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Many congestive heart failure (CHF) patients may not be able to attain a peak respiratory exchange ratio (RER_{peak}) ≥ 1.10 during maximal cardiopulmonary exercise (CPX) testing. Although this is usually attributed to a submaximal effort, a portion of this population may not be able to attain this RER_{peak} level due to pathophysiological complications of heart failure. Currently, little is known about the predictive value of CPX testing in CHF patients with a $\text{RER}_{\text{peak}} < 1.10$. Hence, the purpose of this study was to identify significant predictors of CHF-related adverse events in patients with a low RER_{peak} . The variables analyzed for predicting two-year survival of CHF-related events included $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope, left ventricular ejection fraction (LVEF), etiology of CHF, beta-blocker usage, age, sex and body mass index (BMI). No use of beta-blockers, $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope ≥ 34 , LVEF $< 25\%$, and ischemic etiology of CHF were associated with significantly lower two-year CHF-related event-free survival probability within the $\dot{V}\text{O}_{2\text{peak}} \leq 14$ ml/kg/min stratum. This probability was comparable to the high RER_{peak} (≥ 1.10) group within the same $\dot{V}\text{O}_{2\text{peak}}$ stratum. Exploratory multivariate proportional hazard analysis in this particular group revealed that no use of beta-blockers, $\dot{V}\text{E}/\dot{V}\text{CO}_2$ slope ≥ 45 , LVEF $< 25\%$ and ischemic etiology of CHF were the significant independent predictors of CHF-related events.

PREDICTING SURVIVAL PROBABILITY FOR MAJOR CONGESTIVE HEART
FAILURE EVENTS IN PATIENTS ATTAINING A LOW PEAK RESPIRATORY
EXCHANGE RATIO DURING CARDIOPULMONARY EXERCISE TESTING

by

Aarti Kenjale

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Approved by

Committee Chair

APPROVAL PAGE

This thesis has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

Committee Chair _____
Dr. Paul Davis

Committee Members _____
Dr. Daniel Bensimhon

Dr. Beverly Levine

Dr. Laurie Wideman

16 January 2008
Date of Acceptance by Committee

11 April 2008
Date of Final Oral Examination

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CHAPTER I

INTRODUCTION

This section will define the statement of the problem, purpose of the study, specific aims, and hypotheses.

Statement of the Problem

Cardiopulmonary exercise (CPX) testing is the gold standard for assessing functional capacity and predicting prognosis in ambulatory patients with congestive heart failure (CHF). As a result, many heart failure specialists use CPX testing to help tailor therapy for individual patients based on CPX test results. In particular, CPX testing plays a crucial role in making referral decisions for CHF patients regarding advanced therapies such as heart transplantation and implantation of left ventricular assist devices (LVADs). Given the scarcity of donor organs and the costs associated with treating advanced heart failure, the ability to accurately identify patients who are at the highest risk for adverse outcomes is imperative.

Currently, peak exercise oxygen consumption ($\dot{V}O_{2\text{peak}}$) is the most commonly used CPX testing parameter for assessing the prognosis of CHF patients. Typically, a

$\dot{V}O_{2\text{peak}} \leq 14$ ml/kg/min is the cut point where patients are considered for heart transplantation (Mancini et al., 1991; Roul et al., 1994). Another CPX testing variable, the slope of the minute ventilation ($\dot{V}E$) to CO_2 production ($\dot{V}CO_2$) ratio ($\dot{V}E/\dot{V}CO_2$ slope), has also been shown to have prognostic power. The $\dot{V}E/\dot{V}CO_2$ slope is an effort-independent variable. It has been shown to correlate with cardiac output, left ventricular filling pressures, and ventilation perfusion mismatching (Tomkiewick-Pajak et. al., 2002). Although more recent studies have shown that the $\dot{V}E/\dot{V}CO_2$ slope may be a more sensitive predictor of major cardiac events in patients with CHF (Arena et al, 2004; Bard et al., 2006), it has not received as much attention in the literature as $\dot{V}O_{2\text{peak}}$. Therefore, it has not yet gained the same clinical acceptance.

Despite its widespread use, a common criticism of $\dot{V}O_{2\text{peak}}$ is that it is effort-dependent and thus can be influenced by patient motivation (Myers et al., 2000; Ramos-Barbon et al., 1999). Hence, having a way to ensure that patients are tested at their maximal effort level is important in order to generate meaningful CPX data.

While several criteria exist for assessing a maximal exercise effort, including a plateau in $\dot{V}O_2$ with increased work rate, previous studies have shown that peak respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$) (RER_{peak}) is a simple and useful objective criterion of effort (Howley et al., 1995; Mezzani et al., 2003). There is debate as to the optimal RER_{peak} cut point for identifying a maximal effort. Several studies have suggested an RER_{peak} of 1.10 (Issekutz et al., 1961; Neuberg et al., 1988; Fleg et al., 2000; Arean et al. 2004; American College of Sports Medicine, 2006) while other

authors have suggested a higher cut point of at least 1.15 (Mezzani et al., 2003; Corra et al., 2004). However, Aitken et al. (1988) demonstrated that not all subjects attain an $\text{RER}_{\text{peak}} \geq 1.15$, even when they reach a $\dot{\text{V}}\text{O}_2$ plateau. Based on established guidelines, an $\text{RER}_{\text{peak}} \geq 1.10$ is commonly accepted to be indicative of a maximal effort (American College of Sports Medicine, 2006).

In clinical experience, a significant proportion (~50%) of patients with heart failure are often unable to attain an $\text{RER}_{\text{peak}} \geq 1.10$ (unpublished results, HF Action database, LeBauer Cardiovascular Research Foundation). This may be attributable to certain muscular abnormalities such as lower active skeletal muscle mass (Anainsson et al., 1981), gradual diffusion of acid metabolites from active skeletal muscle into the blood stream (Shephard et al., 1975), and some ventilatory abnormalities due to respiratory muscle fatigue.

Currently, there is controversy about the predictive value of CPX testing in CHF patients with low RER_{peak} and whether or not it may be possible to identify the significant predictors of CHF-related events within low RER_{peak} group with $\text{RER}_{\text{peak}} < 1.10$. Furthermore, it is not yet evident if other variables, including $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope derived from CPX testing, age, sex, body mass index (BMI), left ventricular ejection fraction (LVEF), etiology of CHF (ischemic or non-ischemic), and beta-blocker usage have an ability to predict the rates of major heart failure events in CHF patients with low RER_{peak} for a given $\dot{\text{V}}\text{O}_{2\text{peak}}$.

Purpose of the Study:

The purpose of this study is to determine if specific variables assessed from “maximal” CPX testing can be used to predict future major heart failure events (LVAD implantation, heart transplantation, or death) in CHF patients with systolic dysfunction who have not undergone previous LVAD implantation or heart transplantation.

Specific Aims:

1. After stratifying CHF patients by $\dot{V}O_{2\text{peak}}$ ($\leq 14 \text{ ml/kg/min}$ vs. $> 14 \text{ ml/kg/min}$), examine the effects of RER_{peak} (< 1.10 vs. ≥ 1.10) on the survival probability for major heart failure events over a two-year period.
- 2a. Among those with a low RER_{peak} within each $\dot{V}O_{2\text{peak}}$ stratum, perform bivariate survival analyses examining the effects of the following independent variables (considered one at a time) on two-year survival probability for major heart failure events: $\dot{V}E/\dot{V}CO_2$ slope (low/high), age (young/old), sex (male/female), BMI (non-obese/obese), LVEF (low/high), CHF etiology (ischemic/non-ischemic), and beta-blocker use (yes/no).
- 2b. Based on the bivariate analyses in Aim 2a, identify the subgroups with the statistically significant lower survival probabilities within the low RER_{peak} group and compare to the high RER_{peak} group within the same $\dot{V}O_{2\text{peak}}$ stratum.

Working Hypotheses:

1. Within each $\dot{V}O_{2\text{peak}}$ stratum, CHF patients with a low RER_{peak} will have a higher probability of survival than patients with a high RER_{peak}. This will likely be due to a portion of the low RER_{peak} patients failing to exercise at a maximal effort.
- 2a. In CHF patients in low RER_{peak} group for a given $\dot{V}O_{2\text{peak}}$ stratum, the following groups of patients will have a lower probability of survival: higher $\dot{V}E/\dot{V}CO_2$ slope, older age, lower LVEF, ischemic etiology of CHF, and beta blocker non-users. There is little previous research comparing the survival probability for major heart failure events between male versus female and obese versus non-obese patients. Therefore, the analyses of these variables are exploratory in nature and no hypotheses concerning them have been generated.
- 2b. Within each $\dot{V}O_{2\text{peak}}$ stratum, the subgroups of low RER_{peak} identified in Aim 2a as having significantly lower survival probabilities for CHF events will have similar probabilities of survival as the high RER_{peak} group.

CHAPTER II

REVIEW OF THE LITERATURE

This section will discuss the parameters of cardiopulmonary exercise (CPX) testing and will review the research that examined the impact of CPX and other physiologic derived variables on major heart failure events in congestive heart failure (CHF) population. There will be particular focus on peak oxygen consumption ($\dot{V}O_{2\text{peak}}$), the respiratory exchange ratio (RER), and the slope of minute ventilation to CO_2 produced ($\dot{V}E/\dot{V}CO_2$ slope).

Congestive Heart Failure

CHF is a leading cause of mortality and morbidity and is a public health challenge worldwide. This is related to epidemic increases in hypertension, atherosclerosis, obesity, diabetes, and valvular abnormalities in which CHF is generally the end stage of the disease (Young et al., 2004). According to the American Heart Association 2004 update on heart disease and stroke statistics, CHF affects approximately 5 million Americans and 15 million people worldwide.

Due partly to advanced therapeutics and a rapidly growing aging population, an increased life span of cardiac patients has contributed to an increased prevalence of CHF. CHF has become the major leading cause of hospitalization in older adults

(Kannel et al., 2000). More than 75% of the patients in US are older than 65 years (Rich et al., 1997). The number of hospital admissions for CHF increased to approximately 1 million in 2004. This has imposed an immense financial burden on the health care system in the US, as more than \$30 billion is spent each year for the care of heart failure patients (Rosamond et al., 2007).

CHF is defined as an inability of the heart to maintain or increase cardiac output at a rate commensurate to the aerobic requirements of the body (Fleg et al., 2000). As a result, patients with CHF often experience fatigue and dyspnea with exertion and, in the most advanced cases, dyspnea at rest. Not surprisingly, many of these patients develop difficulties performing their activities of daily living. CHF has two types: systolic and diastolic. Systolic heart failure, which represents approximately 50% of CHF cases, results from abnormalities in the contractile capacity of the heart due to the loss of functional myocardium. This results from myocardial infarction, an excessive preload affecting the pumping capacity of the heart (e.g. valvular regurgitation), an increased afterload (e.g. hypertension), and heart rate disturbances affecting duration of contractility. Diastolic heart failure results from abnormalities in the relaxation of the heart due to cardiac muscle hypertrophy, impaired compliance, and aging. This is seen with myocardial composition disorders that stiffen the heart chambers. CHF is also divided according to etiology into ischemic cardiomyopathy (ICM) and non-ischemic cardiomyopathy (NICM). ICM is defined as myocardial dysfunction due primarily to ischemic injury. In many patients with ischemic myocardial injury, left ventricular

remodeling occurs. This involves necrosis of cardiomyocytes, weakening of the myocardium due to inflammation, formation of a collagenous scar, and dilation and hypertrophy of the ventricle (Sutton et al., 2000). This often leads to ventricular wall weakness, increased ventricular load, distortion of the contractile capacity of the heart, and a decrease in left ventricular ejection fraction (LVEF). NICM includes heart diseases resulting from idiopathic, postpartum, peripartum, alcoholic, hypertrophic, restrictive, and valvular causes, as well as drug toxicity, viral and infiltrative disorders. These etiologies ultimately lead to dilation of the left ventricle as a compensatory mechanism to increase LVEF.

It is important to assess the functional capacity of CHF patients to tailor pharmaceutical and/or surgical therapy. Cardiopulmonary exercise (CPX) testing is an essential standard tool to assess functional capacity in ambulatory CHF patients.

Causes of Exercise Intolerance in CHF:

CHF patients generally terminate exercise testing due to the development of leg fatigue and/or abnormal ECG changes which may be caused by ischemia (due to compromised cardiac output). They may also stop CPX testing due to exertional dyspnea or leg fatigue. Previously, it was believed that the severity of exercise intolerance in CHF patients was solely related to hemodynamic impairment, but it is now known that causes of exercise intolerance are more complex. Abnormalities in *central (cardiac), ventilatory* and *peripheral* factors affect exercise capacity in CHF patients.

Central factors include: 1) systolic dysfunction due to impaired contractility, 2) diastolic dysfunction due to impaired compliance, 3) elevated pulmonary venous pressure affecting ventricular output and hence systemic blood flow during exercise, and 4) reduced beta-adrenergic receptor density and its desensitization, causing abnormal neurohumoral responses during exercise (i.e., chronotropic and inotropic incompetence) (Myers et al., 1991).

Ventilatory factors contribute mainly to exertional dyspnea in CHF. These include: 1) increased physiologic pulmonary dead space due to ventilation-perfusion mismatch [this leads to an increased ratio of total dead space to tidal volume ($\dot{V}d/\dot{V}t$)] and 2) increased ratio of minute ventilation to carbon dioxide produced ($\dot{V}E/\dot{V}CO_2$). It increases ventilation through intact neural and chemoreceptor mediated reflexes (Sullivan et al., 1988). Exertional dyspnea can also be attributed to increased pulmonary capillary wedge pressure. It reduces lung compliance and stimulates pulmonary juxtagapillary receptors. Thus, it ultimately enhances ventilation and produces abnormal ventilatory control, and breathing pattern (Myers et al., 1991). Abnormalities of ventilatory muscles, such as decreased respiratory muscle strength and work, increased diaphragmatic work and accessory respiratory muscle deoxygenation or bronchial hyper reactivity, also cause exertional dyspnea (Mancini et al., 1992; Cabanes et al., 1989).

Peripheral factors, such as vascular and muscular impairment, are major contributors to exertional fatigue in CHF. Abnormal vasomotor tone has been observed in CHF patients, especially in the resistance vessels of skeletal muscle due to increased

sodium content and increased tissue pressures seen in edematous states (Zelis et al., 1975). This can lead to a decreased vasodilatory response to exercise- or ischemia-induced metabolites and increased peripheral resistance due to enhanced ergoreceptor activity (Clark et al., 1996). The decreased skeletal muscle circulation results in increased oxygen extraction [(a- \bar{v})O₂ difference] as a compensatory response (Myers et al., 1991). However, the increased oxygen extraction does not fully make up for the decreased blood supply. The resulting compromise in oxygen supply results in an earlier onset of anaerobic glycolysis, producing excess lactic acid and metabolic acidosis (Zelis et al., 1975). However, Massie et al. (1987) demonstrated that, although CHF patients have significantly lower pH at submaximal levels of exercise compared to normal controls, this is not associated with blood supply to muscles or muscle atrophy. Instead it is attributed to abnormalities within the skeletal muscle itself. In CHF patients, skeletal muscles show metabolic and histological abnormalities due to disease related pathology, including inactivity and/or chronically impaired circulation. Metabolic abnormalities include earlier onset of glycolysis, decrease in oxidative phosphorylation and mitochondrial enzymes (Mancini et al., 1988; Clark et al., 1996). Histological changes include skeletal muscle atrophy resulting from deconditioning, inactivity or malnutrition (Mancini et al., 1988), intramuscular lipid accumulation (Clark et al., 1996), reduction in type-I slow twitch fibers with high oxidative capacity and increase in type-IIb fast twitch fibers with reduced aerobic capacity (Myers et al., 1991; Clark et al., 1996). These vascular and musculoskeletal abnormalities contribute to exertional fatigue. These

histochemical abnormalities are also suspected to involve respiratory muscles causing early respiratory fatigue and dyspnea.

Purpose of Cardiopulmonary Exercise Testing in CHF Patients:

CPX testing is a standard modality of integrative measurement of the hemodynamic, ventilatory and musculoskeletal systems. During CPX testing, a gradually increasing physiological stress is induced. CPX testing is conducted with careful monitoring of the patients and both objective and subjective measurements. CHF patients generally present with dyspnea and/or fatigue. This often limits their daily activities and, in worse cases, self-care. Hence, it is important to measure the functional capacity of CHF patients to assess the extent of their impairment. Patients with heart failure often demonstrate normal cardiac performance at rest. Therefore, measures of left ventricular performance obtained at rest do not correlate well with functional capacity (Franciosa et al., 1981). Physiological stress, such as exercise, is usually needed to determine the extent of functional impairment (Weber et al., 1982).

Standard CPX testing includes the measurement of ventilation and expired gases to determine oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), respiratory rate, tidal volume ($\dot{V}t$) and minute ventilation (\dot{V}_E) during graded exercise. Other important variables include: total exercise duration within a given exercise protocol, maximal oxygen uptake ($\dot{V}O_{2\max}$), ventilatory efficiency denoted by slope of minute ventilation to CO_2 production ($\dot{V}E / \dot{V}CO_2$ slope), respiratory exchange ratio (RER), heart rate (HR),

blood pressure, and oxygen saturation (SaO_2). Additionally, subjective parameters, such as rating of perceived exertion (RPE), can be obtained. These CPX parameters will be explained in the next section. Many of them have been suggested as diagnostic or prognostic markers, independently or in combination with each other, in the heart failure population.

CPX testing is a cost-effective and non-invasive clinical tool. Accurate interpretation of clinical data obtained from CPX testing helps to determine the severity of CHF. This enables clinicians to determine a prognosis (Corra et al., 2004), decide therapeutic options, and assess the efficacy of the treatment provided. CPX also helps in differentiating whether dyspnea and fatigue are of cardiac or pulmonary origin (Neuberg et al., 1988). *Most importantly, CPX testing plays a crucial role in deciding when to refer CHF patients for advanced therapies, such as left ventricular assistive devices (LVADs) and heart transplantation (Myers et al., 1998).* Given the scarcity of donor organs and the costs associated with treating advanced heart failure, the ability to accurately identify patients who are at the highest risk for adverse outcomes is crucial.

Determination of Maximal Aerobic Capacity:

In order to precisely establish their diagnosis and prognosis, it is important that CHF patients give maximal efforts during CPX testing to determine reliable measures of cardiorespiratory reserve. However, many CHF patients do not yield “maximal” values in

some testing variables despite giving maximal effort. Therefore, accurate and objective criteria are needed to determine whether $\dot{V}O_{2\text{max}}$ is reached during exercise.

It has been demonstrated that there is a certain upper limit to the combined functional capacity of the cardiovascular and respiratory systems to transport oxygen to the working muscles. A linear relationship exists between $\dot{V}O_2$ and the increase in work load until a certain point. Beyond this point, there is no increase in the oxygen uptake in spite of an increasing work load. This is defined as $\dot{V}O_{2\text{plateau}}$ (Hill, 1926). Reaching a plateau in oxygen uptake with increased work rate is considered the gold standard criterion for $\dot{V}O_{2\text{max}}$ (Howley et al., 1995). The $\dot{V}O_{2\text{max}}$ achieved serves as an indicator of the maximal cardiovascular capacity provided that pulmonary function is normal. Hence, it plays a vital role in the diagnosis and prognosis of patients with impaired cardiovascular health. $\dot{V}O_{2\text{max}}$ depends not only on the mechanical capacity of the heart to perform but also on the ability to increase $(a-\bar{v})O_2$ difference, which reflects the capacity of peripheral tissues to extract oxygen from the circulation (Mitchell et al., 1958).

Many problems exist with the use of $\dot{V}O_2$ plateau as a consistent criterion for maximal effort. It is open to inter-subject variability depending upon differences in the criteria used for its definition, protocol used (intermittent versus continuous), methods of data collection by automated systems, and interval sampling of the data (Myers et al., 1990), inability of everyone to achieve a $\dot{V}O_2$ plateau, health, age, motivation, and safety of continued work at a maximal level (Myers et al., 1989; Howley et al., 1995; Sidney et al., 1977).

Historically, different cut-off values have been suggested as the criteria for establishing $\dot{V}O_2$ plateau such as (Howley et al., 1995): an increase of $\dot{V}O_2 < 150$ ml/kg/min or < 2.1 ml/kg/min when treadmill grade is increased by 2.5% per 3min stage at 7mph (Taylor et al., 1995), < 54 ml/min when grade is increased by 2.5% at 6mph per 2.5 min stage (Mitchell et al., 1958), ≤ 2 ml/kg/min with a 1-2 % increase of treadmill grade (Sideny et al., 1977), < 100 ml/min when cycling work load is increased by 150 kpm/min (Issekutz et al., 1961), and < 50 ml/min when subject is tested with an intermittent cycle ergometer test until workload could not be maintained for 3 minutes (Cumming et al., 1967). These studies used different equipments and protocols. Although it is commonly accepted that failure to increase oxygen uptake by 150 ml/min with increased work load is the plateau of oxygen uptake (Froelicher and Myers, 2000), a cut-off value has not yet been universally accepted.

Secondly, it may not be possible for everyone to achieve $\dot{V}O_2$ plateau (Wyndham 1959). Previous studies show different percentages of study populations reaching true $\dot{V}O_2$ plateau as 50% (Cumming et al., 1967), $< 40\%$ (Froelicher et al., 1974) and 70% (Sideny et. al., 1977). In 1989, Myers et al. tested healthy subjects and demonstrated that occurrence of plateau is not a consistent observation with repeated testing, even when maximal heart rate, perceived exertion, and maximal gas exchange parameters were high and unvaried.

It is difficult for low fit, elderly, and low motivated individuals to reach $\dot{V}O_2$ plateau as attainment of the plateau requires high subject motivation (Hollenberg et al.,

2000; Sidney et al., 1977). The protocol used also affects the percentage of subjects achieving true $\dot{V}O_2$ plateau and seen as 33% in Taylor protocol, 17% in Balke protocol and 7% in Bruce protocol (Froelicher et al., 1974). This can be affected by large work rate increments. Intermittent protocol or repeat testing increases the number of subjects reaching $\dot{V}O_2$ plateau (Taylor et al., 1955; Sidney et al., 1977).

The reliability and consistency of a plateau is questioned in the heart failure population, as many CHF patients are deconditioned due to disease and old age. They also have reduced daily activities due to symptoms, muscular weakness, poor motivation, and fear of untoward complications of the disease (Sideny et al., 1977). It is difficult to make elderly patients work up to and sustain their maximal levels due to the anaerobic stress produced (Cumming et al., 1972).

Alternatively, the concept of *peak* oxygen consumption ($\dot{V}O_{2\text{peak}}$) has been considered where subject reaches the point of fatigue even in absence of plateau in oxygen uptake. It is important to determine whether $\dot{V}O_{2\text{peak}}$ denotes a maximal effort or not. Hence, certain secondary criteria are developed to help determine if a subject has given a maximal effort. These criteria include: high post-exercise blood lactate concentration, achievement of a certain percentage of age adjusted maximal heart rate and/or exercise capacity, high RER, and high RPE (Howley et al., 1995).

Many of these criteria have limitations associated with their use. For example, obtaining post-exercise lactate response requires blood sampling. In addition, previous researchers have shown variability in post-exercise lactate values obtained as maximal

effort criteria, such as: 7.3 mM (Issekutz et al., 1961), increase by at least 60 mg/100ml above pre-exercise level (Issekutz et al., 1962), 5.5 mM (Doblen et al., 1967), >8 mM (Cumming et al., 1972), and 8.8 mM (Sidney et al., 1977). Blood lactate level of >7-8 has been traditionally considered as a consensus index of maximal effort (Frolicher et al., 2000). A lower percentage of the elderly population can reach this standard (Sidney et al., 1977; Cumming and Borysk, 1972). Lactate levels are also shown to be higher in men than women (Sidney et al., 1977). This can be attributed to a higher ratio of muscle mass to total blood volume in men compared to women. This ratio also results in decreased maximal lactate concentration with aging. Therefore, the lactate responses vary across subject populations, age groups and protocols used and should not be held as a universal standard of maximal effort (Howley et al., 1995).

Achievement of some percentage of age-adjusted maximal heart rate is also considered as a secondary criterion to determine $\dot{V}O_{2\max}$ level. The standard deviation associated with the maximal HR estimate is ± 11 beats/min (Londeree et al., 1984), which reflects large inter-subject variability (Cumming et al., 1972). In addition, this criterion is not useful with patients on beta-blocking drugs and other medications that affect HR, which are very common among CHF patients. Ramos-Barbon et al. (1995) observed that 50% of CHF patients with $VO_{2\text{peak}} < 14 \text{ ml/kg/min}$ did not achieve $\geq 85\%$ of the $HR_{\text{peak}}/HR_{\text{predicted}}$, indicating chronotropic limitation. Hence, they suggested the need for other objective criteria to confirm maximal effort in performing precise risk stratification in CHF patients with low $\dot{V}O_{2\text{peak}}$.

The Borg RPE scale consists of subjective patient-reported fatigue ratings ranging from 6 (very, very light) to 20 (very, very hard). A high RPE level (≥ 17) achieved at the end of the exercise is considered as the attainment of maximal effort (American College of Sports Medicine, 2006). However, this criterion is highly subjective, which can skew the accuracy of maximal effort measured.

Finally, RER measured at the peak of exercise (RER_{peak}) is another secondary criterion for the attainment of maximal effort. It is objective and is determined by gas exchange parameters collected during CPX testing. Hence, it is widely used to determine if maximal effort level is achieved.

Respiratory Exchange Ratio:

Respiratory exchange ratio is defined as the amount of CO_2 produced divided by amount of O_2 consumed (Froelicher and Myers, 2000). The cellular counterpart of RER is the metabolic respiratory quotient (RQ), which is calculated as $\dot{Q}CO_2 / \dot{Q}O_2$ where $\dot{Q}O_2$ is O_2 consumption by the cells and $\dot{Q}CO_2$ is CO_2 production by the cells. RQ reflects metabolic exchange of gases at the cellular level and is dictated by substrate utilization. RQ measured from arterial blood gases is 0.2 times higher with a high carbohydrate diet than with a high fat diet (Wasserman et al., 1967). RER is related to but not equivalent to RQ, as RER reflects RQ only at the steady state, where no CO_2 is being added to or removed from the body CO_2 stores and O_2 body stores remain constant. At higher exercise intensities, RER exceeds metabolic RQ due to acute hyperventilation and acute

metabolic acidosis. In the latter case, excess CO₂ is produced through the buffering of lactic acid with bicarbonate (Wasserman, 1994).

Mechanism of RER Increase with Maximum Graded Exercise:

Resting RER value ranges from 0.70-0.85. At higher exercise work rates (RER>1.0), metabolic demands of working muscle exceed the O₂ supply. This increases anaerobic glycolysis, leading to plasma accumulation of lactic acid. In turn, hydrogen ions (H⁺) dissociate from lactate and are buffered through the carbonic anhydrase reaction:



The reciprocal relationship between arterial plasma bicarbonate and lactate concentration has been identified at each work intensity by Wasserman et al. (1967). As production of CO₂ increases, it sensitizes carotid chemoreceptors to increase ventilation (Neuberg et al., 1988), which acts as a respiratory compensation to regulate the pH (Howley et al., 1995). As explained by Wasserman (1994), increased CO₂ production and increased ventilation augments CO₂ delivery at the lungs, raising $\dot{V}\text{CO}_2$ with progressive exertion. This increase in $\dot{V}\text{CO}_2$ exceeds the increase in $\dot{V}\text{O}_2$, as hemoglobin is saturated with O₂ at the pulmonary capillary level. This leads to an increase in $\dot{V}\text{CO}_2/\dot{V}\text{O}_2$. In CHF patients, delivery of O₂ to the tissues in response to increased metabolic need is impaired due to reduced cardiac output. This also promotes anaerobic glycolysis and accumulation of lactic acid leading to increased RER (Weber et al., 1982).

The magnitude of anaerobic glycolysis during exertion is also related to the types of muscle fibers recruited. Below the anaerobic threshold, type slow-twitch (Type I) fibers of high oxidative capacity are primarily recruited and fatty acids are utilized as the major fuel. Above the anaerobic threshold, the recruitment of fast-twitch (Type II) fibers of low oxidative capacity increases. In these fibers carbohydrate is utilized as the major fuel and anaerobic glycolysis predominates as mitochondrial density is lower (Wasserman, 1994; Neuberg et al., 1988). In CHF, it is possible that abnormalities of skeletal muscle fiber structure and function can interfere with the capacity to work at higher levels. This may result in different RER_{peak} values in conditions affecting above components.

Variable RER Values at Peak Exercise:

Previous research has considered variable values of RER_{peak} to indicate maximal effort, such as: RER_{peak} > 1 (Clark et al., 1994), ≥ 1.10 (Neuberg et al., 1988; Chua et al., 1996; Chua et al., 1997; Hollenberg et al. 2000), ≥ 1.12 (Cumming et al., 1972), and ≥ 1.15 (Sidney et al., 1977). Although RER_{peak} ≥ 1.10 has been traditionally considered as subsidiary evidence of attainment of VO_{2max} in the CHF population (Fleg et al., 2000), RER_{peak} values vary greatly and an accurate physiologic cut-off point to confirm maximal effort is hard to define (Froelicher and Myers, 2000).

Historically, many researchers have studied the changes in RER from rest to maximal exercise and established different values of RER_{peak} as a secondary criterion of $\dot{V}O_{2\text{max}}$. In 1961, Issekutz et al. tested healthy adults by a series of intermittent exercise sessions on a bicycle ergometer for 4-5 minutes until $\dot{V}O_{2\text{max}}$ was achieved. Gas

exchange data was collected throughout exercise and the lactate levels were measured 1-2 minutes post-exercise. They calculated excess (non-metabolic) CO₂ at the end of exercise (excess CO₂= total CO₂ - 0.75 * VO₂) where true metabolic respiratory quotient (RQ) was assumed to be 0.75. A linear relationship existed between the excess CO₂ and change in lactate levels (correlation coefficient, r = 0.92). This excess CO₂ was expressed as ΔRQ (calculated as measured RQ - 0.75) which supposedly resulted from a delayed circulatory response in the early phase and increased lactate concentration in late phase of graded exercise, with the latter representing percent participation of anaerobic glycolysis in total energy expenditure.

In 1962, Issekutz et al. again tested healthy adults on a bicycle ergometer with series of intermittent tests of 5 minute duration until $\dot{V}O_{2\max}$ was achieved. They calculated ΔRQ (ratio of excess CO₂/O₂= work RQ – 0.75) and observed that each subject (at least above 20 years of age), independent of age and sex, reached $\dot{V}O_{2\max}$ when the RQ was 1.15 or higher. This implicated that ΔRQ of 0.4 or RQ of ≥ 1.15 (0.75+0.4) can be used as secondary criterion of VO_{2max}. But this method had certain drawbacks (e.g., exercise mode was limited to cycle ergometry). Hence, application of these results to treadmill CPX testing can be questioned. Similarly, the population included in this study was healthy and thereby limits the general applicability of the results to diseased populations. Also, the subjects underwent intermittent testing instead of continuous testing as is practiced currently. Even though it is agreed that $\dot{V}O_{2\max}$ remains the same across continuous and discontinuous protocols (McArdle et al., 1973),

lactate (Shephard et al., 1968) and RER_{peak} (McArdle et al., 1973) values differ with application of continuous and discontinuous protocols.

Howley et al. (1995) has discussed the studies with different RER_{peak}. An RER_{peak} value of <1.0 has been observed to be associated with low lactate values (Cunningham et al., 1977). However, Cumming et al. (1972) observed no correlation between RER_{peak} and post-exercise lactate. RER_{peak} of ≥ 1.15 as a maximal effort criterion has been questioned as it has also been observed that not all subjects can reach RER_{peak} ≥ 1.15 even though they attain $\dot{V}O_2$ plateau. Hence, this value can not be considered as a universal criterion for $\dot{V}O_{2\text{max}}$. Other researchers have observed different values of RER_{peak} achieved at $\dot{V}O_{2\text{max}}$. Robinson et al. (1938) demonstrated that RER_{peak} ≥ 1.15 can be an indicator of $\dot{V}O_{2\text{max}}$ between 20-60 years, but younger subjects (6-19 years) failed to achieve this standard. In addition, Cumming et al. (1972) tested 40-65 year-old males and females. They observed that mean maximal exercise RER was 1.13 and only 54% of their subjects could reach RER_{peak} ≥ 1.12 . Aitken and Thompson (1988) tested individuals of variable age groups and fitness levels. This study illustrated an RER range of 1.01-1.11 at $\dot{V}O_{2\text{max}}$. None of the tested groups reached RER_{peak} ≥ 1.15 . Sidney et al. (1977) compared RER values obtained at peak exercise (volitional fatigue) between apparently healthy men and women between the ages of 60 and 83 years. Only 37 % of men and 20% of women reached an RER_{peak} ≥ 1.15 . Also, RER_{peak} in women (1.07 ± 0.09) was lower than in men (1.11 ± 0.08). The studies mentioned in this paragraph used the treadmill for exercise testing except Cumming et al. (1972) who used the bike ergometer.

In summary, several previous studies have documented RER_{peak} values lower than the traditional criterion of ≥ 1.15 at maximal effort. A significant amount of this research has been performed in age groups that encompass the majority of the CHF population. Hence, exploration of a lower RER_{peak} cut-off to signify maximal effort is warranted.

Low RER_{peak} in CHF Patients:

A significant proportion of patients with heart failure are unable to attain a plateau of $\dot{V}O_2$ or a RER_{peak} ≥ 1.10 . Thus, it has been argued that CPX testing does not provide a reliable assessment of prognosis for this group due to the “submaximal” nature of the exercise.

Previous researchers have found that several factors affect RER_{peak}. Sidney et al. (1977) observed lower post-exercise lactate levels with increasing age and also in females, which can be attributed to lower ratio of muscle mass to total blood volume. Aitken et al. (1988) demonstrated RER_{peak} at $\dot{V}O_{2\text{max}}$ to be significantly lower in older sedentary subjects (>60 years) when compared with young sedentary controls. This age-related decrease in RER_{peak} may be attributed to several factors including different protocols used for young subjects (running level on treadmill) and old subjects (walking protocol on level treadmill), age related reduction in active skeletal muscle mass, decrease in Type II muscle fibers (Anainsson et al., 1981), lesser amount of glycogen reserve per unit muscle mass, gradual diffusion of lactic acid metabolites from the active skeletal muscle into the circulation leading to low levels of end stage blood lactate and high levels of local muscle lactate (Shephard et al., 1975), and respiratory muscle fatigue.

As CHF is typically a disease of the elderly (Rich et al., 1997), lower RER_{peak} values can be predicted in this population when compared with normal subjects. In conclusion, RER_{peak} shows considerable inter-individual variability. It is important to determine if selected CHF patients with lower RER_{peak} for a given $\dot{V}O_{2\text{peak}}$ peak still warrant consideration for heart transplantation and LVAD implantation.

RER_{peak} And Prognosis in CHF:

RER_{peak} ranging between 1.10-1.20 is generally considered as an index of maximal effort in healthy subjects (Frolicher and Myers, 2000). Yet it is not quite clear to what extent RER_{peak} reflects maximal effort. This impacts the prognostic power of other exercise variables such as $\dot{V}O_{2\text{peak}}$ and $\dot{V}E/\dot{V}CO_2$ slope in CHF population. Some recent studies have tried to establish the role of RER_{peak} as a measure of subject effort and its contribution to prognostic power of $\dot{V}O_{2\text{peak}}$ and $\dot{V}E/\dot{V}CO_2$ slope.

Conflicting data exist regarding the relationship between RER_{peak} and cardiac related events in CHF patients. Gitt et al. (2002) tested CHF patients and followed them (median follow-up time of 1.76 years) to identify prognostic indicators for survival. They observed that RER_{peak} was not significantly different among survivors and non-survivors (1.07 ± 0.13 vs. 1.04 ± 0.14 respectively). Mezzani et al. (2003) demonstrated that the prognostic significance of low $\dot{V}O_{2\text{peak}}$ in CHF patients gets compromised when the RER attained at the last stage of exercise is low. They observed that, in patients who attained $\dot{V}O_{2\text{peak}} \leq 10 \text{ ml/kg/min}$ on maximal exercise testing, the ability to attain RER_{peak} of ≥ 1.15 was seen as the only independent predictor of mortality and transplantation with a

relative risk of 1.65. The percentage of patients achieving $\text{RER}_{\text{peak}} \geq 1.15$ was significantly higher in the CHF event group than in the survivors (65% vs. 39%). When these patients were further stratified based on RER_{peak} , those with $\text{RER}_{\text{peak}} < 1.15$ had a two-year survival rate of 83% which is comparable to patients with $\dot{\text{V}}\text{O}_{2\text{peak}} \geq 14$ ml/kg/min, while those with $\text{RER}_{\text{peak}} \geq 1.15$ had significantly lower two-year survival rate of 52%. This study indicated that RER_{peak} affects the prognosis in CHF patients with very low $\dot{\text{V}}\text{O}_{2\text{peak}}$ (≤ 10 ml/kg/min). Hence, they suggested that patients in this group should be encouraged to exercise until RER_{peak} reach ≥ 1.15 and a cautious decision must be made when RER_{peak} is < 1.15 . However, they did not observe any impact of RER_{peak} on prognostic power of $\dot{\text{V}}\text{O}_{2\text{peak}}$ in the subgroup of patients with $\dot{\text{V}}\text{O}_{2\text{peak}} 10-14$ ml/kg/min and suggested that $\dot{\text{V}}\text{O}_{2\text{peak}}$ of > 10 ml/kg/min is associated with better aerobic capacity and prognosis is independent of achievement of maximal effort as denoted by two-year survival rate of 89% in this group.

Conversely, a study by Arena et al. (2004) observed that the submaximal subject effort impacts prognosis in CHF patients wherein low $\text{RER}_{\text{peak}} (< 1.10)$ influences the prognostic power of both the variables: $\dot{\text{V}}\text{O}_{2\text{peak}}$ and $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope. They tested CHF patients where maximal effort was considered as $\text{RER}_{\text{peak}} \geq 1.10$. The 1-year event rate (cardiac related hospitalization and cardiac related mortality) was 27% in the < 1.10 RER_{peak} subgroup and 32% in ≥ 1.10 RER_{peak} subgroup. The analysis showed that both $\dot{\text{V}}\text{O}_{2\text{peak}}$ and $\dot{\text{V}}\text{E}/\dot{\text{V}}\text{CO}_2$ slope were significant predictors of cardiac related events in both maximal and submaximal RER_{peak} subgroups. However, the prognostic value for

$\dot{V}E / \dot{V}CO_2$ slope was consistently higher than those of $\dot{V}O_{2\text{peak}}$ in both RER_{peak} subgroups.

A review by Howley et al. (1995) showed that almost all of the studies in healthy subjects used an RER_{peak} of 1.0 to 1.05 as a cut off value for $\dot{V}O_{2\text{max}}$ determination. Hence, the guidelines for the care of cardiac transplant candidates published in 2006 mentioned that RER_{peak} of >1.10 may be a very strict criteria for CHF patients (Mehra et al., 2006). According to these guidelines, class I criteria of listing CHF patients for heart transplantation include $\dot{V}O_{2\text{peak}}$ of ≤ 14 ml/kg/min (in absence of beta-blockers) and ≤ 12 ml/kg/min (in presence of beta-blockers) whereby CPX test is defined maximal when patients achieve $RER_{\text{peak}} > 1.05$. But it is possible that all CHF patients, especially the severely impaired, may not be able to achieve RER_{peak} of >1.05 . Further, while stating an RER_{peak} cut-off of >1.05 for maximal effort, these guidelines do not include experimental evidence examining the effects of low RER_{peak} on CHF events.

In summary, these previous studies do not show uniform findings concerning the prognostic impact of RER_{peak} in the CHF population. Since most CHF patients present a $\dot{V}O_{2\text{peak}}$ range from 10-18 ml/kg/min it is important to stratify this $\dot{V}O_{2\text{peak}}$ range and assess the impact of RER_{peak} on the prognosis in CHF patients.

RER_{peak} values also vary according to etiology of CHF (ischemic versus non-ischemic). Arena et al. (2005) observed that overall RER_{peak} was significantly higher in CHF patients with ischemic etiology when compared with non-ischemic etiology (1.12 ± 0.18 vs. 1.07 ± 0.15). RER_{peak} was also significantly higher in the event-free group

of ischemic etiology than the event-free group of non-ischemic etiology (1.13 ± 0.17 vs. 1.08 ± 0.15). But the difference in RER_{peak} was not significantly higher in patients with cardiac related events in ischemic etiology than with non-ischemic etiology (1.12 ± 0.18 vs. 1.05 ± 0.17).

Currently, little is known about the predictive value of CPX testing in CHF patients with low RER_{peak} . In low RER_{peak} groups, no conclusive information is available about probable prognostic indicators: $\dot{V}\text{E}$ / $\dot{V}\text{CO}_2$ slope, age, sex, BMI, etiology of CHF, LVEF and beta-blocker use. Furthermore, it is not yet evident if the subgroup of low RER_{peak} with highest risk can be identified. This subgroup may have comparable risk to high RER_{peak} group for a given $\dot{V}\text{O}_{2\text{peak}}$ strata. Thus, further research can assist in the identification of subgroups in the CHF population of low $\text{RER}_{\text{peak}} (<1.10)$, with lower or higher risk for events.

$\dot{V}\text{O}_{2\text{peak}}$:

Currently $\dot{V}\text{O}_{2\text{peak}}$ is the most commonly used CPX testing parameter for assessing prognosis in CHF population. $\dot{V}\text{O}_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ is the typical cut point in considering patients for cardiac transplantation (Mancini et al., 1991; Roul et al., 1994). A cornerstone study by Mancini et al. (1991) demonstrated $\dot{V}\text{O}_{2\text{peak}}$ as the major variable for risk stratification in CHF population. They showed that the survival rate for CHF patients with $\dot{V}\text{O}_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ was significantly lower (48%) as compared to those with $\dot{V}\text{O}_{2\text{peak}} > 14 \text{ ml/kg/min}$ (94%) who were considered too well for transplantation due

to preserved exercise capacity. This study suggested that cardiac transplantation can be safely deferred in most ambulatory CHF patients with left ventricular dysfunction who have $\dot{V}O_{2\text{peak}} > 14 \text{ ml/kg/min}$. Also, Chua et al. (1997) demonstrated that in CHF patients, $\dot{V}O_{2\text{peak}}$ was significantly lower in non-survivors as compared with survivors (14.0 ± 6.8 vs. 20.0 ± 6.9). CHF patients of > 70 years demonstrated $\dot{V}O_{2\text{peak}}$ as a significant prognostic predictor by univariate as well as by multivariate analysis (Davies et al., 2000). Mezzani et al. (2003) demonstrated that the two-year survival rate was 93% versus 75% in patients with $\dot{V}O_{2\text{peak}} > 14$ and $\leq 14 \text{ ml/kg/min}$ respectively and was 89% versus 69% in patients with $\dot{V}O_{2\text{peak}} > 10$ and $\leq 10 \text{ ml/kg/min}$ respectively. Osada et al. (1998) tested CHF patients and observed that 3-year survival rate was significantly lower in patients with $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ than those with $\dot{V}O_{2\text{peak}} > 14 \text{ ml/kg/min}$. Roul et al. (1994) prospectively tested 75 CHF patients with NYHA class II and III and grouped them into $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ and $\dot{V}O_{2\text{peak}} > 14 \text{ ml/kg/min}$. With a 1-year follow up they observed that prognosis was significantly worse in $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ group as compared to $\dot{V}O_{2\text{peak}} > 14 \text{ ml/kg/min}$. The importance of $\dot{V}O_{2\text{peak}}$ of $\leq 14 \text{ ml/kg/min}$ as a prognostic indicator in CHF has also been supported by Gitt et al. (2000) indicating > 3 -fold risk of early mortality within 6 months.

In 2002, Corra and co-workers observed that the mortality rate was significantly higher in $\leq 10 \text{ ml/kg/min}$ when compared with $\geq 18 \text{ ml/kg/min}$. But it was not significantly different between intermediate $\dot{V}O_{2\text{peak}}$ groups of > 10 to $\leq 14 \text{ ml/kg/min}$ and > 14 to $< 18 \text{ ml/kg/min}$. Kao et al. (1997) also tested 178 CHF patients and observed

prognostic value of $\dot{V}O_{2\max}$ in the intermediate risk group. They showed that patients with $\dot{V}O_{2\max}$ of <12 ml/kg/min had significantly worse prognosis than those with $\dot{V}O_{2\max} \geq 17$ ml/kg/min and its prognostic value did not hold true for intermediate risk group with $\dot{V}O_{2\max}$ of 12 to 17 ml/kg/min.

Certain studies have demonstrated that the prognostic value of $\dot{V}O_{2\text{peak}}$ is established over a wide range and fail to recognize a single threshold value as prognostic marker. Myers et al. (1998) stratified $\dot{V}O_{2\text{peak}}$ in CHF patients as above and below 12, 14 and 16 ml/kg/min where these levels demonstrated significant differences in risk for deaths but the degree of risk was similar at each of these levels. Also, in 2000, Myers et al. conducted another study including CHF patients and dichotomizing them according to $\dot{V}O_{2\text{peak}}$ levels above and below of 10,11,12,13,14,15,16 and 17 ml/kg/min. Their follow-up demonstrated that survival rate was significantly higher in the “above” levels than the “below” levels for each of the above $\dot{V}O_{2\text{peak}}$ cut points. Each cut-off point of $\dot{V}O_{2\text{peak}}$ had the ability to differentiate survivors from non-survivors. Therefore, the authors suggested using $\dot{V}O_{2\text{peak}}$ as a continuous variable to assess risk rather than establishing a particular threshold. Similarly Francis et al. (2000) demonstrated that low $\dot{V}O_{2\text{peak}}$ is a significant predictor of mortality in CHF patients and suggested that lower $\dot{V}O_{2\text{peak}}$ implies worse prognosis across range of 10-20 ml/kg/min, without single threshold.

Limitations of $\dot{V}O_{2\text{peak}}$ as a prognostic indicator:

Although $\dot{V}O_{2\text{peak}}$ has been used for risk stratification in CHF patients to determine optimal timing for cardiac transplantation (Mancini et al., 1991) and to assess

response to therapy, it has certain limitations. As measurement of $\dot{V}O_{2\text{peak}}$ is influenced by factors such as age, sex, muscle mass, deconditioning of the muscles, patient's motivation or body composition, some researchers have speculated that this variable may provide limited prognostic information. Even though many previous studies have demonstrated the prognostic significance of $\dot{V}O_{2\text{peak}} (\leq 14 \text{ ml/kg/min})$ in CHF patients, Osman et al. (2000) indicated that $\dot{V}O_{2\text{peak}}$ adjusted for lean body mass is the better prognostic indicator than unadjusted $\dot{V}O_{2\text{peak}}$ and a cut off value of $<19 \text{ ml/kg}$ of lean body mass/min is considered to be a prognostic determinant of cardiac related death and urgent transplantation. This is because a substantial part of total body weight is fat which is much less metabolically active. $\dot{V}O_{2\text{peak}}$ is impacted by age related body fat changes and conditioning status and declines with age. Hence, it is advised to use lean body mass adjusted $\dot{V}O_{2\text{peak}}$ in CHF patients, especially women and obese patients, as a prognostic indicator.

Many other studies tried to analyze the prognostic power of $\dot{V}O_{2\text{peak}}$ when combined with other variables in the CHF population. Chomsky et al. (1996) suggested using cardiac output and $\dot{V}O_{2\text{peak}}$ in combination to predict survival in CHF. Recently, the slope of minute ventilation to carbon dioxide ($\dot{V}E/\dot{V}CO_2$ slope) during CPX testing has been suggested as an independent and strong predictor of prognosis in CHF (Corra et al., 2004). Francis et al. (2000) demonstrated that low $\dot{V}O_{2\text{peak}}$ and high $\dot{V}E/\dot{V}CO_2$ slope are equivalent and complementary predictors of mortality in CHF patients. Similarly, a study by Arena et al. (2004) in CHF patients demonstrated that $\dot{V}O_{2\text{peak}}$ and $\dot{V}E/\dot{V}CO_2$ slope

were significant predictors of cardiac related events and when $\dot{V}E/\dot{V}CO_2$ slope of ≥ 34 was combined with $\dot{V}O_{2\text{peak}} \leq 14$ ml/kg/min, addition of $\dot{V}O_{2\text{peak}}$ improved the prognostic power of the $\dot{V}E/\dot{V}CO_2$ slope to predict hospitalizations but not cardiac-related mortality.

Undisputed significance of $\dot{V}O_{2\text{peak}}$:

Despite the variable opinions of researchers, $\dot{V}O_{2\text{peak}}$ is still widely used in clinical decision-making. Patients with CHF are at a high risk of sudden cardiac death, hence it is important to identify the population at the highest risk to provide appropriate therapy. Due to increasing incidence of CHF, the demand of heart transplantation is increasing while the supply of donor hearts remains unchanged. This scarce availability of donor hearts requires careful selection of transplant recipients. As discussed above, the prognostic significance of $\dot{V}O_{2\text{peak}}$ has been established and, therefore, is accepted in clinical practice as a determinant of CHF treatment. Patients with $\dot{V}O_{2\text{peak}} \leq 14$ ml/kg/min are typically accepted as candidates for heart transplantation.

To maximize the benefits of therapy, certain objective criteria are considered in determining if a patient gives maximal effort during exercise testing. A limitation observed with the $\dot{V}O_{2\text{peak}}$ studies discussed above is that they all used different indicators of maximal effort to verify $\dot{V}O_{2\text{peak}}$. Also, no previous studies show clear evidence as to how the event rates would differ if CHF patients are grouped into low RER (<1.10) and high RER (≥ 1.10) within a given $\dot{V}O_{2\text{peak}}$ stratum.

$\dot{V}E/\dot{V}CO_2$ Slope:

The relationship between minute ventilation ($\dot{V}E$) and CO_2 produced ($\dot{V}CO_2$) is another important CPX derived parameter. The ratio of $\dot{V}E/\dot{V}CO_2$ represents the ventilation required to clear CO_2 produced by the body. Although CO_2 is produced by both aerobic and anaerobic metabolism, $\dot{V}CO_2$ is the amount of CO_2 generated by the buffering of lactic acid attributable mainly to anaerobic stress generated during exercise. This accumulated CO_2 sensitizes ventilatory reflexes increasing the ventilation to remove CO_2 . $\dot{V}E/\dot{V}CO_2$ reflects acid-base balance, chemoreceptor sensitivity and breathing efficiency (Wasserman, 1994). In normal subjects, $\dot{V}E$ and $\dot{V}CO_2$ act parallel to each other. But in CHF patients, high $\dot{V}E/\dot{V}CO_2$ values are observed due to abnormally high ventilatory responses (Froelicher and Myers, 2000). The $\dot{V}E/\dot{V}CO_2$ ratio can be obtained at any time-point during exercise. Although it is a good prognostic variable and easy to calculate (Arena et al., 2002), it is subject to variability depending upon time-point at which it is calculated. The slope of the regression line relating $\dot{V}CO_2$ to $\dot{V}E$ (i.e., the $\dot{V}E/\dot{V}CO_2$ slope) expresses the relationship between the increase of these variables (Chua et al., 1997). $\dot{V}E/\dot{V}CO_2$ slope considers all the data-points from the beginning till the end of CPX testing. Hence, although it requires regression equation calculations, $\dot{V}E/\dot{V}CO_2$ slope is more linear, less variable (Arena et al., 2003), less susceptible to irregular breathing (Davies et al., 2000) and is effort independent (Arena et al., 2007). $\dot{V}E/\dot{V}CO_2$ slope is highly reproducible and inversely related to peak oxygen consumption (Chua et al., 1997).

An abnormally high $\dot{V}E/\dot{V}CO_2$ slope has been considered as a factor indicating poor prognosis in CHF (Corra et al., 2004). It is an important predictor of mortality in CHF patients and is independent of age, peak oxygen consumption, NYHA class, exercise duration and LVEF (Chua et al., 1997). A high $\dot{V}E/\dot{V}CO_2$ slope indicates that ventilation is increasing at a higher rate than $\dot{V}CO_2$ produced. In CHF patients, high $\dot{V}E/\dot{V}CO_2$ slope is associated with many central and peripheral factors such as: reduced cardiac output during exercise, increased pulmonary artery and pulmonary capillary wedge pressures, reduced pulmonary perfusion [which exacerbates ventilation-perfusion mismatching, leading to increased dead space/tidal volume ratio (Sullivan et al., 1988)], and enhanced hypoxic and central hypercapnic chemoreceptor sensitivity [which correlates significantly to increased ventilatory response during exercise in CHF patients (Chua et al., 1996)].

Previous studies demonstrated that high $\dot{V}E/\dot{V}CO_2$ slope is associated with high mortality in CHF patients. The major findings of this research are summarized in Table 1 below:

Study	Findings
Mezzani et al. (2003)	When survivors were compared with non-survivors (death/ heart transplantation) in CHF patients with $VO_{2\text{peak}} \leq 10 \text{ ml/kg/min}$, the event group had a significantly higher $\dot{V}E/\dot{V}CO_2$ slope (45 ± 13 vs. 39 ± 8).
Corra et al. (2002)	When controlled for LVEF (≤ 25 vs. $> 25\%$) and $\dot{V}O_{2\text{peak}}$ (< 13 vs. $\geq 13 \text{ ml/kg/min}$), patients with $\dot{V}E/\dot{V}CO_2$ slope of ≥ 35 had significantly higher mortality rate than those with $\dot{V}E/\dot{V}CO_2$ slope of < 35 (30% vs. 10% respectively).

Gitt et al. (2002)	CHF patients with a $\dot{V}E/\dot{V}CO_2$ slope of >34 had a 5-fold increased risk of early mortality
Chua et al. (1997)	i. Included CHF patients who reached RER >1.10 . ii. CHF patients with a normal $\dot{V}E/\dot{V}CO_2$ slope (<34) had a significantly higher 1-year survival rate (98%) compared to CHF patients with a higher slope (>34 , 73%).

Table 1- Association of High $\dot{V}E/\dot{V}CO_2$ Slope with High Mortality in CHF Patients

$\dot{V}E/\dot{V}CO_2$ slope has also proven to be a significant prognostic indicator in *elderly* CHF patients.

Study	Findings
Davies et al. (2000)	$\dot{V}E/\dot{V}CO_2$ slope was a significant prognostic factor by univariate as well as by multivariate analysis in CHF patients >70 years.
Cicoira et al. (2001)	$\dot{V}E/\dot{V}CO_2$ slope was a significant predictor of mortality in CHF patients >70 years.

Table 2- Prognostic Value of $\dot{V}E/\dot{V}CO_2$ Slope in Elderly CHF Patients

It also has been established that a high $\dot{V}E/\dot{V}CO_2$ slope alone or when combined with low $\dot{V}O_{2\text{peak}}$ acts as a better predictor of survival in CHF patients. It has been described in Table 3 below.

Study	Findings
Arena et al. (2004)	<p>i. $\dot{V}E/\dot{V}CO_2$ slope was a significant predictor of cardiac related events.</p> <p>ii. When $\dot{V}E/\dot{V}CO_2$ slope of ≥ 34 was combined with $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$, the $\dot{V}O_{2\text{peak}}$ added prognostic power of $\dot{V}E/\dot{V}CO_2$ slope to predict hospitalizations but not cardiac related mortality.</p> <p>iii. $\dot{V}E/\dot{V}CO_2$ slope was a significantly better predictor of cardiac related mortality than $\dot{V}O_{2\text{peak}}$ and was also a better predictor of hospitalizations, although the difference was not statistically significant in the latter case.</p>

Table 3- Prognostic Value of High $\dot{V}E/\dot{V}CO_2$ Slope Combined with Low $\dot{V}O_{2\text{peak}}$ in CHF

Thus, high $\dot{V}E/\dot{V}CO_2$ slope (>34) was associated with a higher risk of mortality when $RER_{\text{peak}} > 1.10$ was attained. However, this study did not indicate whether high $\dot{V}E/\dot{V}CO_2$ slope holds the same prognostic value as an important and independent predictor of mortality when RER_{peak} attained was <1.10 .

Many previous researchers have demonstrated $\dot{V}E/\dot{V}CO_2$ slope as a strong, independent predictor of cardiac related events in the CHF population when a cut off value of 34 was used. CHF patients with $\dot{V}E/\dot{V}CO_2$ slope of ≥ 34 are considered to have worse prognosis than those with $\dot{V}E/\dot{V}CO_2$ slope of <34 (Chua et al., 1997; Gitt et al., 2002; Guazzi et al., 2003; Arena et al., 2004).

Guazzi et al. (2003) demonstrated that $\dot{V}E/\dot{V}CO_2$ slope had a stronger prognostic power than $\dot{V}O_{2\text{peak}}$ in CHF patients. They showed that non-survivors had lower $\dot{V}O_{2\text{peak}}$ and steeper $\dot{V}E/\dot{V}CO_2$ slope. But this correlation with $\dot{V}O_{2\text{peak}}$ did not remain once

$\dot{V}E/\dot{V}CO_2$ slope exceeded a value of 34. In 2007, Arena et al. developed a classification system for $\dot{V}E/\dot{V}CO_2$ slope as class I: ≤ 29 , class II: 30 to 35.9, class III: 36 to 44.9 and class IV: ≥ 45 instead of dichotomizing it at a value of 34. They observed that a prognostic value of $\dot{V}E/\dot{V}CO_2$ slope was maintained throughout the broad spectrum of CHF patients. This classification system stratified the risk in CHF population and proposed its utilization for clinical decision making.

Thus many previous researchers have stated the strong prognostic value of $\dot{V}E/\dot{V}CO_2$ slope in CHF patients, sometimes as a better predictor than $\dot{V}O_{2\text{peak}}$. According to 2006 guidelines for listing cardiac transplant candidates, it is suggested to list CHF candidate with sub-maximal CPX testing with $RER_{\text{peak}} < 1.05$ and $\dot{V}E/\dot{V}CO_2$ slope of > 35 (Mehra et al., 2006). However, acknowledging that not all CHF patients reach $RER_{\text{peak}} \geq 1.10$ during maximal exercise testing, it is important to investigate the survival probability of patients with $RER_{\text{peak}} < 1.10$ with respect to $\dot{V}E/\dot{V}CO_2$ slope.

In addition to $\dot{V}E/\dot{V}CO_2$ slope, it is important to assess the survival probability in the RER_{peak} group over the given $\dot{V}O_{2\text{peak}}$ strata with respect to other physiologic variables. The possible predictors include: age (young/old), sex (male/female), BMI (non-obese/obese), CHF etiology (ischemic/non-ischemic), beta-blocker use (yes/no), and LVEF (low/high). More studies are needed to investigate whether the above stated variables assist in identifying the highest risk subgroup in low RER_{peak} groups.

Age:

Previous literature illustrates that maximal oxygen uptake decreases with age (Mitchell et al., 1958) and elderly individuals have low $\dot{V}O_{2\max}$ (Neuberg et al., 1988). Cumming et al. (1972) tested men and women between 40-65 years with progressive cycle ergometer maximal exercise and observed that mean $\dot{V}O_{2\max}$ decreased slightly from age 40 to 55 years and then declined by 15% from 55 to 60 years and by another 12% from 60 to 65 years.

Cicoira et al. (2001) tested CHF patients of >70 years and showed that valid exercise testing results could be obtained in >50% of the patients. This indicated the feasibility of conducting CPX testing in very elderly CHF population. In this study, patients reaching $RER_{peak} > 1.0$ were included and the rest were excluded as submaximal tests. However, $RER_{peak} > 1.0$ does not indicate the maximal effort according to traditional guidelines.

Previous studies demonstrated that age is not a prognostic indicator in CHF patients and is not different among survivors and non-survivors (Mancini et al., 1991; Chua et al., 1997; Davies et al., 2000). Further studies are needed to examine the effects of age on event risk in patients with lower RER_{peak} .

Sex:

Females have lower $\dot{V}O_{2\max}$ than males (Neuberg et al., 1988). Davies et al. (2000) demonstrated that sex does not have prognostic impact in CHF patients. Thus, strong evidence is lacking to determine role of sex affecting prognosis in CHF.

BMI:

Wasserman (1994) explained that in obese subjects the $\dot{V}O_2/\text{work rate}$ relationship which reflects amount of O_2 utilized by exercising subject to perform quantity of external work, is shifted upwards but parallel as compared to non-obese subjects. The obese subjects require higher $\dot{V}O_2$ to move body mass during exercise testing and hence they reach predicted $\dot{V}O_{2\max}$ at submaximal level and fatigue at lower work rates. It is important to determine if BMI predicts survival probability in low RER_{peak} patients.

Etiology of CHF:

Previous studies tried to investigate whether differences in etiology of CHF (ischemic versus non-ischemic) exist among survivors and non-survivors. Chua et al. (1997) and Mancini et al. (1991) did not observe any difference in etiology of heart failure between survivors and non-survivors among CHF patients.

On the contrary, Myers et al. (1998) observed that etiology of CHF was a significant predictor of death where patients with ischemic cardiomyopathy had greater

risk than non-ischemic cardiomyopathy (RR, 1.73 [95% CI, 1.35 to 2.20]). Recently Arena et al. (2005) illustrated that CHF patients with ischemic etiology had a worse 1-year prognosis than non-ischemic patients. They also showed decreased time to cardiac related events, which approached statistical significance ($p=0.07$). This increased risk of adverse events can be attributed to alterations in left ventricular size and function as a result of ventricular remodeling.

Beta-blocker Drugs:

With recent advances in therapeutic treatment of CHF patients, beta-blockers have gained importance with their impact on improved prognosis in CHF. When CHF patients of $\dot{V}O_{2\text{peak}} \leq 10 \text{ ml/kg/min}$ with events (death/transplantation) were compared to those with no-events, the event group had a significantly lower percentage of beta-blocker use than survivors (11% versus 41%) (Mezzani et al., 2003). Metra et al. (2000) demonstrated that CHF patients treated with beta-blockers improved symptoms and submaximal exercise tolerance due to increased LVEF at rest, improved left ventricular stroke volume during exercise, and decreased mean pulmonary artery pressure and pulmonary capillary wedge pressure. In 2003, Metra et al. conducted a study of CHF patients on long term beta-blockers therapy and observed that 22% of patients had increases in LVEF of $\geq 15\%$ and these patients had an increased cumulative survival rate along with an increased in hospitalization-free survival rate.

Beta-blockers have been found to improve survival in CHF patients without improving $\dot{V}O_{2\text{peak}}$. Hence, many researchers have stated the traditional criteria of $\dot{V}O_{2\text{peak}}$ of ≤ 14 ml/kg/min may not be accurate for determining candidacy for heart transplantation and more studies were conducted to see the effects of beta-blocker therapy on survival in CHF patients in different $\dot{V}O_{2\text{peak}}$ groups. Pohwani et al. (2003) observed that when CHF patients with $\dot{V}O_{2\text{peak}}$ of ≤ 14 ml/kg/min were stratified according to beta-blocker usage, 1 and 3-year survival rate was higher in patients treated with beta-blockers than those not treated with beta-blockers. Peterson et al. (2003) demonstrated that no beta-blocker treatment was an independent predictor of mortality in CHF patients. In CHF patients with $\dot{V}O_{2\text{peak}}$ of ≤ 14 ml/kg/min, patients on beta-blockers had an RER_{peak} of 1.13 ± 0.19 and patients not on beta-blockers had an RER_{peak} of 1.10 ± 0.10 (Pohwani et al., 2003). In another study, RER_{peak} in CHF patients with beta-blockers was observed as 1.1 ± 0.1 and without beta-blockers as 1.2 ± 0.5 (Peterson et al., 2003). Hence, RER_{peak} remained unaffected by status of beta-blocker treatment.

Left Ventricular Ejection Fraction:

LVEF has been found to be reduced mainly in CHF patients with systolic etiology. Many scientists have investigated the impact of LVEF on prognosis. Mancini et al. (1991) demonstrated that LVEF was not significantly different in survivors and non-survivors groups of CHF patients. On the contrary, Chua et al. (1997) observed that non-survivors had significantly lower LVEF (22.8 ± 14.7 vs. 31.1 ± 14.6) compared to survivors

in CHF population. Similarly, Mezzani et al. (2003) also showed significantly lower LVEF in non-survivors than survivors ($17\% \pm 6\%$ vs. $23\% \pm 8\%$) in CHF patients with $\dot{V}O_{2\text{peak}} < 10 \text{ ml/kg/min}$ and similar results were seen with $\dot{V}O_{2\text{peak}} > 10$ to $\leq 14 \text{ ml/kg/min}$ group. Further research is needed to investigate whether LVEF determines survival probability in low RER_{peak} groups.

The proposed study is designed to determine whether or not the survival probability for CHF events indeed varies with RER_{peak} in CHF patients. Also, it will examine the effects of other CPX testing derived and physiologic variables on the survival probability in low RER_{peak} group. It will ultimately help to identify the subgroup of low RER_{peak} with lowest survival probability (highest risk) within given $\dot{V}O_{2\text{peak}}$ stratum. It will assist us to use their CPX data to tailor pharmaceutical or surgical therapies despite low RER_{peak}.

CHAPTER III

OUTLINE OF PROCEDURES

The methodology of this study is discussed in this section. The criteria for patient selection, procedures for data collection and data analysis are described in detail.

Background

The impact of RER_{peak} on the prognostic value of $\dot{V}O_{2\text{peak}}$ in patients with CHF has not yet been clearly defined. In addition, the role of CPX testing derived and other physiologic variables as potential predictors of heart failure events is not well defined in CHF patients with low RER_{peak}. Therefore, the **specific aims** of the proposed study are: 1) after stratifying CHF patients by $\dot{V}O_{2\text{peak}}$ ($\leq 14 \text{ ml/kg/min}$ vs. $> 14 \text{ ml/kg/min}$), examine the effects of RER_{peak} (< 1.10 vs. ≥ 1.10) on the survival probability for major heart failure events over a two-year period; 2a) among those with a low RER_{peak} within each $\dot{V}O_{2\text{peak}}$ stratum, perform bivariate survival analyses examining the effects of the following independent variables (considered one at a time) on two-year survival probability for major heart failure events: $\dot{V}E/\dot{V}CO_2$ slope (low/high), age (young/old), sex (male/female), BMI (non-obese/obese), LVEF (low/high), CHF etiology (ischemic/non-ischemic), and beta-blocker use (yes/no) and 2b) based on the bivariate analyses in Aim

2a, identify the subgroups with the statistically significant lower survival probabilities within the low RER_{peak} group and compare to the high RER_{peak} group within the same $\dot{V}O_{2\text{peak}}$ stratum. To accomplish these objectives, data derived from symptom-limited CPX testing in CHF patients and the occurrence of major CHF related events was analyzed.

The following working hypotheses were tested: 1) within each $\dot{V}O_{2\text{peak}}$ stratum, CHF patients with a low RER_{peak} will have a higher probability of survival than patients with a high RER_{peak}. This will likely be due to a portion of the low RER_{peak} patients failing to exercise at a maximal effort; 2a) in CHF patients in low RER_{peak} group for a given $\dot{V}O_{2\text{peak}}$ stratum, the following groups of patients will have a lower probability of survival: higher $\dot{V}E/\dot{V}CO_2$ slope, older age, lower LVEF, ischemic etiology of CHF, and beta blocker non-users. There is little previous research comparing the survival probability for major heart failure events between male versus female and obese versus non-obese patients. Therefore, the analyses of these variables were exploratory in nature and no hypotheses concerning them had been generated and 2b) within each $\dot{V}O_{2\text{peak}}$ stratum, the subgroups of low RER_{peak} identified in Aim 2a as having significantly lower survival probabilities for CHF events will have similar probabilities of survival as the high RER_{peak} group.

The experimental approach of the proposed study was to collect CPX testing data for CHF patients with systolic dysfunction. The patients were tested earlier and were followed up for a maximum of 24 months at four testing sites. The end points for follow

up were included as the first occurrence of any of the following three major cardiac events: implantation of LVAD, heart transplantation, or death. The patients who did not have any event at the end of follow up period were considered as event-free observations.

The patients were divided into two groups according to their $\dot{V}O_{2\text{peak}}$: ≤ 14 ml/kg/min, and >14 ml/kg/min. The patients in each $\dot{V}O_{2\text{peak}}$ stratum were then be subdivided into low RER_{peak} (<1.10) and high RER_{peak} (≥ 1.10) groups. The survival probability and the magnitude of association (relative risk) was calculated and compared between these subgroups. The rationale for this approach was that $\dot{V}O_{2\text{peak}}$ is considered to be the major criterion for risk stratification and determination of heart transplantation candidacy. In order to assess the impact on $\dot{V}O_{2\text{peak}}$ as a function of maximal effort, RER_{peak} is used as a simple and objective criterion. High RER_{peak} of ≥ 1.10 is considered as the maximal effort index and tests with low RER_{peak} of <1.10 are considered submaximal. Hence, $\dot{V}O_{2\text{peak}}$ obtained in the latter case can not be used as a reliable prognostic indicator. However, not all CHF patients can reach high RER_{peak} (Aitken et al., 1988; Sidney et al., 1977). Although strong evidence is lacking, some physiologic factors may contribute to inability to reach high RER_{peak} such as age related reduction in active skeletal mass, decrease in Type II muscle fibers (Anainsson et al., 1981), lesser amount of glycogen reserve per unit muscle mass and gradual diffusion of lactic acid metabolites from the active tissue into the blood stream (Shephard et al., 1975). Furthermore, it is not yet clear to what extent RER_{peak} defines maximal effort in CHF patients (Mezzani et al., 2003).

In addition, patients in low RER_{peak} group within each $\dot{V}O_{2\text{peak}}$ stratum were categorized into those with low $\dot{V}E/\dot{V}CO_2$ slope (<34) and high $\dot{V}E/\dot{V}CO_2$ slope (≥ 34) (Chua et al., 1997). The reason for stratifying by $\dot{V}E/\dot{V}CO_2$ slope variable was that it has been identified as an independent and strong predictor of prognosis in the CHF population (Chua et al., 1997; Corra et al., 2002). The survival probability and magnitude of association was then be analyzed and compared between these two groups. Similarly, the low RER_{peak} group within each $\dot{V}O_{2\text{peak}}$ stratum was dichotomized and tested for other variables (age, sex, BMI, LVEF, CHF etiology, beta-blocker use) to examine if they predict low survival probability for major heart failure events. The rationale for this approach was that many CHF patients fail to achieve standard high RER_{peak}. It is important to investigate whether these CPX and physiologic variables help to predict the probability of survival in low RER_{peak} patients. Ultimately, the proposed study was to facilitate identification of a subgroup of patients with low RER_{peak} with lowest survival probability (highest risk) that will be comparable to high RER_{peak} group for a given $\dot{V}O_{2\text{peak}}$ stratum. Such findings are important as they will assist the clinicians, to consider $\dot{V}O_{2\text{peak}}$ obtained from CPX tests even with low RER_{peak}, to predict events in CHF patients.

Research Participants:

This retrospective research project included a multicenter analysis of CHF patients who had undergone exercise testing and subsequent observation at the following sites: LeBauer Cardiovascular Research Foundation, Greensboro, NC; Virginia Commonwealth University, Richmond, Va; San Paolo Hospital, Milan, Italy; and the VA Palo Alto Health Care System and Stanford University, Palo Alto, Calif. Reasons for CPX testing included standard CHF assessment, testing for research projects, and assessment for implantation of pacemaker devices, LVAD or heart transplantation. The severity of CHF varied from moderate to severe and represented the general CHF population. The reasons for testing, modes of exercise, exercise testing protocols, and computerized metabolic systems measuring ventilatory expired gas analysis were different across the centers. However, other standards (equipment calibration before each test, monitoring of the patients) and data collection methods were consistent across the sites.

The diagnosis of CHF was based upon physicians' diagnoses documented in medical records. The main inclusion criteria were: 1) moderate to severe left ventricular systolic dysfunction identified as $\leq 40\%$ LVEF (Mezzani et al., 2003; Arena et al., 2007) (as obtained from the echocardiography or cardiac catheterization reports that were closest to the date of CPX testing); 2) termination of the exercise test according to standard ACSM criteria (American College of Sports Medicine, 2006); 3) patients who maintained $>88\%$ of oxygen saturation (SaO₂ %) during last stage of CPX testing; 4)

patients who attained $\text{FEV}_1 > 1 \text{ L}$ during resting spirometry. These criteria avoided inclusion of patients in whom functional impairment was primarily due to pulmonary causes rather than cardiovascular causes. Information of patients meeting all of the above criteria was obtained from medical records. The exclusion criteria included: 1) patients who were on home oxygen therapy; 2) patients with documented history of primary obstructive or restrictive pulmonary diseases; 3) premature termination of CPX due to abnormal signs, symptoms, ECG responses or technical problems.

Data Collection:

For the included CHF patients, demographic variables, medication history, and exercise variables from CPX testing were obtained from medical records. Demographic records were obtained for the following variables: date of CPX test, age, sex, race, BMI, LVEF and CHF etiology. For each patient, age was calculated from the date of birth to the date of CPX testing. BMI on the day of CPX testing was calculated by using the ratio of weight (kg)/ height (m^2). As stated earlier, LVEF was obtained from the echocardiography or cardiac catheterization reports closest to the date of CPX testing. The etiology of CHF was divided into two subgroups as ischemic and non-ischemic. Ischemic cardiomyopathy included patients with history of coronary artery disease or myocardial infarction leading to CHF. Non-ischemic cardiomyopathy included patients in whom CHF resulted from idiopathic, alcoholism, drug toxicity, postpartum or

peripartum, viral or infiltrative disorders, restrictive and valvular causes. Medication history at the time of CPX testing was obtained for intake of beta-blockers.

Exercise variables were obtained from CPX testing data. It has been demonstrated that mode of exercise testing does not impact prognostic characteristics of $\dot{V}O_{2\text{peak}}$ and $\dot{V}E/\dot{V}CO_2$ slope values derived from CPX testing in heart failure patients (Arena et al., 2005). Hence, we included patients who had performed treadmill or bike CPX tests without creating subgroups. In case of patients who had more than one CPX test, the first CPX test data was included in the study in order to avoid the re-entry of the same patient. CPX testing data of respiratory gas measurements generated from a breath-by-breath analysis by computerized metabolic carts was obtained. It was averaged over 10 or 15-second intervals. The following CPX testing variables were obtained: $\dot{V}O_{2\text{peak}}$, RER_{peak} , and $\dot{V}E/\dot{V}CO_2$ slope. The $\dot{V}O_{2\text{peak}}$ was expressed as ml/kg/min. It was obtained as the highest 30-second average value of $\dot{V}O_2$ obtained during the last stage of the exercise test. The RER_{peak} was noted as the highest RER observed during the last minute of the test. The $\dot{V}E/\dot{V}CO_2$ slope was calculated by taking obtained $\dot{V}E$ (L/min) and $\dot{V}CO_2$ (L/min) values from the beginning to the end of exercise session. These values were averaged over 10 or 15-second intervals and entered into Microsoft Excel. The $\dot{V}E/\dot{V}CO_2$ slope was calculated using the least squares linear regression equation, $y=mx+b$ where $m=\text{slope}$.

After collecting required data, all the patients were followed up for up to 24 months starting from the date of CPX testing to record the first occurrence of any of the

following end points: implantation of LVAD, heart transplantation, or death. For those who had any of these events within 24 months, the follow up time was recorded since the date of CPX testing till the date of an event. If no event occurred within 24 months, those cases were considered as event-free observations. Following was the rationale for choosing a follow up time of 24 months. Davies et al. (2000) followed up elderly CHF patients since their CPX testing and observed that they had high mortality within two years (Davies et al., 2000) of follow-up. Additionally, Arena et al (2005) demonstrated that, the prognostic impact of CPX testing derived variables was time sensitive. The specificity of these variables markedly decreased (~20%) as the time past CPX testing increased. The longer follow-up periods may also lead to more lost to follow-up cases as the patients may change their locations, physicians and visiting hospitals. This would particularly have an affect, as this study depends upon hospital records for follow-up information. Any patients, who had no medical records available up to 24 months after the CPX date, were considered as lost to follow-up.

It was speculated that some CHF patients would die out of the hospital and in those cases; deaths were recorded from the social security death index. In the latter cases, it was not possible to trace the cause of death. Hence, the proposed study considered all-cause mortality rather than just cardiac-related mortality.

Data Analysis:

For Specific Aim 1:

Since $\dot{V}O_{2\text{peak}}$ is used as a major criterion to determine candidacy for heart transplantation in CHF population (Mancini et al., 1991), the proposed study's subjects were stratified into two groups according to their $\dot{V}O_{2\text{peak}}$ obtained during CPX testing: ≤ 14 ml/kg/min and > 14 ml/kg/min. Relevant studies have demonstrated that patients with $\dot{V}O_{2\text{peak}} \leq 14$ ml/kg/min have severe functional intolerance and significantly higher risks of morbidity and mortality (Mancini et al., 1991; Chua et al., 1997; Osada et al., 1998; Gitt et al., 2002; Mezzani et al., 2003).

All patients were followed for up to 24 months to identify the date of their first major heart failure-related event (LVAD implantation, heart transplantation, or mortality). At the end of 24 months, if they had not had any event, those cases were considered as event-free observations. Those patients whose event status could not be traced prior to conclusion of the study were considered as losses to follow-up and were thus treated as censored observations. Inherently, the Kaplan-Meier curve accounts for such losses to follow-up as part of its analytical methodology. By constructing a Kaplan-Meier survival curve, the individuals at risk at any given point represented those individuals who were event-free and who had been followed up to at least that point in the survival curve. This allowed an accurate estimation of survival probabilities at various time points accounting for both events and censored data.

The patients in each $\dot{V}O_{2\text{peak}}$ stratum were subdivided according to their RER_{peak} levels (low $RER_{\text{peak}}: <1.10$; high $RER_{\text{peak}}: \geq1.10$) (Figure 1). The rationale for this stratification was that CPX testing with a $RER_{\text{peak}} \geq1.10$ has been traditionally considered as a “maximal” test and a test with $RER_{\text{peak}} <1.10$ has been considered as “submaximal”. However, research has shown that not all patients can reach high RER_{peak} (Aitken et al., 1988; Sidney et al., 1977). Since many patients with CHF cannot attain a high RER_{peak} , it needed to be determined whether a low $\dot{V}O_{2\text{peak}}$ could still predict heart failure events in these patients.

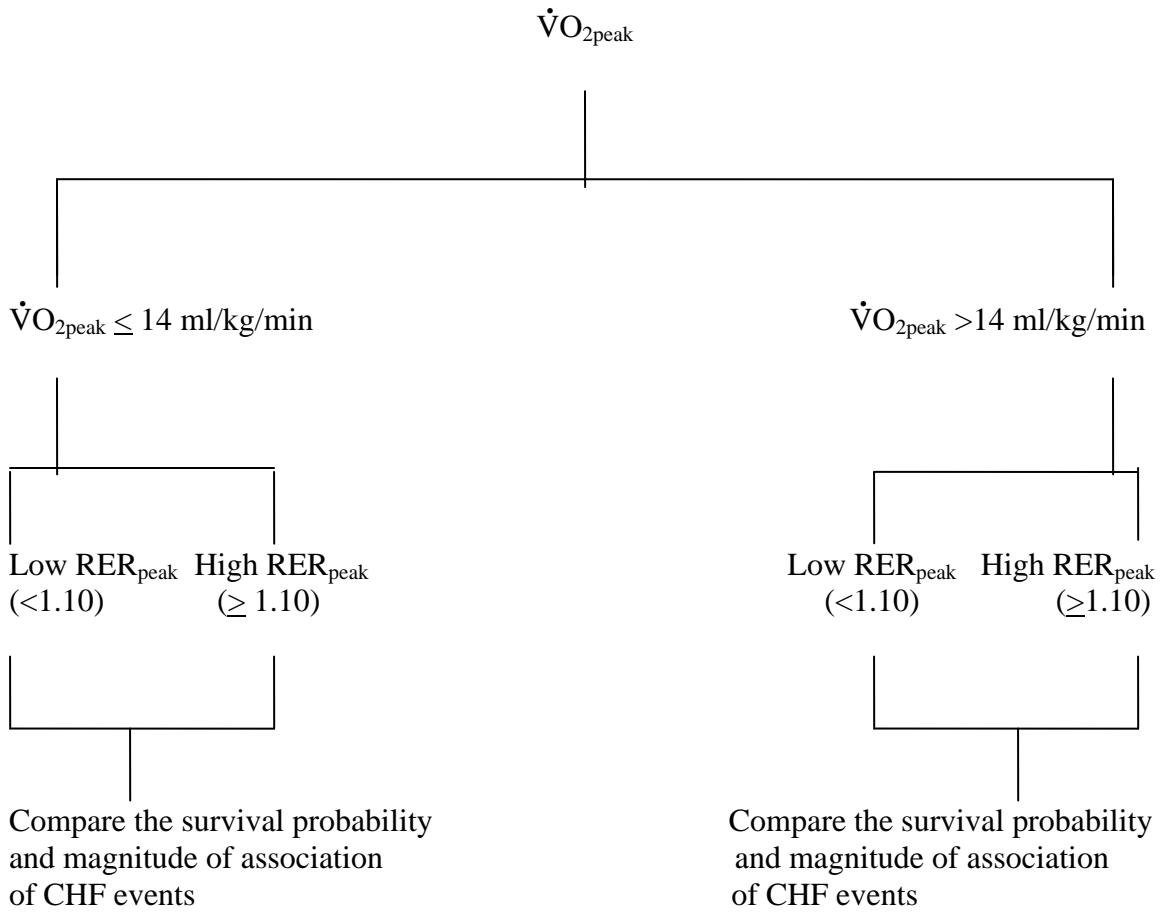


Figure 1- Schematic for RER_{peak} Groups

Analysis for Specific Aim 1:

Within given $\dot{V}O_{2\text{peak}}$ strata, the survival probability in patients with low versus high RER_{peak} was estimated using Kaplan-Meier bivariate survival analyses. Also, the magnitude of association for these two groups was computed using simple relative risk analyses and compared. A p-value of <0.05 was considered statistically significant.

For Specific Aim 2a:

Within each $\dot{V}O_{2\text{peak}}$ stratum, patients with low RER_{peak} group were further subdivided into two subgroups: low $\dot{V}E/\dot{V}CO_2$ slope (< 34) and high $\dot{V}E/\dot{V}CO_2$ slope (≥ 34) (Chua et al., 1997). Rationale for this approach was that previous researchers have found a high $\dot{V}E/\dot{V}CO_2$ slope to be an effort-independent predictor of morbidity and mortality in CHF patients (Chua et al., 1997; Corra et al., 2002). However, its ability to predict heart failure events in patients with low RER_{peak} has not been determined. Hence, the proposed study was designed to determine if $\dot{V}E/\dot{V}CO_2$ slope holds its significant predictive value in low RER_{peak} groups. The survival probability for low and high $\dot{V}E/\dot{V}CO_2$ slope was analyzed within the low RER_{peak} groups of each $\dot{V}O_{2\text{peak}}$ stratum.

Similar to analysis of $\dot{V}E/\dot{V}CO_2$ slope, additional variables were examined to determine if they had predictive value for heart failure events in low RER_{peak} groups within given $\dot{V}O_{2\text{peak}}$ strata. These variables included: age, sex, BMI, LVEF, CHF etiology, and beta-blocker use. Each of these variables was dichotomized in the analyses as shown in Table 4.

Variables	Stratification	
$\dot{V}E/\dot{V}CO_2$ slope	< 34	≥ 34
Sex	Male	Female
CHF etiology	Ischemic	Non-Ischemic
LVEF (%)	< 25%	≥ 25 to 40 %

Beta-blockers	Usage at the time of CPX test	Non-usage at the time of CPX test
Age (years)	≤ 55	> 55
BMI (kg/m^2)	< 30	≥ 30

Table 4- Stratification of Variables

The roles of all these variables as predictors of heart failure events were determined for low RER_{peak} groups within given $\dot{\text{V}}\text{O}_{2\text{peak}}$ strata as shown in Figure 2. Specifically, this study sought to discover which of these variables identified low survival probability (high risk) subgroups (in low RER_{peak} groups within the $\dot{\text{V}}\text{O}_{2\text{peak}}$ strata).

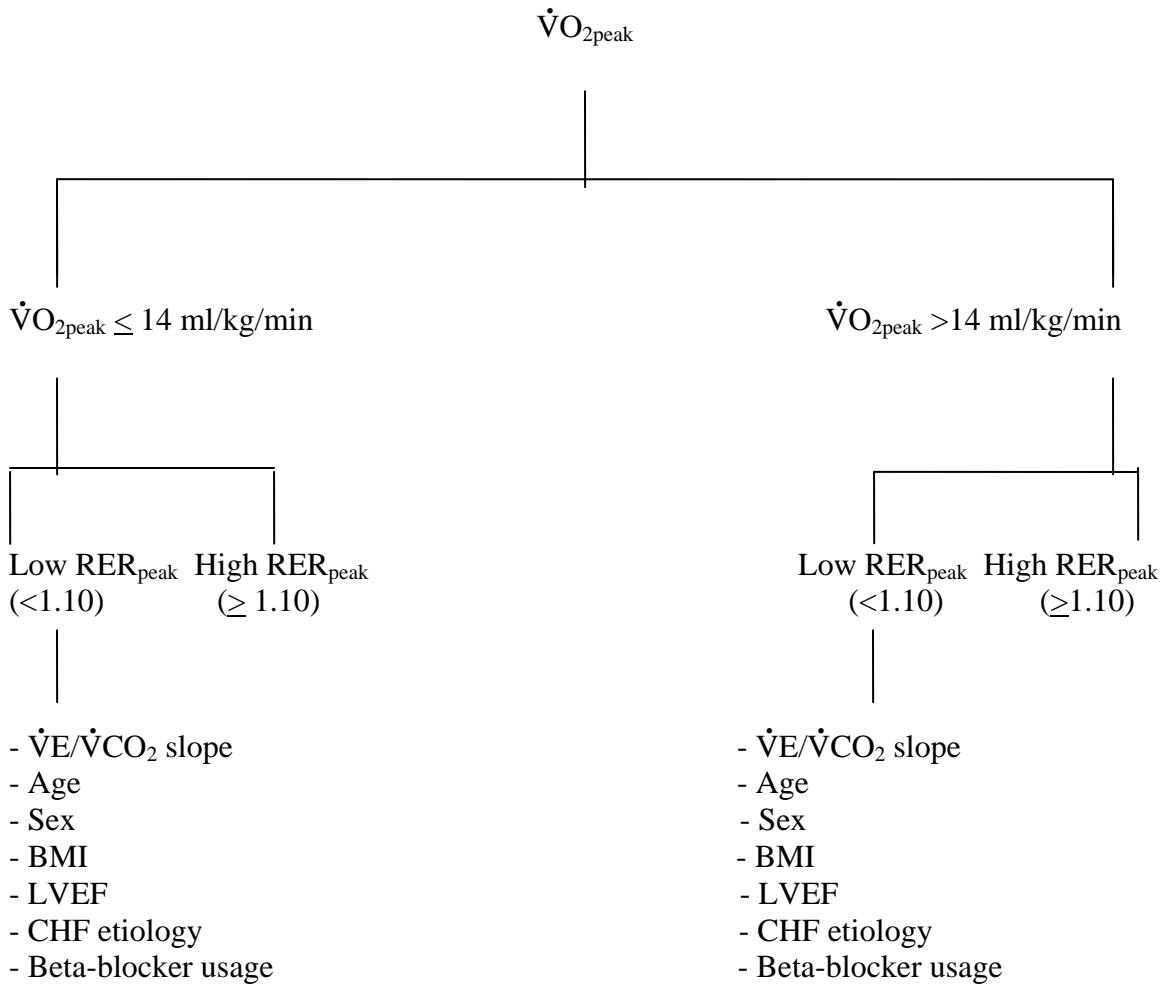


Figure 2- Schematic for Stratification of Variables in Low RER_{peak} Groups

Analysis of Specific Aim 2a:

The significant predictors of heart failure events for low RER_{peak} groups within $\dot{V}O_{2\text{peak}}$ strata were identified from the list of other CPX testing variables ($\dot{V}E/\dot{V}CO_2$ slope, age, sex, BMI, LVEF, CHF etiology and beta-blocker usage) using bivariate survival analyses. The survival probability for CHF events was calculated using

the Kaplan-Meier survival curve method. The difference between the survival probabilities was calculated using the Log-rank method. Also, the magnitude of associations for these groups was computed using relative risk analyses. The survival probabilities and the magnitudes of association were compared between the two subgroups of each variable to identify the better predictor of events in the low RER_{peak} groups within a given $\dot{V}O_{2\text{peak}}$ stratum. A p-value of <0.05 was considered statistically significant.

For Specific Aim 2b:

Finally, based on the bivariate analysis of each variable described in Aim 2a, this study identified the subgroups with statistically significantly lower survival probabilities (higher risk) within the low RER_{peak} group for a given $\dot{V}O_{2\text{peak}}$ stratum. Patients within the higher-risk subgroup of a given variable were then compared to the high RER_{peak} group in the same $\dot{V}O_{2\text{peak}}$ stratum for survival probability of events.

Analysis of Specific Aim 2b:

The survival probabilities for the best predictors of CHF events in low RER_{peak} group were compared to high RER_{peak} group within given strata. This was analyzed by using Kaplan-Meier survival curve method. A p-value of <0.05 was considered statistically significant.

In conclusion, the ultimate goal was to identify a subgroup of CHF patients with low RER_{peak} (based upon above mentioned variables), who would have comparable survival probability as to high RER_{peak} patients for a given $\dot{V}O_{2\text{peak}}$ strata.

Exploratory Analysis:

A multivariate proportional hazard analysis (multivariate analysis) was conducted in low RER_{peak} group within low $\dot{V}O_{2\text{peak}}$ stratum. This helped in identifying the significantly independent predictors of CHF related events in patients with low RER_{peak} within low $\dot{V}O_{2\text{peak}}$ group.

CHAPTER IV

RESULTS

Baseline Patient Characteristics

Table 5 demonstrates the patient characteristics for the low and high $\dot{V}O_{2\text{peak}}$ groups, which are divided further into low RER_{peak} and high RER_{peak} groups. The continuous variables (RER_{peak}, age, LVEF, BMI and $\dot{V}E/\dot{V}CO_2$ slope) are presented as mean \pm standard deviation. The nominal variables [sex (males/females), HF etiology (ICM/ NICM), and beta-blocker usage (users/ non-users) are expressed as the numbers of patients and their percentages for each group.

	Overall Low VO2pk (n=367)	Low VO2pk Low RER (n=207)	Low VO2pk High RER (n=160)	Overall High VO2pk (n=410)	High VO2pk Low RER (n=194)	High VO2pk High RER (n=216)
RER peak	1.07 \pm 0.16	0.98 \pm 0.12	1.20 \pm 0.10	1.11 \pm 0.13	1.01 \pm 0.07	1.20 \pm 0.1
Age (years)	54.33 \pm 13.46	55 \pm 13.81	53 \pm 12.94	53 \pm 14.63	53.27 \pm 15.13	53 \pm 14.18
Sex(male/female)	244/123	136/ 71	108 / 52	339 / 71	163 / 31	176 / 40
% (male/ female)	66.5 / 33.5	65.7 / 34.3	67.5 / 32.5	82.7 / 17.3	84 / 16	81.5 / 18.5
LVEF (%)	22.27 \pm 8.01	23.2 \pm 8.22	21.1 \pm 7.61	26 \pm 8.61	25.4 \pm 8.75	26.5 \pm 8.46
HF etiology						
# ICM / NICM	161 / 205	94 / 112	67 / 92	162 / 242	73 / 121	89 / 127
% (ICM / NICM)	43.9 / 56	45.6 / 54.4	42.1 / 57.9	40.1 / 59.9	37.6 / 62.4	41.2 / 58.8
BMI	29.89 \pm 7.04	29.9 \pm 6.75	29.9 \pm 7.42	28.4 \pm 5.79	29.4 \pm 6.35	27.5 \pm 5.07

Table 5 is continued:

	Overall Low VO2pk (n=367)	Low VO2pk Low RER (n=207)	Low VO2pk High RER (n=160)	Overall High VO2pk (n=410)	High VO2pk Low RER (n=194)	High VO2pk High RER (n=216)
VE/VCO ₂ Slope	41 ± 12.19	40 ± 11.36	43 ± 13.11	32 ± 6.88	32 ± 8.23	31 ± 7.21
BB #(Users/ Non-Users)	(291 / 76)	(169 / 38)	(122 / 38)	(325 / 85)	(155 / 39)	(170 / 46)
% (Users/Non-users)	(79.3 / 20.7)	(81.6 / 18.4)	(76.3 / 23.8)	(79.3 / 20.7)	(79.9 / 20.1)	(78.7 / 21.3)

Table 5- Baseline Patient Characteristics

The events for each group and subgroup, described as the total number, the percentage, and the event-type, are shown in Table 6.

	Overall Low VO2peak	Low VO2pk Low RER	Low VO2pk High RER	Overall High VO2peak	High VO2pk Low RER	High VO2pk High RER
Total Events	104 (77%)	51 (49%)	53 (51%)	31 (23%)	16 (51.6%)	15 (48.4)
LVADS	11	7 (63.6%)	4 (36.4%)	5	3 (60%)	2 (40%)
TRANSPLANTS	39	14 (35.9%)	25 (64.1%)	10	3 (30%)	7 (70%)
DEATHS	54	30 (55.6%)	24 (44.4%)	16	10 (62.5%)	6 (37.5%)

Table 6- CHF Events Distribution According to Groups

Earlier studies have demonstrated that patients with $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ are at increased risk for events (lower survival) when compared to those with $\dot{V}O_{2\text{peak}} > 14 \text{ ml/kg/min}$ (Mancini et al., 1991; Roul et al., 1994; Osada et al., 1998; Mezzani et al., 2003). Hence, the two-year event-free survival probabilities between patients with low $\dot{V}O_{2\text{peak}}$ and high $\dot{V}O_{2\text{peak}}$ were compared as shown in Fig. 3.

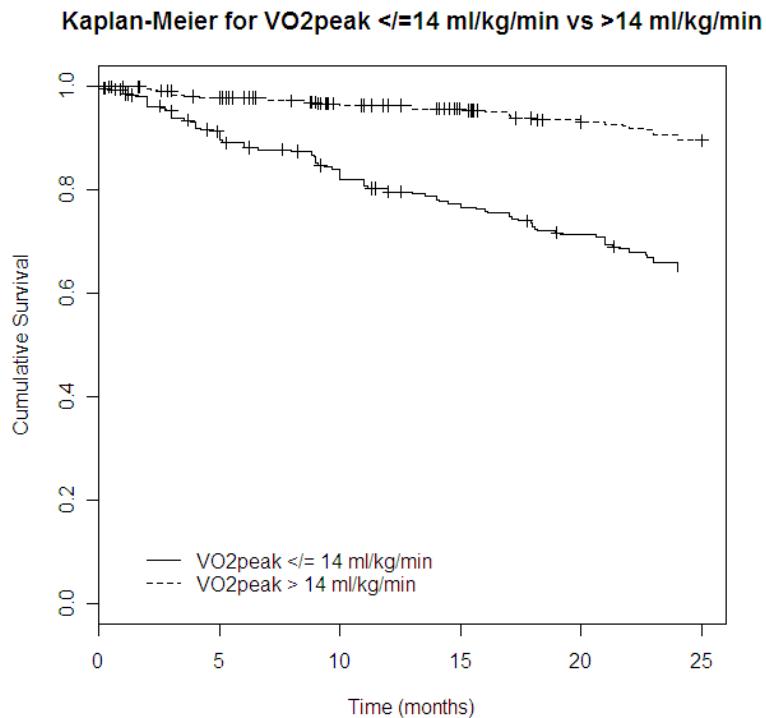


Figure 3- Two-Year Survival Comparison between Low ($\leq 14 \text{ ml/kg/min}$) and High ($> 14 \text{ ml/kg/min}$) $\dot{V}O_{2\text{peak}}$

- Legend:
- i) Each dip in the Kaplan-Meier curve indicates an event.
 - ii) Each vertical line on the curve indicates drop-outs up to that time without an event.

Analysis: In this study, the word ‘survival’ is referred to being free of CHF-related events over the two years of follow-up. The log-rank test is used to analyze if the difference in event-free survival between the compared groups is significant. The two-year survival probability of CHF patients with a low $\dot{V}O_{2\text{peak}}$ (64.2 %) is significantly lower than that of CHF patients with a high $\dot{V}O_{2\text{peak}}$ (89.6 %) (Log rank= 60.1, p<0.0001).

The relative risk of events for $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ versus $\dot{V}O_{2\text{peak}} > 14 \text{ ml/kg/min}$ was calculated as follows:

$$\text{RR} = \frac{\text{Events in low } \dot{V}O_{2\text{peak}} \text{ group / Total number of patients in } \dot{V}O_{2\text{peak}} \text{ group}}{\text{Events in high } \dot{V}O_{2\text{peak}} \text{ group / Total number of patients in high } \dot{V}O_{2\text{peak}} \text{ group}}$$

$$\text{RR} = \frac{104 / 366}{31 / 408} = 3.74 \text{ (95 \% CI} = 2.591 - 5.447) \text{ (p}<\text{0.0001)}$$

The results for all specific aims and hypotheses will be presented first for the low $\dot{V}O_{2\text{peak}}$ group and then for high $\dot{V}O_{2\text{peak}}$ group.

Low $\dot{V}O_{2\text{peak}}$ Analyses:

Specific Aim 1: After stratifying CHF patients by $\dot{V}O_{2\text{peak}}$ ($\leq 14 \text{ ml/kg/min}$ vs. $> 14 \text{ ml/kg/min}$), examine the effects of RER_{peak} (< 1.10 vs. ≥ 1.10) on the survival probability for major heart failure events over a two-year period.

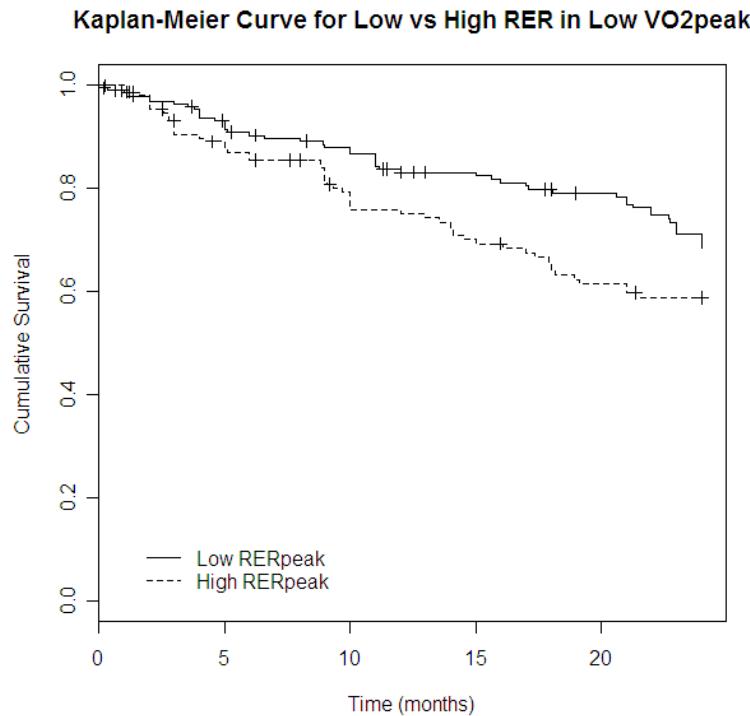


Figure 4- Two-Year Survival Comparison between Low RER_{peak} (≤ 1.1) and High RER_{peak} (≥ 1.1)

Analysis: The two-year survival probability for CHF related events is slightly, but significantly, higher in the low RER_{peak} group (68.4 %) as compared to the high RER_{peak} group (58.8 %). (Log rank = 4.1, p= 0.04).

The relative risk (RR) of events for low RER_{peak} compared to high RER_{peak} was calculated as follows:

$$RR = \frac{\text{Events in low RER group} / \text{Total number of patients in low RER group}}{\text{Events in high RER group} / \text{Total number of patients in high RER group}}$$

$$RR = \frac{51 / 206}{53 / 160} = 0.747 \text{ (95 \% CI} = 0.541 - 1.034) \text{ (p= 0.08)}$$

Working Hypothesis 1: Within each $\dot{V}O_{2\text{peak}}$ stratum, CHF patients with a low RER_{peak} will have a higher probability of survival than patients with a high RER_{peak} . This will likely be due to a portion of the low RER_{peak} patients failing to exercise at a maximal effort.

Conclusion: Based on statistical significance found with the Kaplan-Meier analysis, the working hypothesis for Aim 1 is not rejected for the low $\dot{V}O_{2\text{peak}}$ stratum. However, the relative risk is not statistically significant.

Specific aim 2a:

Specific Aim 2a: Among those with a low RER_{peak} within each $\dot{V}O_{2\text{peak}}$ stratum, perform bivariate survival analyses examining the effects of the following independent variables (considered one at a time) on two-year survival probability for major heart failure events: $\dot{V}E / \dot{V}CO_2$ slope (low/high), age (young/old), sex (male/female), BMI (non-obese/obese), LVEF (low/high), CHF etiology (ischemic/non-ischemic), and beta-blocker use (yes/no).

1) Comparing Survival Probability for Low (<34) versus High (≥ 34) $\dot{V}E/\dot{V}CO_2$ Slope in Patients with $\dot{V}O_{2peak} \leq 14ml/kg/min$ and $RER_{peak} < 1.10$:

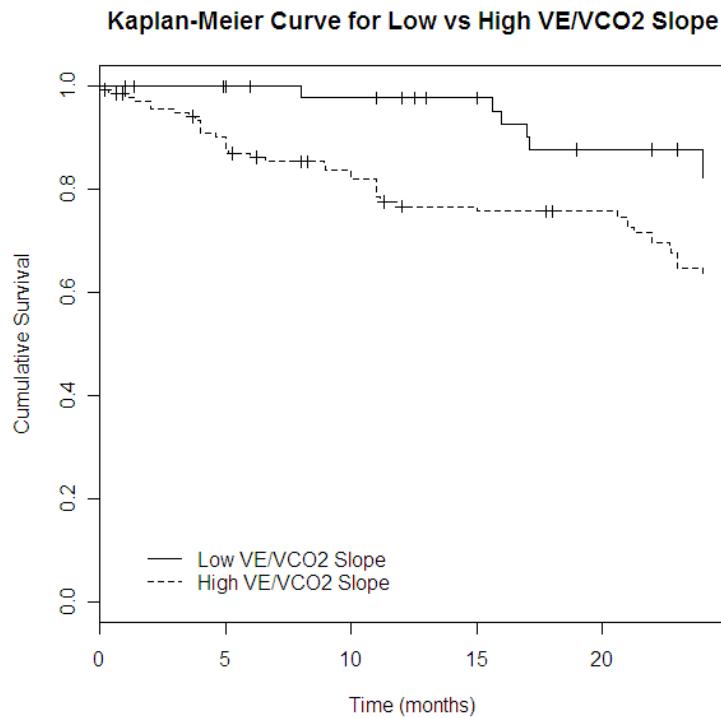


Figure 5- Two-Year Survival Comparison between Low (≤ 34) and High (≥ 34) $\dot{V}E/\dot{V}CO_2$ Slope

Analysis: The two-year survival probability of CHF patients with high $\dot{V}E/\dot{V}CO_2$ slope is significantly lower (63.6%) than those with low $\dot{V}E/\dot{V}CO_2$ slope (82.3%) (Log rank= 6.3, p= 0.01).

The relative risk of events for high $\dot{V}E/\dot{V}CO_2$ slope compared to low $\dot{V}E/\dot{V}CO_2$ slope was calculated as follows:

$$RR = \frac{\text{Events in high slope group} / \text{Total number of patients in high slope group}}{\text{Events in low slope group} / \text{Total number of patients in low slope group}}$$

$$RR = \frac{42 / 146}{7 / 54} = 2.219 \text{ (95 % CI} = 1.116 - 4.678) \text{ (p= 0.026)}$$

2) Comparing Survival Probability for Low ($<25\%$) versus High ($\geq 25\%$) LVEF in Patients with $\dot{V}O_{2\text{peak}} \leq 14\text{ml/kg/min}$ and $RER_{\text{peak}} < 1.10$:

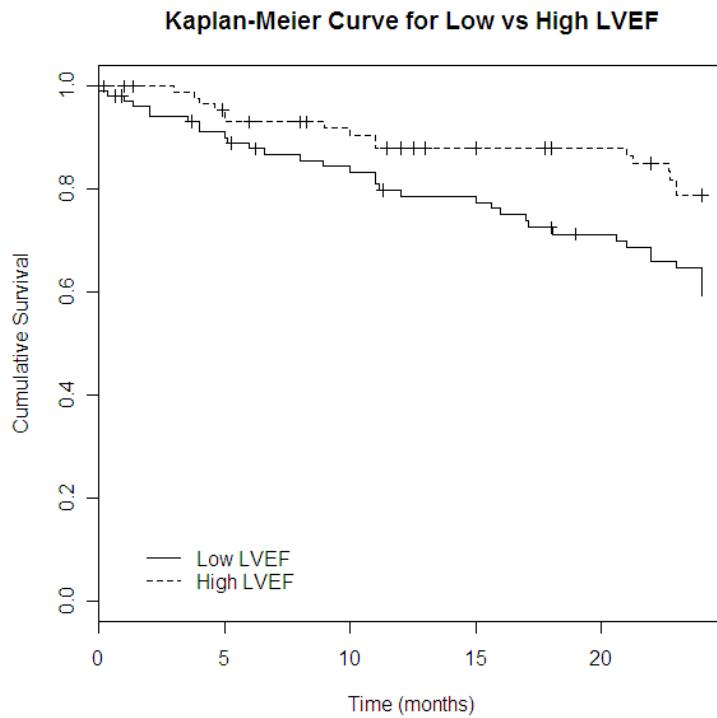


Figure 6- Two-Year Survival Comparison between Low ($\leq 25\%$) and High ($\geq 25\%$) LVEF Analysis: The two-year survival probability of CHF patients with low LVEF is significantly lower (59.3 %) than those with high LVEF (78.8 %) (Log rank= 7, p= 0.008).

The relative risk of events for low LVEF versus high LVEF was calculated as follows:

$$RR = \frac{\text{Events in low LVEF group} / \text{Total number of patients in low LVEF group}}{\text{Events in high LVEF group} / \text{Total number of patients in high LVEF group}}$$
$$RR = \frac{35 / 109}{16 / 97} = 1.947 \text{ (95 % CI} = 1.171 - 3.303) \text{ (p= 0.01)}$$

3) Comparing Survival Probability for Ischemic versus Non-Ischemic etiology of CHF in Patients with $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ and $RER_{\text{peak}} < 1.10$:

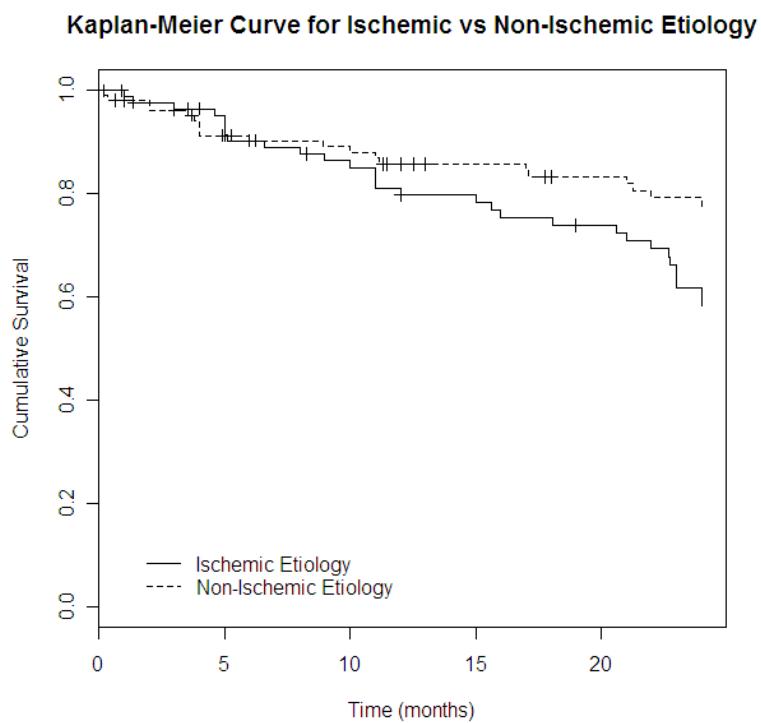


Figure 7- Two-Year Survival Comparison between Ischemic and Non-Ischemic Etiology of CHF

Analysis: The two-year survival probability of CHF patients with ischemic etiology is significantly lower (58.4 %) than those with non-ischemic etiology (76.6 %) of HF (Log rank= 4.5, p= 0.03).

The relative risk of events for ischemic versus non-ischemic etiology of CHF was calculated as follows:

$$\text{RR} = \frac{\text{Events in ischemic group / Total number of patients in ischemic group}}{\text{Events in non-ischemic group / Total number of patients in non-ischemic group}}$$
$$\text{RR} = \frac{30 / 94}{21 / 111} = 1.687 \text{ (95 \% CI} = 1.045 - 2.740 \text{) (p=} 0.036\text{)}$$

4) Comparing Survival Probability for Beta-blocker Users versus Beta-blocker Non-Users in Patients with $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ and $RER_{\text{peak}} < 1.10$:

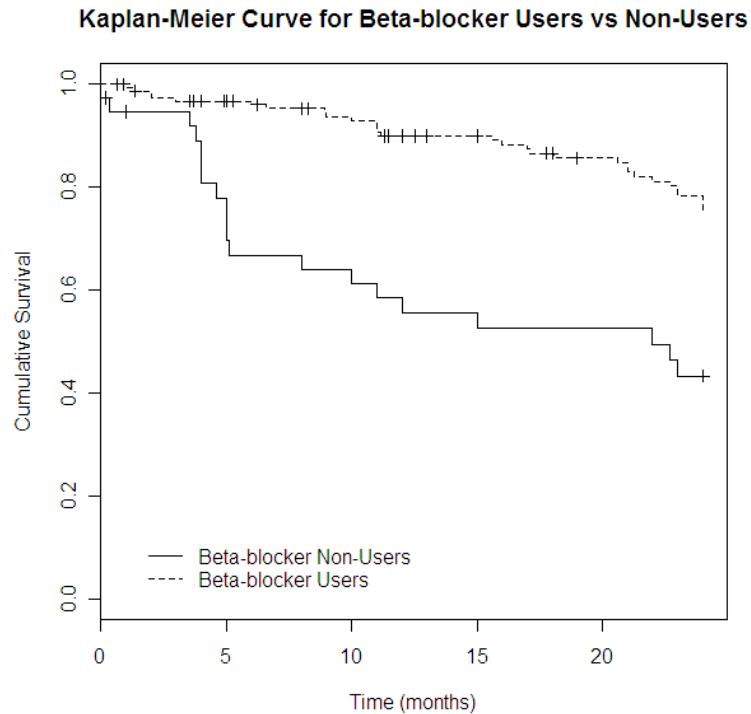


Figure 8- Two-Year Survival Comparison between Beta-blocker Users and Non-Users

Analysis: The two-year survival probability of beta-blocker non-users is significantly lower (43.3 %) than those of beta-blocker users (74.7 %) (Log rank= 20.9, p= <0.001). The relative risk of events for beta-blocker non-users versus users was calculated as follows:

$$RR = \frac{\text{Events in beta-blocker non-users} / \text{Total number of beta-blocker non-users}}{\text{Events in beta-blocker users} / \text{Total number of beta-blocker users}}$$

$$RR = \frac{20 / 38}{31 / 168} = 2.852 \text{ (95 % CI} = 1.819 - 4.209) \text{ (p} < 0.001\text{)}$$

5) Comparing Survival Probability for young (≤ 55) versus old age (> 55) groups in Patients with $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ and $RER_{\text{peak}} < 1.10$:

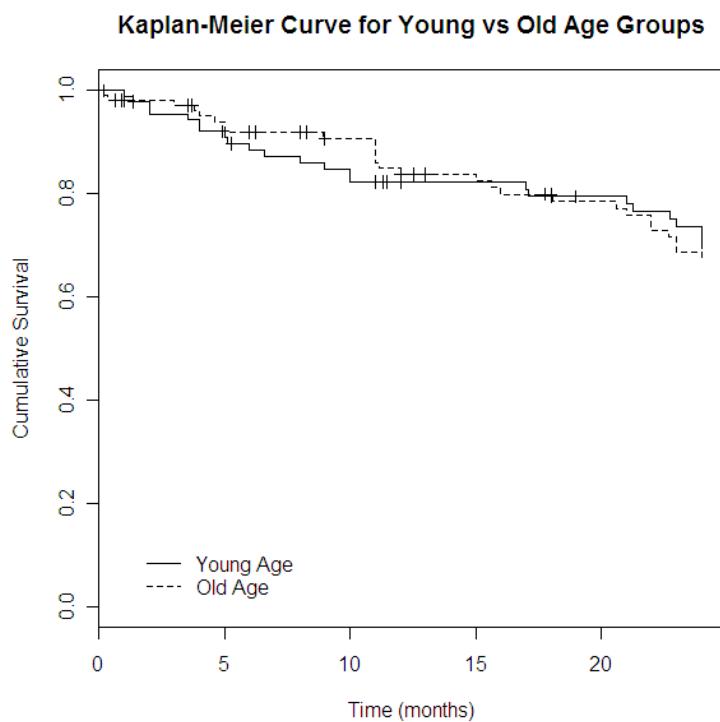


Figure 9- Two-Year Survival Comparison between Young Age (≤ 55) and Old Age (> 55)

Analysis: The two-year survival probability of old age group (67.3 %) is not different than young age group (69.4 %) (Log rank= 0, p= 0.898).

The relative risk of events for old versus young age group was calculated as follows:

$$RR = \frac{\text{Events in old age group} / \text{Total number of patients in old age group}}{\text{Events in young age group} / \text{Total number of patients in young age group}}$$

$$RR = \frac{27 / 108}{24 / 98} = 1.021 \text{ (95 % CI} = 0.636 - 1.645) \text{ (p} > 0.99)$$

6) Comparing Survival Probability for Males versus Females in Patients with $\dot{V}O_{2\text{peak}}$

$\leq 14 \text{ ml/kg/min}$ and $RER_{\text{peak}} < 1.10$:

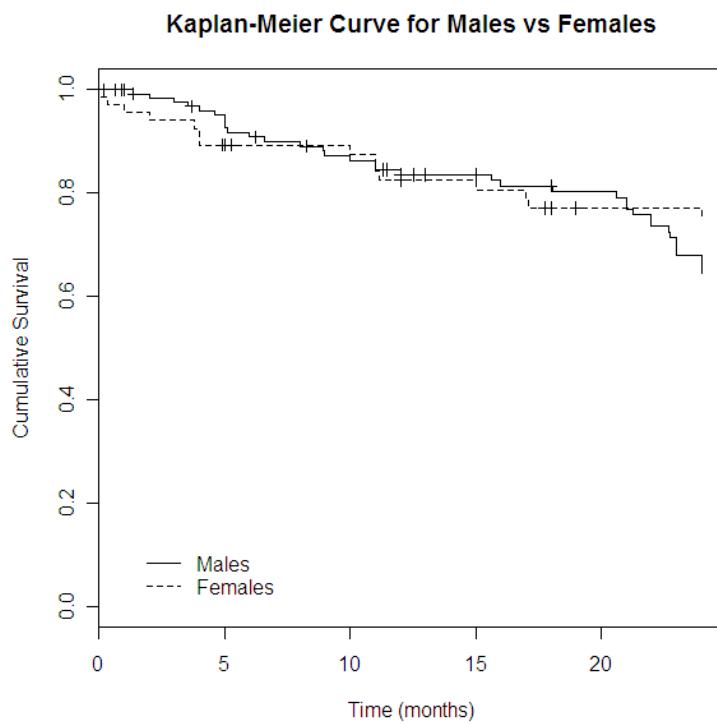


Figure 10- Two-Year Survival Comparison between Males and Females

Analysis: The two-year survival probability is not different between males (64.4%) and females (75.1%) groups of CHF patients. (Log rank= 0.8, p= 0.362).

The relative risk of events for males versus females was calculated as follows:

$$RR = \frac{\text{Events in male group} / \text{Total number of males}}{\text{Events in female group} / \text{Total number of females}}$$

$$RR = \frac{36 / 136}{15 / 70} = 1.235 \ (95\% \text{ CI} = 0.742 - 2.118) \ (p= 0.497)$$

7) Comparing Survival Probability for Low ($<30 \text{ kg/m}^2$) versus High ($\geq 30 \text{ kg/m}^2$) BMI in Patients with $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ and $RER_{\text{peak}} < 1.10$:

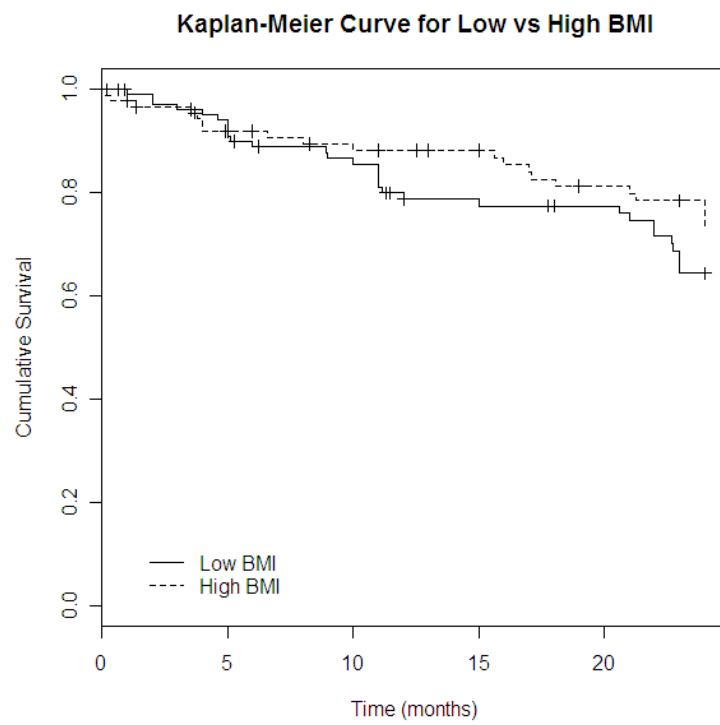


Figure 11- Two-Year Survival Comparison between Low BMI (≤ 30) and High BMI (> 30)

Analysis: The two-year survival probability is not different between low BMI group (64.4 %) and high BMI group (72.2 %) (Log rank= 1.3, p=0.256).

The relative risk of events for low BMI versus high BMI was calculated as follows:

$$\text{RR} = \frac{\text{Events in low BMI group / Total number of patients in low BMI group}}{\text{Events in high BMI group / Total number of patients in high BMI group}}$$
$$\text{RR} = \frac{30 / 113}{21 / 93} = 1.176 \text{ (95 \% CI} = 0.729 - 1.917 \text{)} \text{ (p=} 0.522\text{)}$$

Working Hypothesis 2a: In CHF patients in low RER_{peak} group for a given $\dot{V}\text{O}_{2\text{peak}}$ stratum, the following groups of patients will have a lower probability of survival: higher $\dot{V}\text{E} / \dot{V}\text{CO}_2$ slope, older age, lower LVEF, ischemic etiology of CHF, and beta blocker non-users. There is little previous research comparing the survival probability for major heart failure events between male versus female and obese versus non-obese patients. Therefore, the analyses of these variables are exploratory in nature and no hypotheses concerning them have been generated.

Conclusion: According to the results observed from items 1-7 for specific Aim 2a, the groups of high $\dot{V}\text{E} / \dot{V}\text{CO}_2$ slope (≥ 34), low LVEF ($< 25\%$), ischemic etiology of CHF, and beta-blocker non-users had significantly lower survival probabilities. The results of these four variables are summarized in following Table 7.

Hence, the working hypothesis for Aim 2a is not rejected for high $\dot{V}\text{E} / \dot{V}\text{CO}_2$ slope (≥ 34), low LVEF ($< 25\%$), ischemic etiology of CHF, and beta-blocker non-use

variables in the low $\dot{V}O_{2\text{peak}}$ stratum. However, the working hypothesis for Aim 2a in the low $\dot{V}O_{2\text{peak}}$ stratum is rejected for age.

In addition, exploratory analyses for sex and BMI variables revealed that the two-year survival probabilities for males versus females and for low BMI versus high BMI groups are not different in CHF patients with $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ and $\text{RER}_{\text{peak}} < 1.10$.

Finding	Log rank and Significance	Relative risk and 95% CI
1) Beta-blocker (BB) Non-users have lower 2-year survival probability than beta-blocker users	Log rank= 20.9 p <0.001	Relative risk of event for BB non-users compared to users =2.852 (95% CI = 1.819 – 4.209) (p <0.001)
2) High VE/VCO ₂ slope group has lower 2-year survival probability than low VE/VCO ₂ slope	Log rank= 6.3 p= 0.01	Relative risk of event for high slope compared to low slope =2.219 (95 % CI = 1.116 – 4.678) (p= 0.026)
3) Low LVEF group has lower 2-year survival probability than high LVEF	Log rank= 7 p= 0.01	Relative risk of event for low LVEF compared to high LVEF =1.947 (95 % CI = 1.171 – 3.303) (p= 0.01)
4) Ischemic etiology group has lower 2-year survival probability than non-ischemic etiology	Log rank= 4.5 p= 0.03	Relative risk of event for ischemic etiology compared to non-ischemic etiology =1.687 (95 % CI = 1.045 – 2.740) (p= 0.03)

Table 7- Significant Variables in Aim 2a for CHF Patients with $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$

Specific aim 2b:

Specific aim 2b: Based on the bivariate analyses in aim 2a, identify the subgroups with the statistically significant lower survival probabilities within low RER_{peak} group and compare to the high RER_{peak} group within the same $\dot{V}O_{2\text{peak}}$ stratum.

1) Comparing Survival Probability for Non Beta-blocker Users in Low RER_{peak} group versus the High RER_{peak} group within $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ stratum:

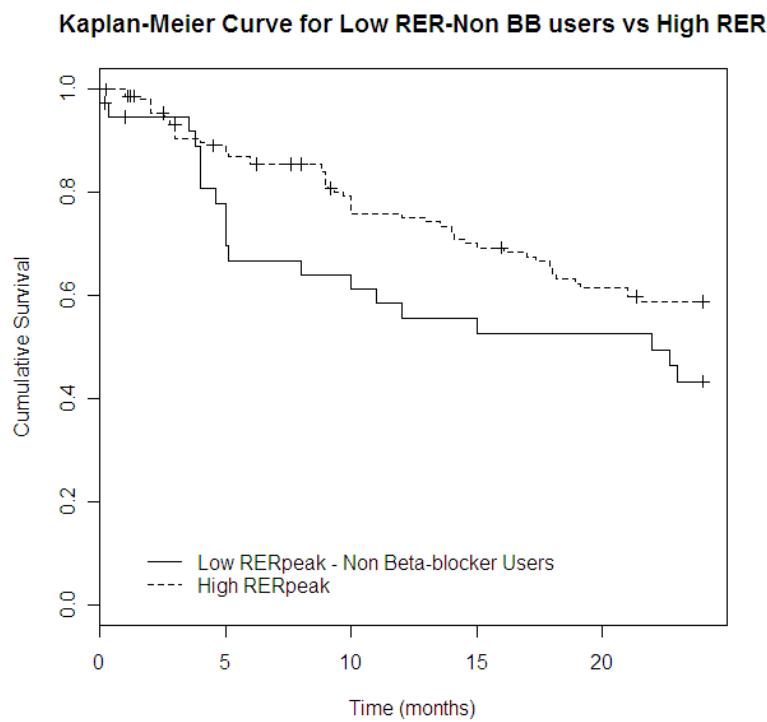


Figure 12- Two-Year Survival Comparison between Beta-Blocker Non-Users in Low RER_{peak} Group versus High RER_{peak} Group within Low $\dot{V}O_{2\text{peak}}$ Stratum

Analysis: The two-year survival probability of CHF patients with low RER_{peak} and non-users of beta-blockers is slightly, but not significantly, lower (43.3 %) than the survival of patients with high RER_{peak} (58.8 %) within the low $\dot{V}O_{2\text{peak}}$ stratum (Log rank= 3.7, p= 0.05).

The relative risk of events for patients with low RER_{peak} with non beta-blocker use as compared to high RER_{peak} was calculated as follows:

$$\text{RR} = \frac{\frac{\text{Events in low RER}_{\text{peak}}^- / \text{Total number of patients in low RER}_{\text{peak}}^-}{\text{Non BB use group}}}{\frac{\text{Events in high RER}_{\text{peak}} \text{ group} / \text{Number of patients in high RER}_{\text{peak}} \text{ group}}{\text{Non BB use group}}}$$

$$\text{RR} = \frac{20 / 38}{53 / 160} = 1.589 \text{ (95 \% CI} = 1.064 - 2.207 \text{)} \text{ (p=} 0.039)$$

2) Comparing Survival Probability for Patients with Low RER_{peak} -High VE-V CO_2 slope versus the High RER_{peak} group within $\dot{V}O_{2peak} \leq 14 \text{ ml/kg/min}$ stratum:

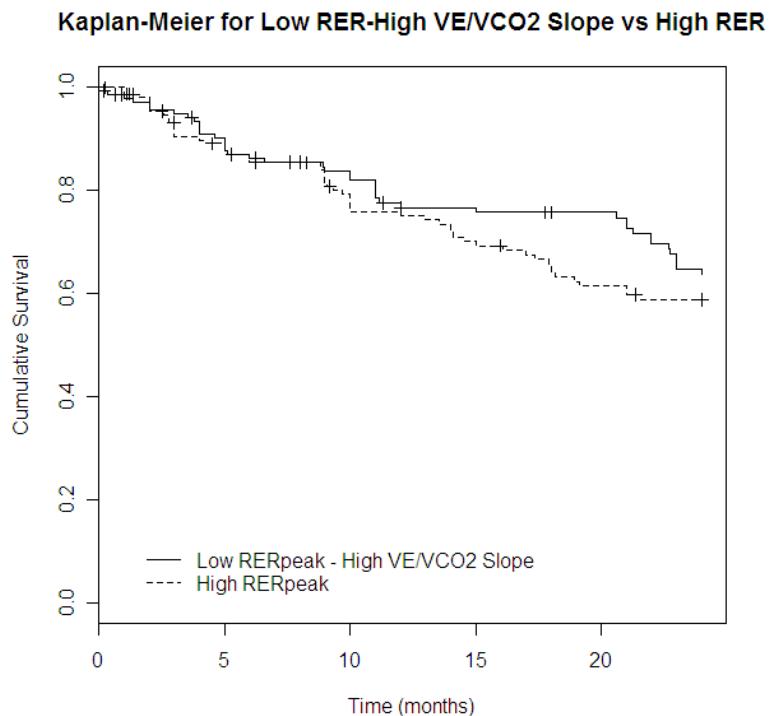


Figure 13- Two-Year Survival Comparison between High VE-V CO_2 Slope in Low RER_{peak} Group versus High RER_{peak} Group within Low $\dot{V}O_{2peak}$ Stratum

Analysis: There is no difference between the two-year survival probability for patients of low RER_{peak} with high $\dot{V}E/ \dot{V}CO_2$ slope (63.6 %) and those with high RER_{peak} (58.8 %) within low $\dot{V}O_{2peak}$ stratum (Log rank= 0.8, p=0.36).

The relative risk of events for patients of low RER_{peak} with high $\dot{V}E/ \dot{V}CO_2$ slope as compared to high RER_{peak} was calculated as follows:

$$\begin{aligned}
 RR &= \frac{\text{Events in low RER}_{\text{peak}}-\text{high VE/VCO}_2 \text{ slope group} / \text{Total number of patients in low RER}_{\text{peak}}-\text{high VE/VCO}_2 \text{ slope group}}{\text{Events in high RER}_{\text{peak}} \text{ group} / \text{Number of patients in high RER}_{\text{peak}} \text{ group}} \\
 RR &= \frac{42 / 146}{53 / 160} = 0.868 \text{ (95 \% CI} = 0.619 - 1.213) \text{ (p} = 0.459)
 \end{aligned}$$

3) Comparing Survival Probability for Patients with Low RER_{peak} -Low LVEF versus the High RER_{peak} group within $\dot{V}O_{2peak} \leq 14 \text{ ml/kg/min}$ stratum:

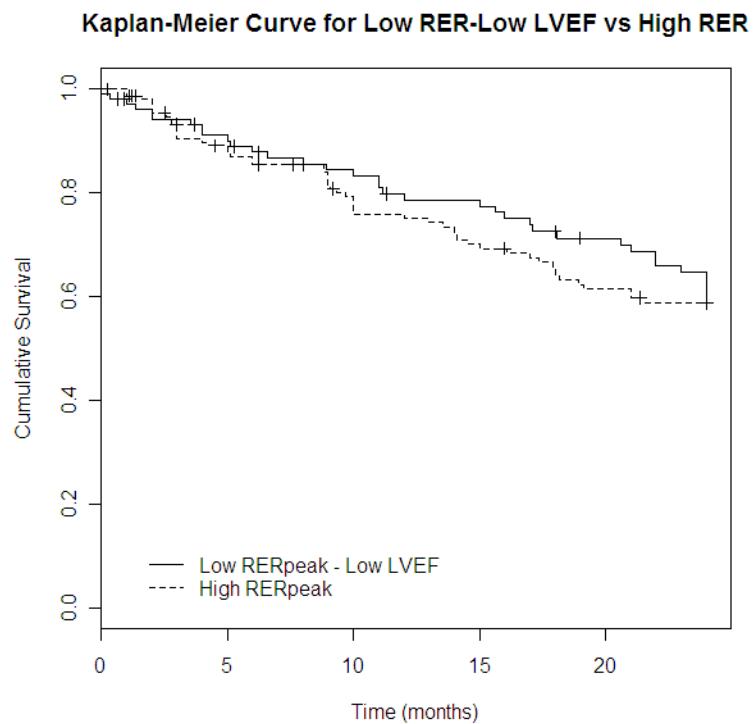


Figure 14- Two-Year Survival Comparison between Low LVEF in Low RER_{peak} Group versus High RER_{peak} Group within Low $\dot{V}O_{2peak}$ Stratum.

Analysis: The two-year survival probability between patients with low RER_{peak} with low LVEF (59.3 %) is not different from those with the high RER_{peak} (58.8 %) (Log rank= 0.2, p=0.695).

The relative risk of events for patients of low RER_{peak} with low LVEF as compared to high RER_{peak} was calculated as follows:

$$\text{RR} = \frac{\text{Events in low RER}_{\text{peak}}-\text{low LVEF group} / \text{Total number of patients in low RER}_{\text{peak}}-\text{low LVEF group}}{\text{Events in high RER}_{\text{peak}} \text{ group} / \text{Number of patients in high RER}_{\text{peak}} \text{ group}}$$

$$\text{RR} = \frac{35 / 109}{53 / 160} = 0.969 \text{ (95 \% CI} = 0.679 - 1.368 \text{)} \text{ (p=} 0.895)$$

4) Comparing Survival Probability for Patients with Low RER_{peak} -Ischemic Etiology versus the High RER_{peak} group within $\dot{V}O_{2peak} \leq 14$ ml/kg/min stratum:

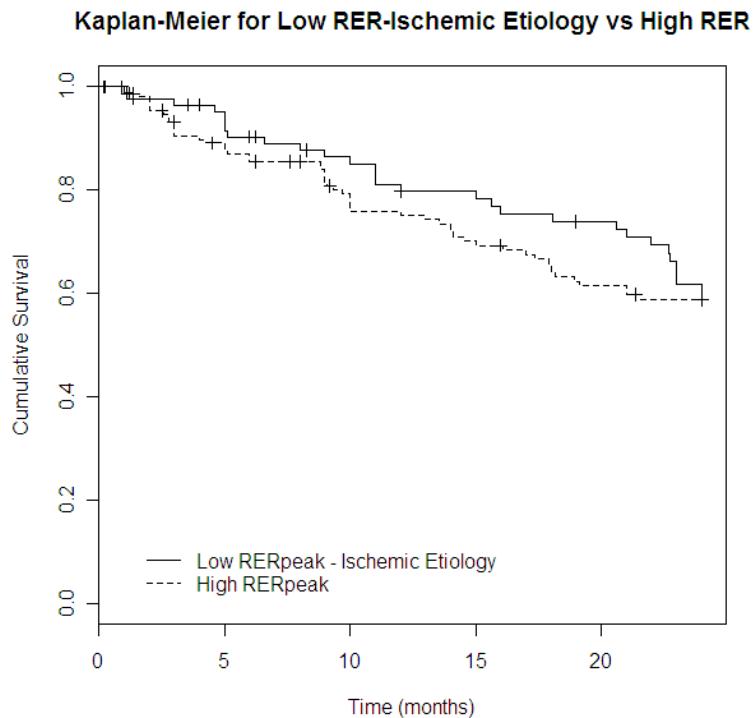


Figure 15- Two-Year Survival Comparison between Ischemic Etiology in Low RER_{peak} Group versus High RER_{peak} Group within Low $\dot{V}O_{2peak}$ Stratum

Analysis: The two-year survival probability between patients of low RER_{peak} with ischemic etiology of HF (58.4 %) and those with the high RER_{peak} (58.8 %) is not different (Log rank= 0.2, p=0.632).

The relative risk of events for patients of low RER_{peak} with ischemic etiology of HF as compared to high RER_{peak} was calculated as follows:

$$RR = \frac{\text{Events in low RER}_{\text{peak}}-\text{ischemic etiology group} / \text{Total number of patients in low RER}_{\text{peak}}-\text{ischemic etiology group}}{\text{Events in high RER}_{\text{peak}} \text{ group} / \text{Number of patients in high RER}_{\text{peak}} \text{ group}}$$

$$RR = \frac{30 / 94}{53 / 160} = 0.963 \text{ (95 % CI} = 0.662 - 1.379) \text{ (p} = 0.89)$$

Working Hypothesis 2b: Within each $\dot{V}O_{2\text{peak}}$ stratum, the subgroups of low RER_{peak} identified in Aim 2a as having significantly lower survival probabilities for CHF events will have similar probabilities of survival as the high RER_{peak} group.

Conclusion: The two-year survival probabilities of low RER_{peak} CHF patients without beta-blocker use, with high $\dot{V}E / \dot{V}CO_2$ slope, with low LVEF, or with ischemic etiology of HF are not significantly different from those of patients with a high RER_{peak} within the low $\dot{V}O_{2\text{peak}}$ stratum.

Hence, the working hypothesis for Aim 2b is not rejected for the low $\dot{V}O_{2\text{peak}}$ stratum.

Exploratory Analyses in Patients with Low RER_{peak} in Low $\dot{V}O_{2\text{peak}}$ Stratum:

A multivariate proportional hazard analysis (multivariate analysis) was conducted by including the variables $\dot{V}E/\dot{V}CO_2$ slope (<34 or ≥ 34), LVEF (<25 or ≥ 25), beta-blocker treatment (user or non-user), etiology of CHF (ischemic or non-ischemic), age (≤ 55 or >55), sex (males or females), and BMI (<30 or ≥ 30). The significant independent predictors of CHF related events were no beta-blocker treatment and low LVEF. This analysis showed that, when beta-blocker usage was included in the model, $\dot{V}E/\dot{V}CO_2$ slope and HF etiology were no longer significant predictors of CHF events. However, HF etiology approached statistical significance ($p=0.06$). Age, sex and BMI were not significant predictors of CHF-related events. The result of this analysis is shown in the Table 8 below.

Variable	p-value
Beta-blocker	<0.001
LVEF	0.004
Etiology	0.06
VE/VCO ₂ slope	0.13

Table 8- Multivariate Proportional Hazard Analysis Results for Low RER_{peak} Group within $\dot{V}O_{2\text{peak}} \leq 14$ ml/kg/min when $\dot{V}E/\dot{V}CO_2$ Slope is Entered with Cut-Off at 34

Beta-blocker use confounded the analysis. Out of 38 patients in the low RER_{peak} group who did not receive beta-blocker treatment, 35 (92.1%) had a $\dot{V}E/\dot{V}CO_2$ slope of ≥ 34 and 19 (54.3%) of these 35 patients had an event.

To expand the exploratory analysis further, the $\dot{V}E/\dot{V}CO_2$ slope was divided into four ventilatory classes (VC) formerly described by Arena et al. (2007). These four classes are- class I: $\dot{V}E/\dot{V}CO_2$ slope of ≤ 29 , class II: $\dot{V}E/\dot{V}CO_2$ slope of 30-35.9, class III: $\dot{V}E/\dot{V}CO_2$ slope of 36-44.9 and class IV: $\dot{V}E/\dot{V}CO_2$ slope of ≥ 45 . As shown in Table 9, the percentage of patients not receiving beta-blocker was higher in classes III and IV than in classes I and II.

	Ventilatory class	N and % of patients
1)	Class I: VE/VCO ₂ slope ≤ 29 :	Total N=20
	Beta-blocker Users	N=18 (90%)
	Beta-blocker Non-users	N=2 (10%)
2)	Class II: VE/VCO ₂ slope 30-35.9:	Total N=57
	Beta-blocker Users	N=54 (94.7%)
	Beta-blocker Non-users	N=3 (5.3%)
3)	Class III: VE/VCO ₂ slope 36-44.9:	Total N=79
	Beta-blocker Users	N=55 (69.6%)
	Beta-blocker Non-users	N=24 (30.4%)
4)	Class IV: VE/VCO ₂ slope ≥ 45 :	Total N=44
	Beta-blocker Users	N=35 (79.5%)
	Beta-blocker Non-users	N=9 (20.5%)

Table 9- Distribution of Beta-blocker Users and Non-Users across Ventilatory Classes

The two-year survival probabilities of CHF patients are compared across the four ventilatory classes within low RER_{peak} group in low $\dot{V}O_{2\text{peak}}$ stratum as shown in Fig. 16 below.

Comparing Survival Probability using four classes of $\dot{V}E/\dot{V}CO_2$ slope in low RER_{peak} group of low \dot{VO}_{2peak} stratum $\leq 14 \text{ ml/kg/min}$:

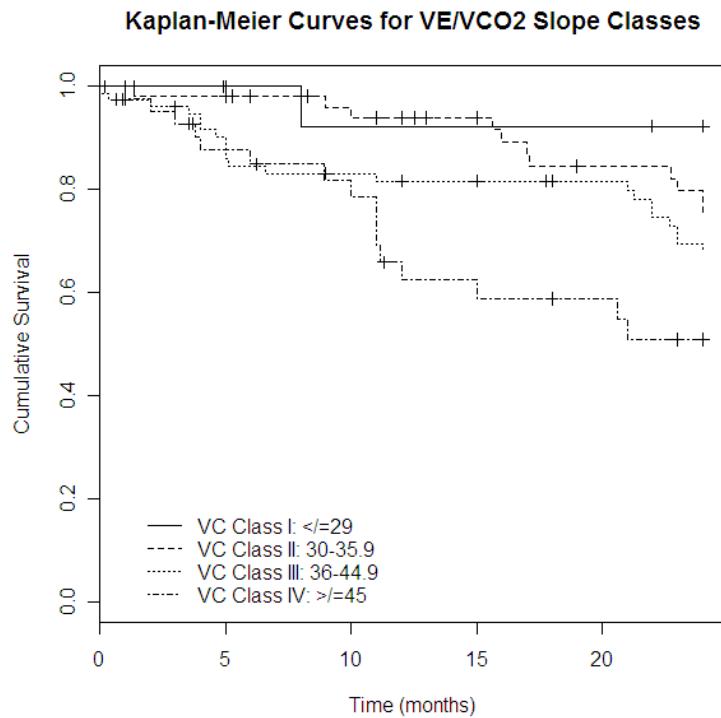


Figure 16- Two-Year Survival Comparison Across Four Ventilatory Classes of $\dot{V}E/\dot{V}CO_2$ Slope in Low RER_{peak} Group within Low \dot{VO}_{2peak} Stratum

This analysis shows that as the ventilatory class increases the probability of survival significantly decreases in CHF patients with low RER_{peak} within the low \dot{VO}_{2peak} group (Log rank= 11.5, p= 0.009).

Next, multivariate analysis was conducted entering $\dot{V}E/\dot{V}CO_2$ slope into the model as the four classes described above. The four variables appeared to be significant independent predictors of CHF-related events from this analysis and they are shown below in Table 10. In contrast to earlier model with $\dot{V}E/\dot{V}CO_2$ slope cut-point at 34, this multivariate proportional hazard model demonstrated that $\dot{V}E/\dot{V}CO_2$ slope maintained statistical significance when the beta-blocker variable was included. Additionally, the significance of the CHF etiology variable increased ($p=0.05$ vs. 0.02). As already shown in the bivariate analysis, age, sex and BMI variables were not significant predictors of CHF-related events in this model.

Variable	Significance
beta-blocker	<0.001
$\dot{V}E/\dot{V}CO_2$ slope	0.01
LVEF	0.01
etiology of CHF	0.02

Table 10- Multivariate Proportional Hazard Analysis Results for Low RER_{peak} Group within $\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ when $\dot{V}E/\dot{V}CO_2$ Slope is Entered as Continuous Variable

The analysis in Fig. 16 demonstrated that patients with $\dot{V}E/\dot{V}CO_2$ slope ≥ 45 (VC IV) had the lowest two-year event-free survival. Hence, this cut-off value was used to dichotomize the $\dot{V}E/\dot{V}CO_2$ slope data as high $\dot{V}E/\dot{V}CO_2$ slope ≥ 45 and low $\dot{V}E/\dot{V}CO_2$ slope < 45 to perform survival analysis as shown in Fig. 17 below.

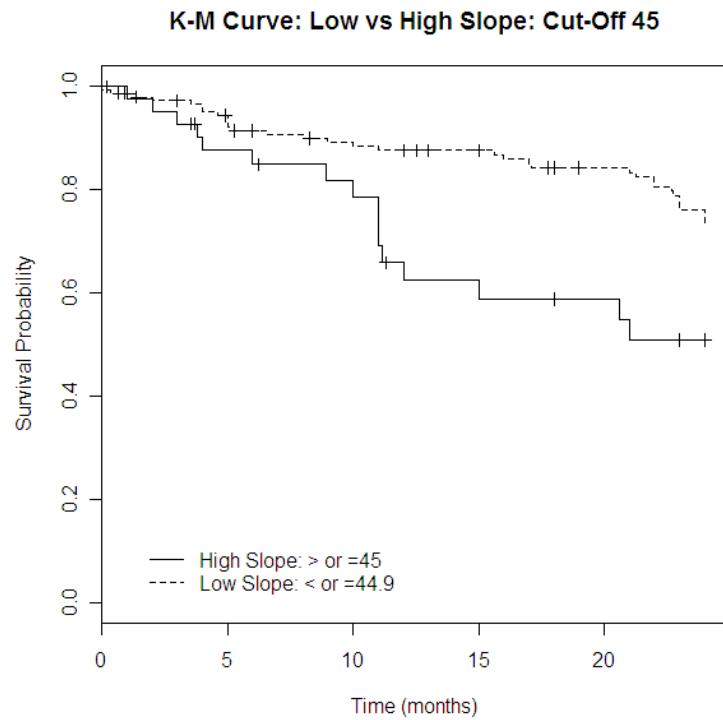


Figure 17- Two-Year Survival Comparison between Low (≤ 45) and High (≥ 45)
 $\dot{V}E/ \dot{V}CO_2$ Slope

Analysis: The survival probability of CHF patients with high $\dot{V}E/ \dot{V}CO_2$ slope is significantly lower (50.9 %) than those with low $\dot{V}E/ \dot{V}CO_2$ slope (73.4 %) (Log rank= 8.4, p= 0.003).

The relative risk of events for high $\dot{V}E/ \dot{V}CO_2$ slope compared to low $\dot{V}E/ \dot{V}CO_2$ slope was 1.719 (p= 0.04) (95% CI= 1.030- 2.734).

The multivariate analysis was performed entering the $\dot{V}E$ / $\dot{V}CO_2$ slope into the model as a dichotomized variable (≥ 45 vs. < 45). Four variables appeared to be significant independent predictors of CHF related events in patients with low RER_{peak} in the low $\dot{V}O_{2peak}$ stratum as demonstrated in Table 11 below. Unlike when 34 was used as the cut-point, the $\dot{V}E$ / $\dot{V}CO_2$ slope ≥ 45 maintained statistical significance when beta-blocker variable was added to the model. The variables age, sex and BMI were not significant predictors.

Variable	Significance
beta-blocker	0.0001
$\dot{V}E/\dot{V}CO_2$ slope	0.003
LVEF	0.007
Etiology of CHF	0.01

Table 11- Multivariate Proportional Hazard Analysis Results for Low RER_{peak} Group within $\dot{V}O_{2peak} \leq 14$ ml/kg/min when $\dot{V}E/\dot{V}CO_2$ Slope is Entered with Cut-Off at 45

High $\dot{V}O_{2peak}$ Analyses:

Specific Aim 1:

Specific Aim 1: After stratifying CHF patients by $\dot{V}O_{2peak}$ (≤ 14 ml/kg/min vs. > 14 ml/kg/min), examine the effects of RER_{peak} (< 1.10 vs. ≥ 1.10) on the survival probability for major heart failure events over a two-year period.

The findings for specific Aim 1 for high $\dot{V}O_{2peak}$ stratum are summarized in Table 12 as shown below.

Finding	Log rank and Significance	Relative risk and 95% CI
The low RER _{peak} group had a lower 2-year survival (88.6 %) than the high RER _{peak} group (90.5 %). The difference is non-significant.	Log rank= 0.3 p= 0.56	Relative risk of event for low RER _{peak} compared to high RER _{peak} = 1.188 (95% CI = 0.610 – 2.317) (p= 0.71)

Table 12- Survival Analysis for Aim 1 in Patients with Low RER_{peak} and High $\dot{V}O_{2\text{peak}}$

Working Hypothesis 1: Within each $\dot{V}O_{2\text{peak}}$ stratum, CHF patients with a low RER_{peak} will have a higher probability of survival than patients with a high RER_{peak}. This will likely be due to a portion of the low RER_{peak} patients failing to exercise at a maximal effort.

Conclusion: The survival probabilities between the low RER_{peak} group and the high RER_{peak} group within the high $\dot{V}O_{2\text{peak}}$ stratum are not different. Therefore, the working hypothesis for Aim 1 is rejected for high $\dot{V}O_{2\text{peak}}$ stratum.

Specific aim 2a:

Specific Aim 2a: Among those with a low RER_{peak} within each $\dot{V}O_{2\text{peak}}$ stratum, perform bivariate survival analyses examining the effects of the following independent variables (considered one at a time) on two-year survival probability for major heart failure events: $\dot{V}E$ / $\dot{V}CO_2$ slope (low/high), age (young/old), sex (male/female), BMI (non-obese/obese), LVEF (low/high), CHF etiology (ischemic/non-ischemic), and beta-blocker use (yes/no).

The Kaplan-Meier bivariate survival analyses are performed for the variables described in Aim 2a for high $\dot{V}O_{2\text{peak}}$ stratum. The findings are described in Table 13 as shown below.

Findings	Log rank and Significance	Relative risk and 95% CI
1) The high VE/VCO ₂ slope group had a significantly lower 2-year survival probability (71.1 %) than low VE/VCO ₂ slope group (95.6 %).	Log rank= 16.3 p< 0.001	Relative risk of event for high VE/VCO ₂ slope as compared to low VE/VCO ₂ slope = 5.1 (95% CI = 1.817 – 14.716) (p= 0.002)
2) The low LVEF group had a significantly lower 2-year survival probability (81.8 %) than the high LVEF group (93.8 %)	Log rank= 7.1 p= 0.007	Relative risk of event for low LVEF as compared to high LVEF = 3.655 (95% CI = 1.297 – 10.570) (p= 0.017)
3) The 2-year survival probability for males (90 %) and females (80.9 %) was not significantly different.	Log rank= 1 p= 0.313	Relative risk of event for males as compared to females = 0.574 (95% CI = 0.213 – 1.640) (p= 0.296)
4) The 2-year survival probability for the old age group (90.1 %) and the young age group (87.4 %) is not significantly different.	Log rank= 0.2 p= 0.642	Relative risk of event for old age group as compared to young age group = 0.779 (95% CI = 0.301 – 1.984) (p= 0.793)

Table 13 is continued on next page:

Findings	Log rank and Significance	Relative risk and 95% CI
5) The 2-year survival probability for ischemic etiology (85.5 %) and non-ischemic etiology of HF (90.5 %) is not different.	Log rank= 0.1 p= 0.775	Relative risk of event for ischemic etiology as compared to non-ischemic etiology = 1.268 (95% CI = 0.504 – 3.163) (p= 0.604)
6) The 2-year survival probability for low BMI (88.8 %) and high BMI (88.1 %) is not different.	Log rank= 0 p= 0.889	Relative risk of event for low BMI as compared to high BMI = 0.846 (95% CI = 0.340 – 2.109) (p= 0.797)
7) The 2-year survival probability for beta-blocker non-users (87.5 %) and beta-blocker users (89.4) is not different.	Log rank= 0 p= 0.98	Relative risk of event for beta-blocker non-users as compared to beta-blocker users = 1.316 (95% CI = 0.459 – 3.612) (p= 0.74)

Table 13- Survival Analyses for Aim 2a in Patients with $\text{RER}_{\text{peak}} < 1.10$ and $\dot{\text{V}}\text{O}_{2\text{peak}} > 14 \text{ ml/kg/min}$

Working Hypothesis 2a: In CHF patients in the low RER_{peak} group for a given $\dot{\text{V}}\text{O}_{2\text{peak}}$ stratum, the following groups of patients will have a lower probability of survival: higher $\dot{\text{V}}\text{E} / \dot{\text{V}}\text{CO}_2$ slope, older age, lower LVEF, ischemic etiology of CHF, and beta blocker non-users. There is little previous research comparing the survival probability for major heart failure events between male versus female and obese versus non-obese patients.

Therefore, the analyses of these variables are exploratory in nature and no hypotheses concerning them have been generated.

Conclusion: According to the findings described in Table 13, high $\dot{V}E/ \dot{V}CO_2$ slope and low LVEF have significantly lower survival probability. The survival analyses performed for etiology of CHF and beta-blockers did not show differences in survival. In addition, exploratory analyses for sex and BMI variables revealed that the two-year survival probabilities for males versus females and for low BMI versus high BMI groups are not different in CHF patients with $\dot{V}O_{2\text{peak}} \geq 14 \text{ ml/kg/min}$ and $RER_{\text{peak}} < 1.10$.

Hence, the working hypothesis for Aim 2a in high $\dot{V}O_{2\text{peak}}$ stratum is not rejected for high $\dot{V}E/ \dot{V}CO_2$ slope (≥ 34) and low LVEF ($< 25\%$). However, the working hypothesis for Aim 2a in high $\dot{V}O_{2\text{peak}}$ stratum is rejected for etiology of CHF, beta-blockers and age variables.

Specific aim 2b:

Specific Aim 2b: Based on the bivariate analyses in Aim 2a, identify the subgroups with the statistically significant lower survival probabilities within the low RER_{peak} group and compare to the high RER_{peak} group within the same $\dot{V}O_{2\text{peak}}$ stratum

The results obtained for specific Aim 2b are described in Table 14 as shown below.

Finding	Log rank and Significance	Relative risk and 95% CI
1) The group of Low RER _{peak} -high VE/VCO ₂ slope had a significantly lower 2-year survival probability (72.6 %) than high RER _{peak} group (90.5 %).	Log rank= 9.2 p= 0.002	Relative risk of event for low RER _{peak} -high VE/VCO ₂ slope as compared to high RER _{peak} group =2.324 (95% CI = 1.148 – 4.662) (p= 0.034)
2) The group of Low RER _{peak} -low LVEF had a significantly lower 2-year survival probability (81.8%) than the high RER _{peak} group (90.5 %).	Log rank= 4.2 p= 0.04	Relative risk of event for low RER _{peak} -low LVEF as compared to high RER _{peak} group =1.977 (95% CI = 0.972 – 3.990) (p= 0.075)

Table 14- Survival Analyses for Aim 2b in Patients with $\dot{V}O_{2\text{peak}} > 14 \text{ ml/kg/min}$

Working Hypothesis 2b: Within each $\dot{V}O_{2\text{peak}}$ stratum, the subgroups of low RER_{peak} identified in Aim 2a as having significantly lower survival probabilities for CHF events will have similar probabilities of survival as the high RER_{peak} group.

Conclusion: For the high $\dot{V}O_{2\text{peak}}$ stratum, the low RER_{peak} groups with high $\dot{V}E / \dot{V}CO_2$ slope and low LVEF have similar, or even lower, two-year survival probabilities than that of the high RER_{peak} group. Hence, the working hypothesis of aim 2b is not rejected for high $\dot{V}O_{2\text{peak}}$ stratum.

Summary of Results:

CHF patients with low $\dot{V}O_{2\text{peak}}$ (<14 ml/kg/min) have significantly lower two-year event-free survival as do those with high $\dot{V}O_{2\text{peak}}$. In the low $\dot{V}O_{2\text{peak}}$ group, patients with a high RER_{peak} (≥ 1.10) have lower event-free two-year survival than those with low RER_{peak} . The bivariate survival analyses in the low RER_{peak} group within the low $\dot{V}O_{2\text{peak}}$ stratum revealed that patients with high $\dot{V}E/\dot{V}CO_2$ slope (≥ 34), low LVEF ($<25\%$), ischemic etiology of CHF, and beta-blocker non-use have significantly lower two-year event-free survival rates that are comparable to that of the high RER_{peak} group within the same $\dot{V}O_{2\text{peak}}$ stratum.

Exploratory multivariate analyses in CHF patients with low RER_{peak} and low $\dot{V}O_{2\text{peak}}$ revealed that beta-blockers, $\dot{V}E/\dot{V}CO_2$ slope, LVEF, and ischemic etiology of CHF were significant independent predictors of CHF-related events when $\dot{V}E/\dot{V}CO_2$ slope was classified into four ventilatory classes.

In conclusion, in the low RER_{peak} (<1.10) group having a $\dot{V}O_{2\text{peak}} < 14$ ml/kg/min, CHF patients with no beta-blocker use, $\dot{V}E/\dot{V}CO_2$ slope ≥ 45 , LVEF $< 25\%$, and ischemic etiology of CHF are at increased risk of CHF related events (LVAD implantation, heart transplantation, death) within the following two years.

CHAPTER V

DISCUSSION

CPX testing is the gold standard modality used to assess functional capacity and to tailor therapeutic and surgical options for the CHF population. Although $\text{RER}_{\text{peak}} \geq 1.10$ is accepted as an indicator of maximal effort in CHF patients, it has been observed that a significant proportion (~50%) of patients are unable to attain this RER (unpublished results, HF Action database, LeBauer Cardiovascular Research Foundation). Controversy exists over the predictive value of CPX testing in CHF patients with a low $\text{RER}_{\text{peak}} < 1.10$ and whether or not significant predictors of CHF related events exist in this particular group. Hence, the focus of this study was to determine if specific variables derived from CPX testing can be used to predict major heart failure events (LVAD implantation, heart transplantation, death) in CHF patients with systolic dysfunction when RER_{peak} is lower than 1.10.

Earlier studies have demonstrated that patients with a $\dot{\text{V}}\text{O}_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ are at increased risk of CHF related events. Therefore, this $\dot{\text{V}}\text{O}_{2\text{peak}}$ value has been used as an important selection criterion for heart transplantation candidacy (Mancini et al., 1991; Roul et al., 1994). The present analysis also shows that the two-year CHF related event free survival probability is significantly lower (64.2%) in patients with $\dot{\text{V}}\text{O}_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ than in patients with $\dot{\text{V}}\text{O}_{2\text{peak}} > 14 \text{ ml/kg/min}$ (89.6%) (Fig. 3). Previously,

Osada et al. (1998) observed $\dot{V}O_{2\text{peak}} \leq 14$ ml/kg/min as an independent predictor of death in CHF patients who performed symptom limited CPX testing when the mean RER_{peak} was 1.11 ± 0.2 . Roul et al. (1994) found a low $\dot{V}O_{2\text{peak}}$ to be predictive of pulmonary edema, hospitalization for HF or severe ventricular arrhythmia, but did not report RER_{peak}. Mancini et al. (1991) observed a lower survival rate in patients with low $\dot{V}O_{2\text{peak}}$ who performed ‘maximal’ CPX testing, but RER_{peak} was not reported. As the present study includes CHF patients with both low and high RER_{peak}, it extends the prognostic value of $\dot{V}O_{2\text{peak}}$ to a wider population of CHF patients.

According to the criteria for maximal CPX testing, a low RER_{peak} may indicate a submaximal effort. Out of total 774 CHF patients who underwent CPX testing, 367 (47.4%) patients had a $\dot{V}O_{2\text{peak}} \leq 14$ ml/kg/min and 408 (52.6%) patients had a $\dot{V}O_{2\text{peak}} > 14$ ml/kg/min. In the lower $\dot{V}O_{2\text{peak}}$ group, 207 (56.4%) patients could not attain a RER_{peak} ≥ 1.10 . When the survival probabilities were compared between patients with a RER_{peak} < 1.10 and a RER_{peak} ≥ 1.10 , the results showed that the patients with higher RER_{peak} had significantly lower survival than those with lower RER_{peak} (Fig. 4). This finding was present in both the low and high $\dot{V}O_{2\text{peak}}$ groups (Table 12). This result may be attributed to the portion of low RER_{peak} patients failing to exercise at a maximal effort. The finding of the present study is similar to that of Mezzani et al. (2003) who employed a $\dot{V}O_{2\text{peak}}$ cut-off of 10 ml/kg/min. They demonstrated that patients with $\dot{V}O_{2\text{peak}} \leq 10$ ml/kg/min and RER_{peak} ≥ 1.15 had significantly worse survival than patients with $\dot{V}O_{2\text{peak}} \leq 10$ and RER_{peak} < 1.15 . Additionally, the latter group’s survival was similar to that of a

higher $\dot{V}O_{2\text{peak}}$ group (10–14 ml/kg/min). Hence, it was suggested that patients should be encouraged to exercise until RER_{peak} approaches 1.15. Arena et al. (2004) also reported that patients with a $RER_{\text{peak}} < 1.10$ had a lower percentage (27%) of events (cardiac related hospitalizations) as compared to patients with a $RER_{\text{peak}} \geq 1.10$ (32%).

Although a low RER_{peak} can be attributed to a submaximal effort, it may also be present in more severe cases of CHF which can be associated with conditions such as a lower ratio of muscle mass to total blood volume (Sidney et al., 1977), reduction in active skeletal mass (Anainsson et al., 1981), or gradual diffusion of lactic acid metabolites from active skeletal muscle into circulation (Shephard et al., 1975). In the present study, many patients with a low $\dot{V}O_{2\text{peak}}$ seem to be unable to attain a RER typically representative of maximal effort (i.e., 1.10). However, a portion of this group may have been exercising maximally, but may not have been able to attain a $RER_{\text{peak}} \geq 1.10$. Hence, an understanding of other variables that may predict CHF-related events within this group is critical. This will help in differentiating the patients at an increased risk of an event due to actual advanced disease from those who just have a low RER_{peak} due to a submaximal effort. In this study, the dichotomous variables included to assess the event risk in the low RER_{peak} group were $\dot{V}E/\dot{V}CO_2$ slope, LVEF, CHF etiology, age, sex, BMI and beta-blocker usage. A strength of this study is that all patients were first divided into low and high $\dot{V}O_{2\text{peak}}$ groups.

Comparison of two-year CHF related event-free survival for CPX derived variables and beta-blockers in the low RER_{peak} group of each $\dot{V}O_{2\text{peak}}$ stratum:

Higher $\dot{V}E/\dot{V}CO_2$ slope has been identified as an independent and strong predictor of poor prognosis in CHF patients (Corra et al., 2004). CHF patients show high $\dot{V}E/\dot{V}CO_2$ slope due to many central and peripheral factors such as reduced cardiac output, increased pulmonary artery and pulmonary capillary wedge pressure, increased ventilation-perfusion mismatching, and increased hypoxic chemoreceptor sensitivity. Because previous research has shown worse prognoses in patients with a $\dot{V}E/\dot{V}CO_2$ slope ≥ 34 (Chua et al., 1997; Gitt et al., 2002; Guazzi et al., 2003; Arena et al., 2004), this cut-off was used in bivariate analysis in the present study. The high $\dot{V}E/\dot{V}CO_2$ slope (≥ 34) group had a lower CHF-related event-free survival over two years (63.6%) than the low $\dot{V}E/\dot{V}CO_2$ slope group (83.2%) in the low RER_{peak} group (<1.10) of the low $\dot{V}O_{2\text{peak}}$ stratum ($<14 \text{ ml/kg/min}$) (Fig. 5). This finding was also present in the low RER_{peak} group in the high $\dot{V}O_{2\text{peak}}$ stratum (Table 13) as the high $\dot{V}E/\dot{V}CO_2$ slope group had a lower event-free survival (71.1%) of patients than the low $\dot{V}E/\dot{V}CO_2$ slope group (95.6%).

Poor survival with a higher $\dot{V}E/\dot{V}CO_2$ slope is consistent with findings of other researchers. Gitt et al. (2002) showed that CHF patients with a $\dot{V}E/\dot{V}CO_2$ slope >34 had a 5-fold increased risk of early mortality. In patients with a RER_{peak} ≥ 1.05 , Corra et al., (2002) found patients with a higher $\dot{V}E/\dot{V}CO_2$ slope (>35) to have a significantly higher mortality rate than those with lower $\dot{V}E/\dot{V}CO_2$ slope (<35) (30% vs. 10% respectively). In patients with a RER_{peak} ≥ 1.10 , Chua et al. (1997) demonstrated that patients with a low

$\dot{V}E / \dot{V}CO_2$ slope (<34) had significantly higher event-free survival (98%) than those with a higher slope (>34) (73%). The present study is unique in that a high $\dot{V}E / \dot{V}CO_2$ slope (≥ 34) predicted CHF events in a group of patients with *low* RER_{peak}.

LVEF is another important variable known to have an impact on prognosis in CHF patients. All patients included in this study had systolic heart failure with LVEF $\leq 40\%$. To assess the importance of LVEF in determining CHF prognosis, it was dichotomized as $<25\%$ or $\geq 25\%$. A LVEF $<25\%$ is typically considered to be severely depressed and is associated with higher mortality (Corra et al., 2002). Patients with a low LVEF had a lower CHF-related event-free survival (59.3%) over two-years than those with high LVEF (78.8%) within the group of low RER_{peak} in the low $\dot{V}O_{2\text{peak}}$ stratum (Fig. 6). The results were similar in the low RER_{peak} group of the high $\dot{V}O_{2\text{peak}}$ stratum (Table 13), where the event-free survival was lower (81.8%) in low the LVEF group than in the high LVEF group (93.8%). This finding is similar to earlier research done by Chua et al. (1997) and Mezzani et al. (2003) in patients with higher RER_{peak}. Chua et al. (1997) included CHF patients with RER_{peak} >1.10 and observed that non-survivors had a lower LVEF when compared to survivors. They also identified low LVEF as an independent predictor of event (death/transplant) in the multivariate analysis. However, the LVEF had not been dichotomized. The present study identifies the lower LVEF ($<25\%$) patients to have increased risk of CHF related events even in patients with RER_{peak} <1.10 of low and high $\dot{V}O_{2\text{peak}}$ strata.

Etiology of CHF (ischemic versus non-ischemic) is another important prognostic variable in the CHF population. In the bivariate analysis for low RER_{peak}, low $\dot{V}O_{2\text{peak}}$ group, two-year event free survival was significantly lower (58.4%) in patients with ischemic etiology than those with non-ischemic etiology (76.6%) (Fig. 7). This finding is similar to that of both Myers et al. (1998) and Arena et al. (2005). The patients in the latter study had a mean RER_{peak} >1.0. Myers et al. (1998) observed that, in univariate analysis, the type of HF was a significant predictor of death whereas patients with ischemic etiology had significantly higher risk than those with non-ischemic etiology. Unlike the present study, the above mentioned studies did not observe the prognostic effect of etiology of CHF in low versus high RER_{peak} groups. The worse prognosis associated with ischemic etiology of CHF may be attributed to reduced functional capacity (De Feo et al., 2005), and alteration in left ventricular size and function as a result of ventricular remodeling following an ischemic insult.

In recent years beta-blockers have been shown to improve the prognosis in CHF patients even without affecting $\dot{V}O_{2\text{peak}}$ (Pohwani et al., 2003). They have been shown to reduce the number of hospitalizations and improve the overall survival in CHF. In the low RER_{peak} group within the low $\dot{V}O_{2\text{peak}}$ stratum, the two-year event-free survival was lower in beta-blocker non-users (43.3%) as compared to beta-blocker users (74.7%) (Fig. 8). Several other investigators have reported similar findings (Mezzani et al., 2003; Pohwani et al., 2003; Peterson et al., 2003). Pohwani et al. (2003) included patients of

$\dot{V}O_{2\text{peak}} \leq 14 \text{ ml/kg/min}$ with $RER_{\text{peak}} \geq 1.0$ and followed them up for same CHF events as this study did. Conclusively, Pohwani et al. (2003) also suggested non-usage of beta-blockers as a criterion for heart transplantation candidacy. This observation is supported by Peterson et al. (2003) who demonstrated that beta-blocker non-users in a $\dot{V}O_{2\text{peak}} < 14 \text{ ml/kg/min}$ group had better survival with heart transplantation. The present study supports these results when RER_{peak} is < 1.10 in the low $\dot{V}O_{2\text{peak}}$ stratum. The mechanism of improving survival in CHF by treatment with beta-blockers is not yet clear. It may be attributed to increased LV stroke volume, and decreased pulmonary artery pressure and pulmonary capillary wedge pressure (Metra et al., 2003). Additionally, blocking the sympathetic nervous system in CHF may contribute to further reduction of myocardial damage.

It also has been suggested that heart transplantation will probably not add any additional survival benefits to CHF patients who are already receiving treatment with beta-blockers (Pohwani et al., 2003). However, these results did not hold true for the high $\dot{V}O_{2\text{peak}}$ group in the present study (Table 13). This is most likely due to the effect of high $\dot{V}O_{2\text{peak}}$ on improved survival in CHF. Peterson et al. (2003) also found that beta-blocker non-users in a patient group with $\dot{V}O_{2\text{peak}} \geq 14 \text{ ml/kg/min}$ had even better survival rates than patients who had undergone heart transplantation.

No differences were found in the two-year risk for age (young vs. old), sex (males vs. females), or BMI (low vs. high) in the low RER_{peak} groups in either $\dot{V}O_{2\text{peak}}$ strata (Fig. 9, 10, 11 and Table 13). Several other investigators have failed to demonstrate a

relationship between age and risk of CHF events (Mancini et al., 1991; Chua et al., 1997; and Davies et al., 2000). In addition, Davies et al. (2000) did not show sex to be related to CHF events.

Comparison of significant risk variables in the low RER_{peak}, low $\dot{V}O_{2\text{peak}}$ group to the high RER_{peak} group:

Two-year survival rates in the subgroups with variables shown to predict lower survival in the low RER_{peak} group were compared to survival rates in the high RER_{peak} group within each respective $\dot{V}O_{2\text{peak}}$ stratum. In the low RER_{peak}-low $\dot{V}O_{2\text{peak}}$ group, the survival of high $\dot{V}E$ / $\dot{V}CO_2$ slope, beta-blocker non-use, low LVEF and ischemic etiology subgroups were compared against high RER_{peak} group. It was observed that event-free survival in the low RER_{peak}-non beta-blocker users was not only similar to, but even slightly lower than that of the high RER_{peak} group (Fig. 12). In addition, survival was just as poor in low RER_{peak} patients with high $\dot{V}E$ / $\dot{V}CO_2$ slope (Fig. 13), low LVEF (Fig. 14), or ischemic etiology of CHF (Fig. 15) as was survival in the high RER_{peak} group within low $\dot{V}O_{2\text{peak}}$ stratum.

For the high $\dot{V}O_{2\text{peak}}$ stratum, the patients in low RER_{peak} group with either a high $\dot{V}E$ / $\dot{V}CO_2$ slope or a low LVEF were found to have significantly lower survival. When these two subgroups were compared against the high RER_{peak} group, they had even lower event-free survival than high RER_{peak} group (Table 14).

Overall, present study demonstrates that, the significant variables identified in the low RER_{peak} groups in both $\dot{V}O_{2\text{peak}}$ strata have similar or even higher risk of CHF related events as the high RER_{peak} group within a given $\dot{V}O_{2\text{peak}}$ stratum.

Exploratory Analyses in Low $\dot{V}O_{2\text{peak}}$ Group:

A multivariate proportional hazard analysis was performed to confirm the findings obtained on bivariate analyses and to identify independent predictors of CHF related events in patients with low RER_{peak} in the low $\dot{V}O_{2\text{peak}}$ stratum.

The multivariate analysis was performed by including the variables $\dot{V}E/ \dot{V}CO_2$ slope (<34 or ≥ 34), LVEF (<25 or ≥ 25), beta-blocker treatment (users or non-users), etiology of CHF (ischemic or non-ischemic), age (≤ 55 or > 55), sex (males or females) and BMI (<30 or ≥ 30). The significant independent predictors of CHF related events were no beta-blocker treatment ($p < 0.001$) and low LVEF ($p < 0.004$) (Table 8). When beta-blocker usage was included in the model, $\dot{V}E/ \dot{V}CO_2$ slope ($p = 0.13$) and HF etiology ($p = 0.06$) were no longer significant predictors of CHF related events.

Beta-blocker usage confounded the analysis. Hence, $\dot{V}E/ \dot{V}CO_2$ slope was then divided into four ventilatory classes (VC) described by Arena et al. (2007) as class I: $\dot{V}E/ \dot{V}CO_2$ slope of ≤ 29 , class II: $\dot{V}E/ \dot{V}CO_2$ slope of 30-35.9, class III: $\dot{V}E/ \dot{V}CO_2$ slope of 36-44.9 and class IV: $\dot{V}E/ \dot{V}CO_2$ slope of ≥ 45 (Table 9). This ventilatory classification system has been established to help in better clinical decision-making by assessing the severity of the disease more accurately than merely dichotomizing the variable at a value of 34. Kaplan-Meier analysis revealed that

increasing $\dot{V}E/\dot{V}CO_2$ slope was associated with a steadily lowering two-year event-free survival [VC I (92.3%), VC II (74.7%), VC III (67.8%) and VC IV (50.9%)] (Fig. 16).

A multivariate proportional hazard analysis was conducted entering $\dot{V}E/\dot{V}CO_2$ slope as the continuous variable as described above. In contrast to the earlier model, the $\dot{V}E/\dot{V}CO_2$ slope maintained statistical significance when beta-blocker use was included in the model. Additionally, the significance of the HF etiology variable increased from $p=0.05$ to $p=0.02$. Beta-blocker use ($p < 0.001$), $\dot{V}E/\dot{V}CO_2$ slope ($p=0.01$), LVEF ($p=0.01$), and etiology of CHF ($p=0.02$) were shown to be significant independent predictors of CHF related events in patients with low RER_{peak} of low $\dot{V}O_{2\text{peak}}$ stratum (Table 10).

When the effects of other clinical factors were considered, the $\dot{V}E/\dot{V}CO_2$ slope cut-point of 34 did not hold true as the significant independent predictor of CHF related events on multivariate analysis (Table 8). Among the four VC classes mentioned above (Fig. 16), patients with $\dot{V}E/\dot{V}CO_2$ slope ≥ 45 (VC IV) had the lowest two-year event-free survival (highest risk). Hence, the $\dot{V}E/\dot{V}CO_2$ slope was dichotomized as ≥ 45 and < 45 . The Kaplan-Meier analysis showed that high $\dot{V}E/\dot{V}CO_2$ slope group had significantly lower event-free survival (50.9%) than low $\dot{V}E/\dot{V}CO_2$ slope group (73.4%) (Fig. 17). Lastly, the multivariate analysis was conducted using $\dot{V}E/\dot{V}CO_2$ slope dichotomized at a value of 45. The results showed that $\dot{V}E/\dot{V}CO_2$ slope maintained the significance even after entering beta-blocker use to the model. This multivariate analysis (Table 11) revealed that the following four variables appeared to be significant independent predictors of CHF related event: beta-blocker usage ($p=0.0001$), $\dot{V}E/\dot{V}CO_2$ slope ($p=$

0.003), LVEF ($p= 0.007$), and etiology of CHF ($p= 0.01$). The statistical significance found with these variables was higher than with the earlier multivariate proportional hazard model. Age, sex, and BMI were not significant predictors of CHF related events. In summary, the following variables appear to be significant independent predictors of CHF related events in the low RER_{peak} group within the low $\dot{V}O_{2\text{peak}}$ stratum: no treatment with beta-blockers, $\dot{V}E/ \dot{V}CO_2$ slope ≥ 45 , LVEF $< 25\%$, and ischemic etiology of CHF.

The strengths of this study are as follows: 1) The sample size ($N=774$) was large compared to other studies conducted in the past; 2) It included CHF patients with a wide range of functional capacity; 3) This study included LVAD implantation, heart transplantation, and deaths as the end points of follow-up, contrary to some other studies which used only mortality as an end-point; 4) This study assessed the risk of patients not attaining a RER_{peak} typically required to justify a test as “valid”; 5) Patients from multiple research sites were included, increasing the study’s external validity.

This study also has some limitations: 1) The follow-up period is limited to only 24 months; 2) Duration of the medications that the patients are on is not controlled for; 3) This study included all-cause mortality instead of cardiac related mortality; 4) The follow-up information was dependent upon available hospital records; 5) Age at the onset of CHF, duration of illness, and previous physical activity levels were not considered.

In conclusion, this study is unique in that it analyzed the CHF patient population based upon RER_{peak} stratification after controlling for $\dot{V}O_{2\text{peak}}$. Within the low

$\dot{V}O_{2\text{peak}}$ group, the high RER_{peak} group had lower survival than the low RER_{peak} group. However, certain factors (no use of beta-blockers, $\dot{V}E/\dot{V}CO_2$ slope ≥ 45 , LVEF $< 25\%$ and ischemic etiology of CHF) significantly predicted CHF events within the low RER_{peak} group. These results suggest that advanced therapies, such as LVAD implantation and heart transplantation might still need to be considered for CHF patients who do not attain a RER_{peak} of 1.10 during CPX testing. Furthermore, although ≥ 34 is traditionally accepted as a prognostic value for $\dot{V}E/\dot{V}CO_2$ slope, the present study suggests that a slope of ≥ 45 may be a more independent predictor of CHF-related events in patients with low RER_{peak} and low $\dot{V}O_{2\text{peak}}$. These results show promise for more appropriate treatment for certain CHF patients who may not “perform well” during cardiopulmonary exercise testing. Future studies using more sophisticated statistical modeling are needed to confirm these findings. Also, although the above mentioned variables have been identified as the significant independent predictors of CHF-related events in particularly low RER_{peak}-low $\dot{V}O_{2\text{peak}}$ group, it is important to study the interaction between these variables and to find any confounders if exist. Finally, it is also important to stratify RER_{peak} at lower cut-points, such as 1.05 and 1.0, to test if these variables in addition to others hold the same results as independent predictors of events. This will help clinicians in better decision making within the low RER_{peak} population.

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