescribed appropriate HF regimes, including a RAAS inhibitor and beta-adrenergic blockers, to ensure a homogenous sample. Because of the small sample size, inclusion criteria were developed to enhance the metabolic homogeneity of the sample.

Exclusion criteria were selected to eliminate subjects that might have altered metabolic needs and varied substrate utilization due to pathophysiologic states known to alter these measures. Women were excluded due to known changes in body composition associated with menopause, which is prevalent in female HF patients within the included age range (Ley, Lees, & Stevenson, 1992; Svendsen, Hassager, & Christiansen, 1995). Patients with known cardiac cachexia were excluded because they represented a metabolic extreme that was beyond the scope of this feasibility study. Patients with metabolic disorders known to influence energy expenditure and substrate utilization, including diabetes mellitus, hypothyroidism, and active cancer, also were excluded. Additional rationale for the exclusion of potential participants included (a) consumption of alcohol 24 hours prior to the 24-hour indirect calorimetry measure to ensure accurate RQ measures; (b) inability to perform activities of daily living safely in the calorimetry chamber by themselves; (c) inability to complete dietary logs to ensure accurate calorimetry measures; and (d) inability to lay supine for DEXA scanning.

Enrollment

Study particpants were recruited from the HF program in the Vanderbilt Heart and Vascular Institute. Patients with Class 1 or 2 obesity (BMIs of 30.1–40 kg/m^2) who were referred to the institute with a diagnosis of ischemic HF were approached by a clinical

nurse or physician while the patients were attending either initial appointments or follow-up clinic visits to determine their interest in participating in the study. After a patient provided verbal consent to discuss the study, the primary investigator approached the patient to explain study procedures and to obtain informed consent.

Study Procedures

The following procedures were employed during the study. Each of the 6 days involved for each patient have been described.

Day 0. Following consent, the primary investigator completed a chart review to ensure that the participant met study criteria. If the participant was eligible and provided written consent, the individual was given the 3-day food diary to complete (Appendix A) starting the following morning. This food diary and accompanying instructions were designed to provide a record of what and when the patient ate prior to GCRC admission. Subjects scheduled their inpatient stay at the time of their consent and were instructed to return the food diaries on the dates of their calorimetry stays.

The following data were collected from the participant's electronic medical record on Day 0: (a) demographics (age and race); (b) weight at previous HF follow-up (6 months +/- 1 month); (c) left ventricular ejection fraction on most recent echocardiogram; (d) concomitant medications; (e) past medical history to determine the presence of hypertension, previous coronary interventions, previous ischemic heart disease, diabetes mellitus, previous atrial fibrillation, previous cardiac arrest, previous metabolic disorder, history of permanent pacemaker or internal cardioversion device, chronic obstructive

pulmonary disease or emphysema, hyperlipidemia, chronic anemia, renal failure or insufficiency, and arthritis.

Days 1, 2, 3. Participants filled out their food diaries per instructions. Following Day 3, participants were asked to return their diaries at the time of their calorimetry stays. Participants were also asked to bring their medications with them and to be responsible for taking their own medications during their inpatient stays.

Day 4. Day 4 was scheduled sometime within a month following consent. Table 1 shows the schedule subjects followed on Day 4. On Day 4, the subject's match with study inclusion/exclusion criteria was re-evaluated. After the subject's study eligibility was reconfirmed, anthropometric measures and a DEXA scan were taken. The inpatient calorimeter 24-hour stay with assessment of physical activity was then initiated.

Day 5. On this day, the last day of the protocol, subjects followed the schedule shown in Table 1.

Food Diary Description

During a 3-day period prior to entry into the whole-room indirect calorimeter, subjects maintained dietary logs of all the foods they consumed. These dietary logs were collected prior to the subjects' admission to the Vanderbilt GCRC and were evaluated for patterns of food and fluid intake. The GCRC dietitian and kitchen were responsible for formulating a diet for each subject based on the guidelines described previously.

Table 1. *Schedule for Days 4 and 5 of Study Protocol*

Time		Activity
Day 4	7:00 a.m.	Check in at GCRC* and have body measures and DEXA scan taken
	8:00 a.m.	Entry into Calorimeter: Sitting and resting (resting energy expenditure evaluation)
	8:30 a.m.	Breakfast
	10:00 a.m.	Free time
	10:30 a.m.	Physical activity: sorting objects (10 minutes), shelf reach (10 minutes), writing by hand (10 minutes), laundry sorting (10 minutes), floor sweep (10 minutes), sit to stand (10 minutes). The duration of each activity was 10 minutes. Each activity was followed by a rest period of 10 minutes. Activity concluded at 12:30 p.m.
	12:30 p.m.	Lunch
	1:30 p.m.	Free time
	3:00 p.m.	Physical activity: sorting objects (10 minutes), shelf reach (10 minutes), writing by hand (10 minutes), laundry sorting (10 minutes), floor sweep (10 minutes), sit to stand (10 minutes). The duration of each activity was 10 minutes. Each activity was followed by a rest period of 10 minutes. Activity concluded at 5:00 p.m.
	5:00 p.m.	Free time
	5:30 p.m.	Dinner
	6:30 p.m.	Free time
	9:30 p.m.	Bedtime (subject's preference). Chamber door opened; assistant enters and sets up bed.
Day 5	6:00 a.m.	Wake up
	6:30 a.m.	Sitting and resting (formal resting energy expenditure evaluation)
	8:00 a.m.	Exit calorimetry room
	8:30 a.m.	Discharge

*GCRC = Vanderbilt University General Clinical Research Center

Dual Energy X-Ray Absorptiometry Scan Description

Body composition was measured using a GE Lunar DEXA scanner. The DEXA scanner is designed to use two X-ray energies to determine fat free mass, lean mass, bone mass, and percentage of body fat. Low-dose x-rays are passed through the subject to

determine body composition. The amount of x-ray exposure is less than that of a single chest radiograph. The scan takes approximately 15 minutes.

This technique was originally validated using ex-vivo water, muscle, and fat sampling. The original validation study revealed acceptable precision error (*SD*, *CV*) for each of the measures (i.e., lean mass, 1.4kg [6.4%]; fat mass, 1.1kg [3.1%]; (Haarbo, Gotfredsen, Hassager, & Christiansen, 1991). This technique also showed good test–retest reliability. In a recent paper, researchers discussed three successive scans of normal controls that revealed almost perfect correlation between lean mass and fat mass (r = 0.99 and r = 1.00, respectively; (Lohman, Tallroth, Kettunen, & Marttinen, 2009).

For this study, each scan conducted took approximately 15 minutes. Each subject was required to lie flat on an x-ray table while the scan was performed.

Whole-Room Indirect Calorimetry Description

The Vanderbilt GCRC whole-room calorimeter is an airtight environmental room with an entrance door and an air lock for passing food and other items. To provide facilities for daily living and to bridge the difference between laboratory and free-living environments, the room has been equipped with a desk, a chair, an outside window, a toilet, a sink, a telephone, a TV/VCR, an audio system/alarm clock, and a fold-down mattress. Temperature, barometric pressure, and humidity of the room are precisely controlled and monitored. Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) are calculated by measuring the difference in the content of oxygen and carbon dioxide from the air entering and exiting the chamber, and then accounting for the rate of purged air.

After hardware and software modifications, the whole-room indirect calorimeter has consistently shown the highest accuracy and fastest response time compared with the reported data for similar room calorimeters. Results from routinely performed ethanol combustion tests over past the 6 years indicated that the system error is controlled within 1% (*STD* = 0.37% for energy expenditure, *STD* = 0.61% for RQ, *n* = 18) over large oxygen and carbon dioxide concentration ranges. Because of the fast response (> 90% reading in 1 minute), investigators have been able to study energy expenditure and substrate oxidation during acute physiological changes and during clinical interventions. Thus, because of the accuracy and fast response of the whole-room indirect calorimeter, investigators have been able to study alterations in energy regulation not previously feasible.

All subjects in this study were admitted to the GCRC for their inpatient calorimetry assessments. During their stays in the calorimeter chamber, subjects were provided 24-hour monitoring by the GCRC nursing staff. The primary investigator was also present on-site for the 24-hour measurement. A call button was located in the calorimeter room in the event the patient needed to contact a GCRC nurse or the primary investigator. In the event of an emergency, the calorimeter room was accessible by all Vanderbilt emergency teams and their services. The collaborating HF physician for this study, Dr. Henry Ooi, was also notified of any change in any subject's clinical status.

Accelerometer Description

Physical activity was measured during the calorimeter stay using two GT3X ActiGraph tri-axial accelerometers. The GT3X ActiGraph is an instrument designed to

measure accelerations from 0.5 to 2.5 Gs, with each acceleration defined as a “count” with corresponding G amplitude. A variety of studies revealed validation for the ActiGraph accelerometers against measures of energy expenditure, primarily through doubly labeled water techniques with *R* ranging from 0.51 to 0.96 (Laporte et al., 1979; Melanson & Freedson, 1996; Plasqui & Westerterp, 2007). Of the commercially available accelerometry-based activity monitors, ActiGraphs have shown the best reliability (G coefficient = 0.64, *SEM* = 34; (Welk et al., 2004).

Summed counts per unit of time were used as measures of the participants’ physical activities. One GT3X ActiGraph was placed on the wrist of the subject’s dominant side and one was placed on the subject’s hip on that side. With this placement, whole body movements via the hip sensor could be differentiated from small, upper extremity movements via the wrist sensor. During their stays, subjects were asked to do some basic physical activities (see Table 1) to assess their physical energy expenditure, which was measured both with the calorimeter and the accelerometers.

Risks

Little physical risk was associated with this study. Each participant was subject to an estimated dose of 7 mrem from the DEXA scan, which is comparable to two anterior–posterior chest x-rays.

The whole-room calorimeter is an airtight environmental room with an entrance door, an air lock for passing food and other items, and an outside window. This room was made airtight through the use of a specially designed door, which could be opened by the participant at any time. Although the chamber was relatively small, comparable to a small

hospital room, some subjects might have felt claustrophobic during their stays. Subjects were allowed to discontinue their stays in the room calorimeter at any time. To provide facilities for daily living and to increase comfort, the room was also equipped with a desk, a chair, a toilet, a sink, a telephone, a TV/VCR, an audio system/alarm clock, and a bed for sleeping. The Vanderbilt GCRC provided 24-hour nursing care for study participants, who were routinely observed by the nursing staff as if they were staying in standard inpatient rooms. Subjects also had access to a call button to summon nursing or research staff, if needed.

Subjects were asked to participate in several activities throughout the day as outlined in Table 1: standing, sitting, writing, sorting objects, and sweeping. These were common activities of daily living that should have been consistent with patients' typical days at home. The activities were selected to increase energy expenditure associated with physical activity but to minimize potential injury. Anyone requiring assistance with activities of daily living were excluded from the study, as noted previously, to minimize the risk associated with these basic activities. However, some level of injury potential existed, such as shortness of breath or, more severe, falling down. Also, the potential for heart problems, such as a myocardial infarction, existed that could be life threatening. Therefore, a research staff member was present during the activity periods and was prepared to terminate any activities that appeared unsafe for the subjects. Subjects were also able to stop doing any of the activities if they wished, as outlined in the informed consent.

Although subjects were unlikely to develop changes in their condition, the primary investigator (an intensivist NP) was on site for immediate intervention. The

attending study physician, Dr. Henry Ooi (HF cardiologist) was also to be notified and consulted should any subject develop such changes.

Reporting of Adverse Events

Dr. Michael Vollman, Vanderbilt University School of Nursing (and dissertation adviser), served as chair of the Data Safety and Monitoring Board (DSMB). Other DSMB members included the project biostatistician, Dr. Mary Dietrich, and the project physician, Dr. Henry Ooi. After enrollment was initiated, the DSMB conducted an overview after each 24-hour chamber measurement. Oversight by the DSMB included (a) a review of any proposed amendments to the study protocol; (b) expedited monitoring of all serious adverse events; (c) ongoing monitoring of drop-outs and nonserious adverse events; (d) a determination of whether study procedures should be changed or whether the study should be halted for reasons related to the safety of study subjects; and (e) periodic reviews of the completeness and validity of the data to be used for analyses of safety and tolerability. The DSMB also ensured subject privacy and research data confidentiality.

The primary investigator, Joshua Squiers, was onsite during each subject's inpatient admission and was responsible for the reporting of adverse events. The Institutional Review Board and DSMB members were notified of any adverse events within 24 hours of their occurrence.

Study Withdrawal/Discontinuation

Participants could withdraw from the study at any time. If a patient discontinued the inpatient stay, all research procedures were to be immediately stopped. The primary investigator was also to be notified at that time.

Participants could also be discontinued from the study by a research team member. Reasons for doing so included ineligibility due to exclusion criteria, failure to return the food diary, and any safety concern during the time the patient was admitted.

Statistical Considerations

The sample size (N = 10; 5 per group) was selected to determine initial feasibility of using whole-chamber calorimetry in this population. To this point, feasbility data had been collected, including the ratio of collected-to-expected data collection (90% of all calorimetry data were expected to be collected),, and whole-room calorimeter tolerance (great than 20 hours of cumulative data were expected to be collected on each subject).

Formal data analysis was conducted using Statistical Package for Social Sciences (SPSS, Version 18) software. Demographic and anthropometric characteristics of the patient groups were summarized using descriptive statistics (e.g., frequencies, means, ranges). Of specific interest were the magnitude and variability of the differences in these key variables between the obese and non-obese groups. Although the research team was hesitant to suggest sufficient power existed statistically to compare the observed differences or to test the hypotheses of group differences, the REE and RQ data for the two groups were compared using the Wilcoxon sum-ranked test. Data from this exploratory study will be used to determine the appropriate effect sizes for powering

future studies and for hypothesis generation. Dr. Mary Dietrich served as the primary bio-statistician for this dissertation research study.

Privacy/Confidentiality Issues

All efforts, within reason, were made to keep the participants' protected health information private. All data were transported to the investigators and maintained in their locked office in a locked file cabinet. Data collected from the whole-room indirect calorimeter were electronically collected on a portable encrypted drive at the conclusion of each subject's calorimetry stay. Calorimetry and summary data were manually entered, or uploaded, into a password-protected data entry and management platform (RedCap) developed by the bioinformatics core in the Vanderbilt Institute for Clinical and Translational Research.

Follow-Up and Record Retention

The study duration was approximately 8 months. All study participants were recruited and completed the protocol within that time. Study records will be retained for 6 years. However, these records may be indefinitely archived in the RedCap data storage.

CHAPTER IV

RESULTS

In this chapter, the study results have been presented in three formal sections: sample characteristics, descriptive statistics, and hypothesis testing. When appropriate, tables have been included to display the data.

Sample Characteristics

Six adult males with ischemic cardiomyopathy completed the research protocol, including the inpatient 24-hour indirect calorimetry stay. Due to a lack of subjects meeting the criteria for inclusion in the non-obese arm of the study, only the five subjects with obesity and their matched controls were used to supply data in this study. Demographic and clinical information for the five obese subjects with HF has been included in Table 2.

Overall, the HF participants ranged in age from 49 to 60 years (*M* = 54.5 years, *Mdn* = 57 years), and in weight from 88.27 kg to 128.1 kg (*M* = 102.82 kg, *Mdn* = 102.05 kg). They had BMIs ranging from 30.8 kg/m^2 to 38.3 kg/m^2 (*M* = 32.67 kg/m^2, *Mdn* = 31.5 kg/m^2; see Table 3) and had body fat percentages from 34.3% to 42.3% (*M* = 35.5%, *Mdn* = 35.5%). These subjects all had ischemic cardiomyopathy, with systolic HF and EF less than 40%. All were being seen routinely by a cardiologist specializing in HF, and all were on angiotensin converting enzyme inhibitor (or angiotensin receptor blocker) and beta-adrenergic blocker therapy. Reviews of the dietary logs prior to the subjects'

calorimeter stays showed all subjects' dietary habits were consistent with a Western diet. None of the subjects reported ethanol intake within 48 hours of their chamber stays.

Table 2. *Demographic and Clinical Information for the Obese Heart Failure Group*

	Subject				
Descriptor	1	2	3	4	5
Age	57	58	49	60	57
Race*	C	C	C	C	AA
EF (%)	35	35	30	30	20
NYHA Class	II	II	II	II	II
ICD[ŧ]	Yes	Yes	Yes	Yes	Yes
Chronic obstructive pulmonary disease**	No	No	No	Yes	No
DM**	No	No	No	No	No
HTN**	Yes	No	No	No	Yes
HLPL**	No	No	Yes	No	No
Anemia**	No	No	No	No	No
Renal disease**	No	No	No	No	No
Arthritis**	No	No	No	No	No

C = Caucasian; AA = African American;
[Ŧ] yes = device implanted; no = no device
** yes = history of the disease; no = no history of the disease
EF = left ventricular ejection fraction, NYHA = New York Heart Association functional classification, ICD = implantable cardiac defibrillator, DM = diabetes mellitus, HTN = hypertension, HLPL = hyperlipidemia

Five healthy obese men who matched the five obese HF subjects in race, age, and obese classification were selected from the Vanderbilt University Energy Balance Laboratories database (see Table 3). These men ranged in age from 40 to 58 years (*M* = 52.8 years, *Mdn* = 56 years) and in weight from 87 kg to120 kg (*M* = 99.84 kg, *Mdn* = 98.2 kg). They had BMIs ranging from 30.1 kg/m^2 to 36.63 kg/m^2 (*M* = 32.14 kg/m^2,

Mdn = 30.65 kg/m^2) and had body fat percentages ranging from 23.7% to 39.8% (*M* = 33.16%, *Mdn* = 34.2%). Body composition data were collected to provide a description of total fat mass and to quantify lean mass for indexing energy expenditure values.

Table 3. *Body Composition Data for Obese Heart Failure and Control Groups*

Subject	Age	Race	Weight (kg)	Height (cm)	Body fat (%)	Fat mass (kg)	Lean mass (kg)	Lean mass (%)	Body mass index
Obese heart failure group									
1	57	C	102.6	177.8	34.3	33.572	64.164	62.5	32.5
2	49	C	128.1	182.8	39.8	48.338	73.219	57.2	38.3
3	58	C	105.3	185.0	42.3	42.540	57.953	55.0	30.8
4	60	C	107.9	180.2	35.1	36.016	66.498	61.6	33.2
5	57	AA	85.1	165.2	37.7	30.717	50.734	59.6	31.2
Obese control group									
1C	57	C	98.2	179.0	36.0	34.136	60.713	61.8	30.65
2C	56	C	120.0	181.0	39.8	45.737	69.271	57.7	36.63
3C	40	C	101.5	175.0	34.2	33.817	65.193	64.2	33.14
4C	53	C	92.5	175.0	32.1	28.532	60.455	65.4	30.1
5C	58	AA	87.0	177.1	23.7	19.502	62.848	72.2	30.1

C = Caucasian; AA = African American

None of these matched subjects had known comorbidities, including liver, thyroid, kidney, and heart disease; hypertension; and cerebrovascular incidents. In addition, none were taking medications known to alter energy metabolism or autonomic functions.

Resting energy periods were confirmed with accelerometer data and analyzed using the Weir equation. REE in the obese HF group averaged 1.66 kcal/min (*Mdn* = 1.67

kcal/min, range = 1.42–1.97 kcal/min); in the healthy obese group, REE averaged 1.42 kcal/min (*Mdn* = 1.40 kcal/min, range = 1.4–1.627 kcal/min). REE was indexed with lean mass for each subject. The group of obese HF men averaged 0.0267 kcal/min/lm (*Mdn* = 0.0270 kcal/min/lm, range = 0.0221– 0.0296 kcal/min/lm); the healthy obese men averaged 0.0223 kcal/min/lm (*Mdn* = 0.0230 kcal/min/lm, range = 0.0198–0.0233 kcal/min/lm). RQ was assessed during the resting periods with minute-to-minute averaging. RQs among the obese HF group averaged 0.74 (*Mdn* = 0.724, range = 0.65–0.84). In the healthy obese group, RQs averaged 0.87 (*Mdn* = 0.880, range = 0.76–0.94). REE and RQ data have been presented in Table 4.

Table 4. *Resting Energy Expenditure (REE) and Respiratory Quotients (RQ) for Obese Heart Failure and Obese Control Groups*

Subject	RQ	REE (kcal/min)	REE (kcal/min/lm)
Obese heart failure group			
1	0.84	1.42	0.0222
2	0.76	2.05	0.0270
3	0.72	1.69	0.0283
4	0.71	1.94	0.0268
5	0.65	1.50	0.0297
Obese control group			
1	0.88	1.40	0.0231
2	0.90	1.62	0.0234
3	0.94	1.44	0.0221
4	0.87	1.40	0.0232
5	0.76	1.25	0.0199

Specific Aims and Hypothesis Testing

The primary aim of this research study was to determine the feasibility of 24-hour indirect calorimetry measurement of energy expenditure and substrate utilization in the HF population. A total of six obese patients with HF initiated the study. Of those, one subject (16.7%) discontinued the study due to an adverse event. For the purposes of this study, a feasible calorimeter stay was defined as the collection of greater than 22 hours of useable data during the course of a 24-hour measurement period. All of the five subjects who completed the 24-hour indirect calorimeter stay provided more than 1,320 minutes of useable calorimetry data during their 1,440 minute chamber stays, which ranged from a minimum 1,340 minutes to a maximum of 1,406 minutes. All subjects provided more than 91.7% of the calorimetry data that could be collected during this time period, exceeding the 90% feasibility threshold for the study. During these five subjects' stays, no clinical or systems-related problems were noted by the investigator.

REE (kcal/min/lm) was higher 16.6% on average between the subjects with HF than among the control group (0.02677 kcal/min/lm vs. 0.02231 kcal/min/lm, respectively). However, matched pairs analysis using the Wilcoxon rank-sum test indicated no statistically significant differences ($p = 0.08$) between the groups on REE. RQ was reduced among the HF subjects ($M = 0.74$, $Mdn = 0.724$, range = 0.65–0.84) versus the control group ($M = 0.87$, $Mdn = 0.880$, range = 0.76–0.94). A statistically significant difference was found in RQ between the two groups ($p = .043$). These results have been presented in Table 5.

Table 5. *Resting Energy Expenditure (REE) and Respiratory Quotient (RQ) Differences Between the Obese Heart Failure and Obese Control Groups*

Variable	Obese heart failure group	Obese control group	*p**
REE (kcal/min/kg lm)	0.0268	0.0223	0.08
RQ	0.738	0.898	0.043

**Wilcoxon rank-sum test*

Adverse Events

A single adverse event consisting of an appropriate discharge from an implantable cardioverter-defibrillator in response to ventricular tachycardia during a subject's overnight sleep period was reported during the course of this research study. This subject, the only non-obese subject who consented, was discontinued from the study at that time and transferred to the care of the Vanderbilt emergency department. This subject completed only 14.5 hours of the 24-hour calorimetry protocol and had no formal REE measure taken. Data collected from this subject were not included in this analysis. The Institutional Review Board and the DSMB were notified of the adverse event. No changes to the protocol were deemed necessary.

CHAPTER V

DISCUSSION

In this chapter, a discussion of the study results have been presented. The chapter has been organized into five formal sections: study feasibility, hypotheses, study strengths and limitations, conclusion and implications, and recommendations for future research.

Study Feasibility

Although data collection feasibility goals were easily achieved, non-obese subjects with HF were difficult to identify. Only a single individual subject meeting the inclusion/exclusion criteria for the non-obese HF group agreed to participate. Historically, researchers studying obesity and HF have had little difficulty enrolling subjects with HF and normal BMI (Curtis et al., 2005; Gustafsson et al., 2005; Horwich et al., 2001; Mehra et al., 2004). The academic medical center where the subjects were screened for enrollment is located in Tennessee, a state with one of the highest prevalence rates for obesity in the United States (Galuska et al., 2008; Jackson, Doescher, Jerant, & Hart, 2005). Therefore, with a high rate of obesity among the general population within the referral radius of the Vanderbilt Heart Failure Program, the difficulty of finding subjects who met the non-obese weight requirements is plausible.

The difficulty experienced in recruiting normal weight patients with HF could also have been due to the type of patients found at this particular tertiary academic medical center. A variety of smaller community hospitals in the area have well-established HF programs and typically only refer advanced HF patients to the Vanderbilt Heart Failure Program for transplantation or ventricular assist devices. Many of these patients are long-term HF patients who have been treated well at outside centers. Because subjects with increased BMIs have improved survival, these advanced HF patients may tend to represent an obese HF population when compared with HF programs at other local centers.

Based on the findings of this dissertation research study, whole-room indirect calorimetry appears to be a feasible technique for the assessment of energy expenditure and substrate utilization in the HF population. Thus, a novel, highly accurate technique exists for future examination of substrate and energetics questions related to the HF disease process. Nonetheless, because of the difficulty in recruiting participants into the non-obese HF arm of the study, adequate assessments of energy expenditure and substrate utilization between non-obese and obese HF patients was difficult. Future studies may need to include broader sampling strategies (e.g., recruiting from multiple institutions) to allow for increased sample sizes and better sampling of subjects at various BMI levels.

Hypotheses

Results from this study suggest that obese HF patients had a 16.6% relative increase in REE (0.0267 vs. 0.0223 kcal/min/kg LM, $p = 0.08$) and a lower RQ (0.738 vs.

0.898, $p = 0.043$) compared with healthy obese individuals. These results suggest an increasing metabolic demand associated with HF, along with a preference toward fat metabolism at rest. This result is surprising because the obese HF subjects were all on medications that suppress metabolic rate, such as angiotensin converting enzyme inhibitors and beta-adrenergic blockers (Anker et al., 2003; Lainscak, Keber, & Anker, 2006; S. von Haehling, Sandek, & Anker, 2005). The differences in these medications between the groups should result in reducing the increased energy expenditure found among the HF patients. This suggests that the increase in energy expenditure found in the HF subjects may have been even more pronounced had they been off these medications at the time of measurement.

This increase in energy expenditure has several physiologic and clinical implications. First, an increase in REE suggests an increase in energy expenditure associated with the pathophysiologic processes of HF. Based on the neurohormonal model of HF and its implied energetic cost, this increase in energy expenditure is likely associated with the compensatory efforts of the body necessary to maintain homeostasis during a chronic pathologic state. For an adult male with a baseline 2,000 kcal/day energy requirement to increase energy expenditure by 16.6%, he must increase his intake by 121,180 kcals per year to maintain energy balance. If the individual is unable to increase intake beyond 2,000kcal/ day, significant changes in body composition are likely to occur over that period of time. Assuming only a loss of fat mass, the increased metabolic demand will equate to a total loss of 34.6 pounds of fat over a 1-year period. Considering the recent definition of cardiac cachexia, which only requires a loss of 6% body weight in 6 months to increase mortality to 50% in 6 months, the possibility that increased REE

may have a role in advancing HF is startling (Springer, Filippatos, Akashi, & Anker, 2006). This appears consistent with known increases in energy expenditure among patients with cancer cachexia and HIV (Delano & Moldawer, 2006; Kosmiski et al., 2003).

Second, a lower RQ suggests that obese subjects with HF had a shift in systemic substrate utilization toward fat-based metabolism when compared with obese healthy patients. This shift toward fat-based metabolism may be explained by several different mechanisms. First, the myocardium of HF patients is known to shift towards a free fatty acid-based metabolism rather than towards a carbohydrate-based metabolism as in their healthy counterparts (Eichhorn et al., 1994; Taylor et al., 2001). This may account for the reduction in systemic RQ found in this study. Previous measures of myocardial RQ suggest that myocardial tissue in HF patients may have an RQ as low as 0.67 (Eichhorn et al., 1994). Unclear, however, is whether changes in myocardial tissue RQ alone may affect systemic RQ enough to provide the reduction in systemic RQ found in this study. Both cardiac and non-cardiac mechanisms are likely to have roles in this shifting RQ during HF, although they have yet to be fully described. In particular, there may be differences in shifting RQ between obese and non-obese HF subjects, possibly related to an increased number of natriuretic peptides receptor “C” clearance receptors (NPR-C) found in adipose tissues (Lommi, Kupari, & Yki-Jarvinen, 1998; Taylor et al., 2001).

Recent advances in the understanding of the effects of natriuretic peptides may suggest a unique mechanism for shifting myocardial and potentially systemic substrate utilization. Natriuretic peptides have been shown to be elevated in HF patients (O'Donoghue, Januzzi, O'Donoghue, & Januzzi, 2005). Levels of these peptides have also

been shown to be elevated throughout the course of HF and are independent predictors of HF severity (Berger et al., 2002; Fisher, Berry, Blue, Morton, & McMurray, 2003; Masson et al., 2006). From a metabolic standpoint, natriuretic peptides may have a role in lipid mobilization during periods of high myocardial workload. This may be a primary mechanism to provide free fatty acids for myocardial tissues during increased myocardial workload and may be the explanation for the increase in free fatty acids found during the course of HF (Lommi, Kupari, & Yki-Jarvinen, 1998; Taylor et al., 2001). Laboratory studies of adipose tissues have revealed the adipose cell signaling pathway via natriuretic peptides receptors "A" (NPR-A) and "C" (NPR-C) on the adipose cell wall, which result in free fatty acid release. Although free fatty acid mobilization with an intravenous injection of natriuretic peptides has been demonstrated in the laboratory setting, whether this occurs during the course of HF is unclear. Together, these two specific signaling pathways may result in increased lipid mobilization and may be the explanation for the reduction in resting RQ found in this study. Further research may be necessary to include these mechanisms in the neurohormonal model of HF. These mechanisms may also explain the shifting substrate utilization found in HF.

Studies evaluating systemic metabolic changes in HF are relatively new in the literature, with the first use of hood-based indirect calorimetry in 1994 (Poehlman et al., 1994). Further studies appeared to indicate an increased metabolic demand associated with the disease state (R. Aquilani et al., 2003; Lommi et al., 1998; Poehlman et al., 1994), while other studies suggested little or no change in metabolic demands associated with HF when compared with healthy controls (Norrelund et al., 2006; Toth, Gottlieb, Fisher, et al., 1997). Although these studies revealed valuable insights for future

hypothesis generation, they were limited by the accuracy of the measurement technique (hood calorimetry and doubly labeled water) and lacked appropriate metabolic control via non-homogenous HF samples. In this current study, an initial description of the energetic cost of HF in a tightly controlled sample utilizing the gold-standard measurement system via whole-room indirect calorimetry has been presented.

Strengths and Limitations

The primary strength of this study was the use of whole-room calorimetry for the assessment of energy expenditure and substrate utilization in this population. Although whole-room calorimetry is the gold standard for measuring energy expenditure and substrate utilization, to date, this method had not been used to measure systemic metabolism in patients with HF. Studies of energy expenditure and substrate utilization have been limited by the availability of whole room calorimeters. In addition, few of the limited number of facilities with whole-room calorimeters have available staff for energy expenditure and substrate assessments over 24-hour periods.

This study was conducted as the first step toward filling a significant gap in the literature by showing the feasibility of 24-hour whole-room indirect calorimetry in the HF population and by providing a description of the increased energy expenditure of patients with HF. These results will be useful for estimating effect size for future research.

This study also had a variety of limitations. The study sample, which consisted only of men with systolic HF, was obtained through non-random convenience sampling. This sampling method could affect the generalizability of the study findings, even though

the size was appropriate for an early feasibility study. Ideally, subjects should be placed on a 3-day prescribed diet to control for any diet-related changes in energy expenditure and substrate utilization. Although subjects were all confirmed to be eating a standard Western diet, diet variations were not controlled during the course of the study. For the purposes of this feasibility study, confirming a consistent Western diet among all subjects was considered to be adequate.

Caution should be taken not to over generalize the results from this study. Although the results appear consistent with the neurohormonal model of HF, which suggests an increase in metabolic response to the physiologic burden of disease over time, these findings should be confirmed with a larger, appropriately powered study.

Conclusion and Implications

This research study was the first study to use an indirect room calorimeter to measure energy expenditure and substrate utilization in HF patients. The findings suggested an increase in REE and a lower RQ among obese patients with HF compared with healthy obese control subjects. Although limited by sample size, these findings might be clinically significant because a relative 16.6% increase in resting metabolic demands may have a significant impact if present throughout the course of HF. These results suggested that obese HF patients may have an increased basal metabolic rate with a shift towards fat-based metabolism at rest. Overall, these findings appeared consistent with the increase in metabolic demands hypothesized in the neurohormonal model of HF and likely represented the energy demands of a prolonged compensatory response to a failing heart.

In conclusion, whole-room indirect calorimetry is a feasible method to measure energy expenditure and substrate utilization in patients with HF. Results from this dissertation research study suggested an increase in REE and a shift in resting RQ away from carbohydrate metabolism to fat metabolism among obese subjects with HF when compared with healthy obese controls.

Recommendations for Future Research

This was a cross-sectional study of one point during the course of the subjects' HF course. Ideally, a future longitudinal study should be undertaken to determine if these metabolic changes are present throughout the course of HF. With a large prospective cohort study, including both genders and subjects with all HF types, researchers could conduct longitudinal assessments of energy expenditure and substrate utilization. Such research should result in identification of effect size for energy expenditure and RQ across the HF population, as well as in further information regarding the changing energetics found during the course of HF. In particular, a longitudinal study might reveal information concerning the metabolic role of common comorbidities found during HF, such as diabetes mellitus. A further description of HF progression and severity utilizing cardiac and metabolic biomarkers could be used as a framework to understand better the longitudinal changes in metabolic demands and shifting substrate utilization. Of particular interest, determining whether RQ is correlated with natriuretic peptide levels over time could result in a better description of this potential substrate shifting mechanism.

Once effect size and energy expenditure mechanisms specific to heart disease patients are clarified, a variety of clinical interventions could be considered for future study. Dietary manipulations are of particular interest because they tend to be low cost and could be useful substrate for increased energy demand. Along with dietary manipulation, a variety of pharmacologic targets for intervention, including the NP system, SNS, and gastrointestinal systems, could be considered for future studies.

APPENDIX A: FOOD DIARY

Vanderbilt University Medical Center
General Clinical Research Center
Bionutrition Unit

As a part of this study, you will be asked to keep a diary of *everything* you eat and drink for three days. Begin with the first food or drink in the morning and write down what you eat as you go through the day. The nutritionist will review your completed food diary. If possible, please save any food labels from food you have eaten.

RECORDING FOOD INTAKE

1. Write down on the Food Diary the day, time, and place (home, home of a friend, restaurant) of each meal and snack.

2. Write down one food item per line on the Food Diary. Space is provided on both sides of the form. Include gum, candy, and drinks.

3. Write down the amount and name of food on the Food Diary using common household measures, such as tablespoons, cups, package sizes.

4. When you write down a food, also write down how it was cooked. For example: baked, boiled, broiled, fried, or roasted. **This is very important.**

6. Write down anything you add to your food. This would include milk on cereal, cheese or lettuce on a sandwich, salad dressing on your salad, butter or jelly on bread, etc.

7. When eating out, write down the place where you ate, the food ordered, and amount eaten.

For example: Taco Bell, Burrito Grande, ate 1/2
Or, McDonald's, Big Mac, ate all.

8. If you have any questions, please call the nutritionist at 615-322-2430.

Food Diary

Name: _____ID#_____ Protocol No:_____

Today's Date:_____ Day of Week:_____

Please write down everything you eat and drink today. Include the type of food, brand names, and serving size (if possible, please save food labels). In the first column under meal and place, please put what meal you ate and where you ate it. You may use the back side of the page also. Thank you.

Time, Meal and Place	Serving size	Type of Food You Ate	Office Use Only

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