ESTIMATES OF CENTRAL HEMODYNAMICS USING GAS EXCHANGE IN PATIENTS WITH CYSTIC FIBROSIS

A THESIS
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY:

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF:

Master of Science

ADVISOR: Eric M. Snyder Ph.D.

July 2016

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ACKNOWLEDGEMENTS

The following thesis was prepared under the direction of Eric M. Snyder, Ph.D., Donald R. Dengel, Ph.D. and Aaron S. Kelly, Ph.D., at the University of Minnesota.

I wish to thank each of them individually for their contributions to my work and their continued guidance, leadership and patience. I would like to also thank my family, friends and classmates for which without their support this would not be possible.

ABSTRACT

Pulmonary artery capacitance (PV_{CAP}) is the ability of the pulmonary artery to accept a volume of blood at a given pressure. Traditionally measured invasively with heart catheterization; Pa_{CAP} may be estimated non-invasively through the measurement of end-tidal CO_2 (P_{ETCO2}) and stroke volume (SV), known as gas-exchange capacitance (GX_{CAP}) where a higher capacitance means improved pulmonary vasodilation. The degree of pulmonary vascular dysfunction at rest and during exercise remains unclear in patients with cystic fibrosis (CF). **PURPOSE:** To determine the effects of exercise on GX_{CAP} in patients with CF, when compared to healthy subjects. **METHODS:** 19 patients with CF (age=22±2yrs, BMI=23±1kg/m^2, VO_2=56±6%pred., FVC=83±5%pred., FEV_1=72±6%pred., FEV_1/FVC=0.72±0.02) and 17 healthy subjects (age=22±1yrs, BMI=23±1kg/m^2, VO_2=81±5%pred., FVC=93±3%pred., FEV_1=89±2%pred., FEV_1/FVC=0.81±0.02) were recruited for this study. Exercise testing was performed on a cycle ergometer. P_{ETCO2} was assessed using a metabolic cart, SV was assessed using the acetylene rebreathe technique and GX_{CAP} was calculated from the product of P_{ETCO2} and SV. **RESULTS:** At rest, SV and GX_{CAP} were higher in healthy subjects when compared to CF (SV=72±6 vs. 54±5ml, GX_{CAP}=22±2 vs. 17±2, for healthy and CF, respectively. P_{ETCO2} remained unchanged between healthy and CF subjects (P_{ETCO2} 30±1 and 30±1 respectively). Healthy subjects exercised at a higher absolute intensity, but

intensity expressed as a percentage of max was similar between healthy and CF (watts=159±10 vs. 102±8, watts/max watts=96±3 vs. 95±5% for healthy and CF, respectively). At peak exercise, SV and GX_{CAP} increased in both healthy and CF but remained higher in healthy subjects when compared to CF (SV=108±5 vs. 84±6ml, GX_{CAP}=40±3 vs. 29±2, for healthy and CF, respectively, $p<0.05$). When matched for a workload designed to match for SV, there was no difference in percent of max watts (%MaxW=63±4 vs. 66±5W), Q (11±1 vs. 13±1L/min), or SV (89±4 vs. 90±4ml/beat). When matched, the previous difference in GX_{CAP} in healthy and CF was abolished (GX_{CAP}=32±2 vs. 32±2mL/BEAT · min).

CONCLUSION: Gas exchange capacitance is lower in patients with CF at rest and through peak exercise. However, when matched for SV and workload, GX_{CAP} was statistically similar between healthy and CF. This lower GX_{CAP} is likely due to lower SV at rest and with peak exercise in CF patients, when compared to healthy subjects. Therefore, these findings suggest that there is no evidence of pulmonary vasculature dysfunction in these CF patients. Future, more invasive studies are warranted to confirm the lack of difference in pulmonary vascular function in patients with CF.

Supported by NIH Grant RO1 HL108962-02

Key words: Cystic fibrosis, pulmonary capacitance, exercise, central hemodynamics, cardiac output, stroke volume.

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CHAPTER 1. INTRODUCTION

Cystic Fibrosis (CF) is the most common autosomal recessive genetic disorder affecting 1 in 2,500 births among Caucasians. Cystic fibrosis is characterized by altered ion regulation throughout the body which manifests as chronic lung infection, exacerbations of the pulmonary tree, and death from lung disease, leading to the majority of the research being directed towards the pulmonary system. With the development of new pharmacotherapies allowing subjects to live longer into adulthood, a shift is warranted from this pulmonary-specific focus on mortality to multisystem research and clinical practice that includes the cardiac and vascular systems. This shifted focus should initially be set on potential co-morbidities, most notably cardiovascular dysfunction associated with potential central and peripheral hemodynamic dysfunction.

Here is encompassed a complete literature review, as well as background, methodology, results, discussion, and a conclusion surrounding the proposed study are detailed in the following chapters. Please see the overview below:

Chapter two summarizes the current literature related to cardiovascular function and central hemodynamics in CF. A brief overview of CF, the associated changes in the pulmonary vasculature, the consequences of those changes on the heart and validated techniques for assessment. Also, in chapter two, the parallels in and differences between cardiovascular function and central hemodynamics between healthy and diseased populations will also be

discussed. Additionally, specific aims and hypotheses of the present study will be clearly stated.

Chapter three summarizes the methodology of this study including data collection and measurement techniques, anthropometric assessment, measurement of pulmonary function, gas exchange, and description of the equations used within the study. Chapter three also details the statistical analyses utilized in this study.

Chapter four contains detailed findings of this study. In this chapter we examine differences between controls and CF subjects in the study population regarding anthropometric and pulmonary function at rest. Further, changes in cardiac function and estimates of pulmonary capacitance with exercise are described, as well as differences between these two pertinent variables at rest and peak exercise, between healthy and CF.

Chapter five summarizes and discusses the implications of the study findings in relation to the existing literature. Initial results as well as subsequent matching of study groups are discussed. Further, discussion of physiologic differences between healthy and CF subjects are also reviewed.

Chapter six offers conclusions of the resulting study. Additionally, in chapter six, the necessity and future direction of research in cardiovascular function and central hemodynamics in CF will be reviewed.

CHAPTER 2. REVIEW OF LITERATURE

Cystic Fibrosis

Cystic fibrosis (CF) was first described by Anderson in 1938 through the recognition that these patients presented with digestive and nutritional disturbances, infections of the respiratory tract, as well as postmortem lesions of the pancreas and respiratory system (1, 2). Cystic fibrosis is now known to be an autosomal-recessive disease affecting one in 2,500 births making it the most common life shortening inherited genetic disorder among Caucasian individuals (3, 4, 5). There are roughly 30,000 people in the United States (US) living with CF and 70,000 cases worldwide. Around 1000 new cases of CF are diagnosed each year in the US alone, with 75% of those patients being diagnosed by age two (6). Cystic fibrosis is characterized by chronic disease progression and multisystem involvement. Although multiple organ systems are affected by CF, pulmonary dysfunction receives the greatest focus as CF patients continue to die primarily from lung disease. Despite this focus on the pulmonary system, CF affects several organ systems including the gastrointestinal, immune, endocrine, reproductive, and musculoskeletal (3, 7).

Interestingly, at present, nearly half of the CF population is 18 years of age or older, which may be attributed to more widespread use of carrier screening (6, 8, 9), improved drug delivery, and improved pharmacotherapy that targets specific genetic mutations of the cystic fibrosis transmembrane

conductance regulator (CFTR). There are more than 1800 known mutations in CFTR that cause CF, although widespread genetic testing screens for the most common, the Delta-F508 (ΔF_{508}) mutation. The mutations in the gene that encodes for CFTR range from those that are common to some mutations that affect only a few people worldwide; this is important because some mutations are associated with a wide range of symptoms leading to variation in disease severity, treatment options, and survival (8, 9).

The CFTR is a protein anion channel that participates in the fluctuation of electrolytes and fluid movement across mucosal surfaces (8, 10). Specifically, CFTR has two primary functions that are lost or reduced in patients with CF; (1) Cl^- secretion to the apical portion of epithelial cells, and (2) inhibition of Na^+ reabsorption into the cell through epithelial Na^+ channels (ENaC). Due to this loss of normal ion regulation, CF patients have hyperapsorption of NaCl and, therefore, fluid shifts away from the apical portion of cells. Functional CFTR is critical at the epithelial surface not only in the respiratory tract but the gastrointestinal tract as well in the exocrine gland ducts (8, 10). It is also important to note that the CFTR protein is also expressed in the cardiac and vascular smooth muscle tissue and may play an important role in cardiac contraction and vascular function (11).

The pulmonary manifestation of CF is noted by the production of thick mucus (due to the loss of airways surface liquid from NaCl hyperabsorption) leading to the obstruction of the airways from bronchial trunk to alveoli; secondary to this mucus build-up is chronic inflammatory reaction and pulmonary multiresistant bacterial infections (4, 12). Most serious of these bacterial colonization's is Pseudomonas aeruginosa or Stenotrophomonas maltophilia which account for roughly one to two hospitalizations per year and represents a large burden among CF patients (13). The aforementioned chronic inflammation over time leads to progressive remodeling of the pulmonary tissue, bronchiectasis, and parenchymal fibrosis (4, 14). This cycle of chronic inflammation, infection and hospitalization continues throughout the life of a patient battling CF. The progressive destruction of the lung tissue in CF leads to one of two outcomes: lung transplantation or eventual death. The life expectancy of patients with CF is 37.5 years but has the promise of growing with each new marked therapeutic development (11).

Increased longevity in CF has warranted increased focus on extra-pulmonary complications and co-morbidities. A variety of systemic complications including gastrointestinal, immune, endocrine musculoskeletal and cardiovascular have been noted (7,15). Issues explicit to the cardiac systems and pulmonary vasculature have been given some, albeit minimal, attention compared to issues of the pulmonary trunk in CF. Because the heart and lungs

lie in series, pulmonary hemodynamics are a critical component in the determination of right ventricular performance and overall cardiac health (16, 17). Additionally, adult patients with mild to moderate CF severity exhibit evidence of systemic large arterial circulation abnormalities (12, 18). Vasculature dysfunction causes an increase in arterial stiffness, seen even in children with CF, and vasoconstriction of the pulmonary vasculature. Pulmonary vasoconstriction in CF is likely initiated by chronic systemic hypoxia that is the result of impaired ventilation and gas exchange (1, 19, 20).

The general mechanism of hypoxic pulmonary vasoconstriction in CF is largely unknown although the phenomenon was first described by Liljestran in 1946 (21, 22). It is understood, however, that pressure is increased within the lung in an effort to attenuate the non-uniform distribution of blood flow and inspired air within the pulmonary tree to better match for ventilation and perfusion (19, 21, 23).To optimize ventilation to perfusion in instances of alveoli becoming hyperinflated, and/or hypo-inflated in poorly ventilated portions, pulmonary vasoconstriction causes blood to shunt away from the poorly-ventilated areas to well-ventilated areas (21, 23). This is normal in the healthy lung with environmental hypoxic conditions such as ascending to high altitude; however when the cause is pathophysiologic, and continual, as in chronic obstructive pulmonary disease (COPD), or in CF, stress on the pulmonary vascular system, including pulmonary hypertension (PH) and pulmonary vascular remodeling

emerge (24, 25). This chronic pulmonary vasoconstriction or PH occurs primarily in the smaller pulmonary blood vessels causing a remodeling of the peripheral pulmonary trunk (18). This remodeling includes masculinization of the smooth muscle and progressive fibrosis of the intima of the pulmonary arterioles. (21). However in contrast to the arterial system this remodeling does not seem to occur within the venous pulmonary vascular tree (1). Although the general mechanism for pulmonary vascular dysfunction has been described in several disease states (COPD, heart failure (HF), etc.) this has been poorly characterized in patients with CF.

Pulmonary Hypertension in CF

Pulmonary hypertension has been defined as a mean pulmonary artery pressure of greater than 25 mm Hg as assessed via invasive right heart catheterization. In CF, PH is associated with advanced lung disease and negative clinical outcomes (3). Pulmonary hypertension has been recognized in the natural progression and development of CF since Anderson first described it in 1938, but this co-morbidity remains relatively unstudied (26). Pulmonary hypertension has been observed in children with CF as well, with an incidence of nearly 70% having been reported (1). Pathology of vasoconstriction within the pulmonary trunk is due not only to hypoxia but is confounded by the destruction and subsequent vascular remodeling, increasing vascular resistance and,

ultimately irreversible PH (22, 27, 28). The prevalence of PH in CF ranged from 26 up to 63% in previous studies, however the clinical implications of PH from young, stable, CF as well as end-stage CF patients awaiting lung transplantation has not been yet elucidated (3, 12, 16, 27). Previous work has demonstrated that progressive respiratory failure and PH will lead to eventual right HF in other disease states that may have similarities to CF (3, 13, 29). As previously mentioned the heart and lungs lie in series and are subjugated to similar pressures within the thoracic cavity (17). As resistance increases within the lung, the afterload the heart needs to overcome to maintain stroke volume (SV) meets increased resistance, thus increasing the work of the heart leading to an enlargement of the right ventricle (30). This enlargement of the ventricle is due to increasing pressure in the lungs. As early as 1988 Burghuber and associates indicated preclinical geometric remodeling and ventricular dysfunction in children with CF (30). In this same population, decreased right ventricular ejection fraction (EF) was also apparent. However, right ventricular EF is highly dependent on afterload as had been previously shown in COPD and the authors questioned the validity of the measure in assessing right ventricular contractility, let alone function (25, 30).

Cardiopulmonary Hemodynamic Dysfunction in CF

Regardless of increased pulmonary pressures and vascular stiffening, the severity of cardiac dysfunction in CF has had varied findings. Cardiac output (Q) has been reported previously as normal at rest as well as during exercise. More recently, however, it has been shown that SV and Q may be lower during increasing exercise intensity in CF (21, 31, 32). These conflicting findings are due to several factors such as the modality and intensity of the exercise as well as techniques used for assessing cardiac variables. Adult CF patients with mild to moderate severity show evidence of abnormalities of large arterial circulation (18). Concurrently there is an abnormal central hemodynamic response apparent in CF patients during exercise which is expressed by greater pressure within the pulmonary circulation, when compared to age, gender, and BMI matched controls (18). It has also been shown previously that CF patients with increased mean pulmonary artery pressure trended towards worse survival, similar results were also observed in those patients with decreased EF (3). It has been suggested that patients with CF exhibit a deterioration of pulmonary hemodynamics in the end-stage of the disease (16). At this end-stage of CF it is far more likely that several compounding factors are present causing parenchymal destruction, obstruction, and fibrosis to affect the pulmonary circulation (16). Dysfunction in central hemodynamics has been associated with low life expectancy and increased risk of mortality (16, 26). Studies assessing

central hemodynamic impairment are varied in disease and severity suggesting multisystem involvement and multifactorial control (16). Prevalence of this ventricular dysfunction in CF and advanced lung disease is controversial being shown to be high in some studies and low in others (3, 33). These findings have been confirmed in younger patients, suggesting abnormal early vascular aging even in the setting of normal peripheral blood pressure and may constitute important clinical implications in cardiovascular health as longevity increases in CF (29). Previous work also suggests premature or accelerated vascular aging of the large artery hemodynamics in CF approximately ten years that of their chronologic age. Premature vascular aging has been described previously as the increased stiffening of the central arterial circulation to that of their aged and sex-matched healthy controls. The premature aging demonstrated in these studies could not be explained by increased blood pressure, physical activity level, and smoking (11, 13, 29, 34). Hemodynamic dysfunction contributes to extrapulmonary complications that persist into the adult stage of the disease and involves the heart, in addition to the pulmonary vasculature (29).

Assessment of Cardiopulmonary Vascular Function

There are several techniques available for assessing cardiovascular hemodynamics and vascular function, *in-vivo*. Methods range from very reliable to questionable and expensive to cost effective as well as invasive to non-

invasive. Like most measures of organ system function, measures of cardiovascular hemodynamics in humans have their faults and strong suits. Here we discuss three techniques for assessing Q: the direct Fick method, thermodilution, and acetylene rebreathe. The gold standard for assessing Q is the direct Fick method where the quotient of oxygen uptake (VO_2) and the difference of the arterial and mixed venous oxygen content are used to calculate Q (12, 17, 32, 35). This technique is used sparingly in clinical practice due to the specialty of measuring oxygen uptake and the invasive nature (requirement of arterial and venous blood sampling) of pulmonary artery catheterization. In the clinical setting the thermodilution technique has been used extensively. Thermodilution is performed by injecting ice-cold isotonic saline through the proximal right atrial lumen; the difference in temperature from is then calculated. This requires a thermistor at the end of the catheter and one in a distal location (35). Thermodilution has been shown to be accurate in healthy subjects as well as patients with cardiovascular disease. Although the accuracy of the thermodilution method is suspect in subjects with low Q or severe tricuspid regurgitation both of which present themselves in patients with severe PH (32, 35). Acetylene rebreathe technique has been used widely as a reliable non-invasive determinate of Q. Acetylene (C_2H_2) is an inert, non-physiologic gas giving it a low solubility in tissue but a high affinity within the blood. When inhaled, the gas is taken up by the pulmonary capillary blood stream at a rate proportional to the volume within the pulmonary system (35, 36). As the

pulmonary system receives nearly all of the Q the acetylene rebreathe technique has been shown to be accurate in estimating Q and SV in animals and humans at rest and during exercise (17, 35).

The most accurate method for the assessment of cardiac function and pulmonary vascular pressures is cardiac catheterization. During the catheterization of the heart a catheter is advanced through the right internal jugular vein and into the right side of the heart by way of the superior vena cava. The indwelling catheter is then wedged in the pulmonary artery under fluoroscopic guidance (17, 32, 37). The placement allows for several metrics to be directly measured: systolic, diastolic and mean arterial pressure as well as the mean pulmonary artery pressure and pulmonary artery wedge pressure (which is important in the assessment of PH. Other measures obtained during cardiac catheterization are mixed-venous blood gasses, the aforementioned Q, and SV. From these measures peripheral vascular resistance can be assessed as well as pulmonary capacitance (PV_{CAP}). Pulmonary capacitance is a measure of the pulmonary arteries ability to distend to accept a volume of blood under a given pressure (17, 38). This measure of PV_{CAP} may be an important in the assessment of PH, right ventricular function and central hemodynamic health in individuals with severe lung disease (39).

Although feasible; there are several limitations to invasive heart catheterization, especially during exercise, in healthy subjects and patients with

CF (40). Catheterization must be performed by a cardiologist and specialized groups of nurses which increases the cost greatly. The fluoroscopy used to insure proper placement of the catheter exposes the subject to radiation and, therefore, must be used sparingly to minimize the exposure risk. The measure also requires several pieces of specialized equipment including a supine cycle ergometer. This specialized bike allows the subject to peddle at increasing workloads while laying supine, similar to a bed with pedals at the foot. When exercise commences, and as work load increases, it is difficult to maintain the position of the catheter and to ensure the measures are being maintained properly becomes question. Beyond simple equipment limitations, the supine cycle ergometer has an important limitation in that it places the heart and lungs in an unnatural exercise position that artificially enhances venous return and influences pulmonary capillary recruitment. Other non-invasive measures have shown promise in estimating measures obtained via right heart catheterization but are not without limitations.

Echocardiography has been utilized for the assessment of both left and right heart function as well as hemodynamic variables and pressure assessments in CF (16, 21), It has been shown to be useful in the examination of ventricular morphology, most notably right ventricular enlargement and hypertrophy (16, 23). Echocardiography has been used extensively in the assessment of PH, right ventricular free-wall thickness, and limitations in EF, all of which are useful in the

determination of the severity and progression of disease (12, 23, 33). Echocardiograms have become a routine part of standard patient evaluation clinically, due to widespread availability and non-invasive nature of the measures obtained (33).

Despite its utility, echocardiography has limitations and is largely unreliable for several reasons. Echocardiography requires highly trained personnel, even in healthy subjects, and the level of training needed is even greater for this assessment in patients with CF; specifically, technicians need to have considerable experience with the disease for accurate echocardiography (23). Due to air trapping in patients with CF the pulmonary valve may be difficult or even impossible to visualize. This issue of physiologic vision is problematic in CF patients as estimates of pressure, flow and size require multiple vantage points that may not be available. It has been shown that the most severely ill patients that may benefit most from echocardiographic assessment have the highest failure rate with this method (23). Similarly, there have been high failure rates across the board among studies utilizing echocardiography in CF. In one such study it was not possible to measure pulmonary artery pressure in one third of their subjects (12). The same was found in another where the pulmonic valve was not visible in one third of the subjects imaged (23). In (33) only 65% of subjects had satisfactory examinations and in 13% of subjects in (12) echocardiographic assessment was not possible (12, 33). The shortcomings in

physiologic vision are present in echocardiography when the subject is in optimal position and completely still. Echocardiography provides no valuable information during exercise (39). Pressure and hemodynamic adaptation to increasing workload may provide beneficial insight into the functional capacity and disease severity for patients with CF (16, 39). However, the probe used in echocardiography relies on stillness and a steady hand to capture relevant images for proper calculations.

Emerging Technique for the Assessment of Cardiopulmonary Vascular Function; Pulmonary Capacitance

Regardless of limitations, the need for estimating central hemodynamics is of the utmost importance in the proper assessment of cardiovascular function and disease progression. Pulmonary hemodynamics has a critical role and is of great clinical interest in various cardiac conditions such as right ventricular performance, congenital heart disease, cardiomyopathies and PH (39). Non-invasive measures of pulmonary gas exchange at rest and during exercise may be useful in elucidating altered pulmonary vascular pressures in patients with and without PH, including end-tidal CO_2 (P_{ETCO2}), and ventilatory efficiency (V_E/VCO_2) (17). Another common measure used to assess pulmonary hemodynamics is pulmonary vascular resistance (PVR) which has been shown to reflect small vessel resistance and pulmonary vascular cross-sectional area (39). A measure

that may assess medium and large pulmonary circulation, or account for pulsatile adaptation, is needed. Pulmonary capacitance has been associated with right ventricular work and assessment of clinical outcomes in COPD, PH and congestive HF (33, 35, 37, 38, 40). Pulmonary capacitance is expressed by the change in volume of blood to the change in pressure within the vessel (17, 39, 41).

$$PV_{CAP} = \text{Stroke Volume} / \text{Pulmonary Artery Pressure}$$

The distensability of the large and medium pulmonary arteries during right ventricular ejection is an important determinant of right ventricular work (16). Pulmonary capacitance may be an important factor and assessment tool influencing and predicting right ventricular function. Until recently, PV_{CAP} has necessitated invasive right heart catheterization to directly assess PV_{CAP} via pulmonary artery pulse pressure and SV (39). The aforementioned echocardiogram has also shown promise in non-invasive assessment of PV_{CAP}; yet again this technique has been unreliable, at times, and can only be performed at rest (16, 39). Venuta et al clearly states that “no current test is universally applicable (for assessing CF severity) in fact, even spirometry might well depict the status of one patient and in other cases may not determine a rapid fatal outcome” (16). It has been suggested that it be possible to estimate PV_{CAP} using non-invasive pulmonary gas exchange surrogates (17, 38). Oxygen pulse

(O_2 pulse) which is a correction for O_2 uptake for HR has correlated well with the SV response to exercise. While either SV or O_2 pulse is representative of blood volume coming from the heart; End- tidal CO_2 is thought to be a surrogate for pulmonary vascular pressure as there is a widening of the pulmonary arterials to differences in $P_{ET}CO_2$ providing presumably a significant limitation in forward flow of blood through the pulmonary vasculature. This alteration is not attenuated during exercise and is specific to the pulmonary arterial circulation as the alteration is secondary to the increase in left atrial and pulmonary venous pressure. (17, 38). End-tidal CO_2 has been shown to be sensitive enough to discriminate between differing severities within PH patients (38). Thus, this gas exchange estimate of pulmonary capacitance (GX_{CAP}) is expressed as:

$$GX_{CAP}\,(mL / BEAT \cdot mmHg) = \text{Stroke Volume}\,(mL) \cdot P_{ETCO2}\,(mmHg)$$

Gas exchange estimate of pulmonary capacitance has been shown to be useful in HF, PH and healthy subjects (17, 28, 38, 42). The method has also been shown to correlate well with the gold standard of invasive heart catheterization (17). Unlike echocardiography this methodology would allow for continuous measures at rest and throughout peak exercise allowing for differential assessment. However this method has not yet been elucidated in CF at any stage in the disease.

Thus, the aim of the present study was first to determine the effects of exercise on GX_{CAP} when compared to healthy subjects. Secondly, to ascertain whether a difference in GX_{CAP} between healthy and CF subjects remains when workload is matched to control for SV, which seems to weigh heavily into the equation for GX_{CAP} and is lower in patients with CF due to specific cardiac abnormalities.

CHAPTER 3. METHODOLOGY

Study Population

Data were collected at the University of Arizona and the study protocol was reviewed and approved by the University of Arizona Institutional Review Board (IRB). Additionally, the procedures followed in the study adhered to the University of Arizona's IRB, the declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA) guidelines. All subjects provided signed informed written consent prior to the initiation of the study protocol.

Seventeen mild to moderate CF patients, confirmed by a positive chloride sweat test (≥ 60 mmol/l Cl^-) were recruited through the University of Arizona respiratory Center and its affiliated CF Clinic. Seventeen matched control subjects were recruited via advertising posted at the University of Arizona campus, and by word of mouth. Subjects were matched for age, gender, height, weight and BMI (Table 1. Subject Demographics). Patients with CF were excluded if they exhibited a FEV_1 ≤40% predicted for their age, height, weight and gender, had experienced a pulmonary exacerbation within the last two weeks or a pulmonary hemorrhage in the six months prior to study (with a hemorrhage resulting in 50 cc of blood sputum). Subjects were also excluded if they were currently taking antibiotics or experimental drugs related to CF; these exclusion criteria ensured that CF patients within the study were clinically stable.

A urine-based pregnancy test was completed for female participants when applicable.

Population Subset

As a secondary study, a subset of the original subjects with CF were matched for similar workload and SV with healthy subjects. Matching these subjects resulted in 13 healthy normal control subjects and 9 CF patients.

Measurements

Rest

Upon arrival to the laboratory height and weight were obtained using a standard stadiometer and electronic scale. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared. Subjects were than outfitted with a 12-lead electrocardiogram (EKG) to monitor heart rate and rhythm (Marquette Electronics, Milwaukee, WI). Subjects then completed a full pulmonary function test (PFT) in accordance with American Thoracic Society (ATS) standards. From this maneuver it was possible to assess forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC, and forced expiratory flow at 25 to 75% of maximal effort (FEF_{25-75}). Prediction estimates for pulmonary function measures were calculated per subject from NHANES III equations (43).

Cardiac output was assessed utilizing the acetylene rebreathe method and SV was determined by dividing the measured Q by HR assessed via 12-lead EKG. The rebreathe technique involves the subject breathing through a mouthpiece attached to a non-rebreathing Y-valve via a pneumotachograph (Hans Rudolph, KC, MO). The Y-valve inspiration port is controlled by a pneumatic switching valve allowing for instantaneous conversion from breathing room air and re-breathing in a 5-liter anesthesia bag containing 0.7% C_2H_2, 9% helium, 0.03% carbon monoxide ($C^{18}O$) and balance nitrogen. Slope of the disappearance curve was calculated over ten breaths at rest and eight breaths during exercise to allow better toleration for the rebreathe method during exercise. Gases and inspiratory and expiratory flows were analyzed using a metabolic cart (Medical Graphics, St. Paul, MN) interfaced with a Perkins Elmer MGA-1100 mass spectrometer (Wesley, MN) for determination of gas concentration.

Exercise

All exercise testing took place on the same upright cycle ergometer (Corival Lode, The Netherlands). A subject specific testing protocol was utilized based on the type and intensity of the subject's self-reported normal physical activity regiment as well as their body size. The initial workload also served as

the amount of work increased during each progressive stage of the exercise testing protocol. Subjects were asked to maintain a pedal rate between 60 and 80 RPM. Workload was recorded throughout yielding watts (W), peak power, and allowing the percentage of max watts to be calculated from predicted equations. Failing to maintain a pedal rate of 60-80 RPM was a determinate of exhaustion. Other criterion for termination of the exercise test were a rate of perceived exertion (RPE) greater than 18 and a respiratory exchange ratio greater than 1.15. When two of these criteria were met or the subject requested to stop the test was concluded.

Statistical Analysis

SPSS version 21.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses. Results are expressed as mean $\pm$ standard error of the mean (SEM). An independent sample t-test was used to compare subject demographic characteristics. Independent sample t-test was also used to describe differences between resting and exercise measures as well as differences between control and experimental groups. Correlations were performed to allow interpretation of strength of GX_{CAP} to its component variables, SV and P_{ETCO2}. An alpha value of 0.05 was used to signify statistical significance. GX_{CAP} was calculated by the product of the average SV at the particular stage and the P_{ETCO2} among the same.

CHAPTER 4. RESULTS

Subject Characteristics

Healthy control and CF subjects were well matched within the study for all parameters other than lung function and exercise capacity, which were anticipated to be lower in CF. Seventeen control subjects and 19 CF subjects completed the study. There were no statistically significant anthropometric differences between the CF patients and healthy control subjects (Table 1).

To determine the weight of SV and to evaluate its impact and influence on GX_{CAP}, a population subset 13 healthy and 9 CF subjects were matched for exercise workload and SV. Healthy subjects again were well matched to CF subjects; age, height, weight and BMI. Cystic fibrosis subjects were not significantly different from the healthy controls with age, height, weight or BMI (Table 2).

Pulmonary Function

As would be expected, control subjects demonstrated greater values in all pulmonary function measures with the exception of FVC% (table 1).

Within the matched subjects there was no significant difference between healthy and CF in FVC or FEF_{25-75} percent predicted ($p > 0.05$). There was

however a significant difference in FEV_1 percentage between heathy subjects and CF patients respectively (Table 2).

Hemodynamics

At rest; SV was higher in healthy subjects compared to CF patients. GX_{CAP} was also higher in healthy subjects when compared to CF ($p<0.05$). However, P_{ETCO2} remained unchanged between the two study groups (Table 3).

During peak exercise, healthy subjects reached a higher absolute intensity. When absolute workload was expressed as a percentage of maximum however, there was no significant difference between healthy and CF (Table 1). Stroke volume and GX_{CAP} increased in both healthy and CF from rest to peak exercise but remained significantly higher in healthy subjects when compared to CF at peak workloads (SV = 108 ± 5 vs. 84 ± 6 ml, GX_{CAP} = 40 ± 3 vs. 29 ± 2, for healthy and CF, respectively ($p<0.05$) (Figure 1, 2). As in rest, at peak there was no significant difference in healthy and CF groups in P_{ETCO2} (34±1 and 35±1 respectively) (Figure 4). There was a strong positive correlation in both heathy and CF subjects between SV and GX_{CAP} (R^2 of .86 for healthy and .89 for CF, $p<0.05$) (Figure 3).

Within the population subset in which we sought to match SV there was a significant difference in absolute workload (Watts=72±6 vs. 90±4W CF and healthy subjects, respectively) but no difference in relative workload expressed as percentage of max wattage 63±4 %MaxW for CF and 66±5 %MaxW for their healthy counterparts (Figure 5). There was also no difference in Q or SV when CF and heathy subjects were matched respectively (Q 11±1 vs. 13±1L/min), or SV (89±4 vs. 90±4ml/beat) (Figure 6). Interestingly, when matched for SV, the previous difference in GX_{CAP} between the groups was abolished (GX_{CAP} for the healthy subjects =32±2 and CF subjects = 32±2 mL/BEAT · min, Figure 6). P_{ETCO2} remained similar between CF and healthy subjects when matched (P_{ETCO2} 36±1 and 35±1mmHg).

CHAPTER 5. DISCUSSION

The degree to which pulmonary vascular dysfunction occurs at rest and during exercise in CF remains unclear. The aim of the present study was to ascertain differences in pulmonary vascular distensability using non-invasive inert gas-exchange methodology. To accomplish this goal this study utilized well-matched CF and healthy control subjects to understand differences in PV_{CAP} associated with CF. Subjects shared basic anthropometric characteristics such as height, weight, and BMI. Both groups were also well matched in absolute and relative oxygen consumption as well as measures of pulmonary function at rest. Percent predicted values for CF subjects on pulmonary function maneuvers based on their height; weight and gender were relatively high; 83 percent predicted for FVC and 72 percent predicted for FEV_1. This indicates that CF patients within the study population were generally healthy compared to similar studies (3, 4, 12, 14, 16, 27). We found that patients with CF had a lower GX_{CAP}, when compared to healthy subjects, but that these differences were abolished in a subset of the population performing work that was matched for SV. These results suggest that the non-invasive GX_{CAP} estimate may not be accurate in CF, due to the heavy reliance on SV.

Pulmonary capacitance is a measure of the dispensability of the pulmonary arteries during right ventricular ejection and has been elucidated as an important metric in determining right ventricular work (17, 39, 41). The non-invasive measure used within this study has already been shown to be a

surrogate for PV_{CAP}, correlating well with direct measures within the catheterization laboratory in healthy subjects and patients with HF (17). Recently it has been suggested the PV_{CAP} is associated with right ventricular work and a better predictor of clinical outcomes than that of more established methods. Pulmonary capacitance has also been shown to correlate higher than PVR, pulmonary wedge pressure, and pulmonary artery pressure in predicting negative clinical outcomes in HF and PH (17, 39, 41). Pulmonary capacitances, as well as other central hemodynamic measures have been described previously in CF patients awaiting lung transplant or within the end-stages of the disease; however, little work has been accomplished in young, relatively healthy, stable CF (5, 23, 26). Similarly the same technique has been used to evaluate an estimate of PV_{CAP} within other diseased populations, such as PH and HF, but the present study is the first known use of this methodology in CF (17, 38). Within these other diseased populations the gas exchange estimate for pulmonary capacitance, $GX_{CAP,}$ has been shown to be sensitive enough to detect increases in this measure due to exercise as well as differentiate between disease severities. The GX_{CAP} measure may prove useful in future diagnosis as well as ascertaining disease progression and severity within study populations where central hemodynamic dysfunction occurs, however this did not hold true within our study population (17, 38). The ability of this surrogate measure to assess and differentiate disease severity within HF and PH, but not in CF, may be due to the preservation of EF within the CF patients (18, 21, 30, 33). Ejection fraction is the

quotient of blood ejected from the left ventricle during systole to the amount of blood left in the ventricle during diastole (45). Although there appears to be a reduction in SV among CF patients within this study, there may be a preservation of EF in the CF subjects which has been shown previously when compared to PH (30, 33).

Gas exchange estimate of pulmonary capacitance was utilized to assess cardiopulmonary hemodynamics at rest to peak exercise. This provides dynamic information not permitted with methods such as echocardiography, where exercise is an impossibility due to the need of a steady hand and a motionless patient. Exercise is also not well tolerated in methods such as the direct Fick or thermodilution, as invasive heart catheterization and multiple venous and arterial lines make exercise cumbersome and patients uneasy.

Initially, within the entire pool of subjects, there was a significant difference in SV between CF patients and healthy subjects at rest and at peak exercise. This has been described elsewhere within the research and is likely due to CFTR-specific effects on cardiac contractility (8, 21, 30). It was also evident that GX_{CAP} was significantly lower in patients with CF compared to their healthy matched counterparts. There was however, no significant difference in P_{ETCO2} leading to the assumption that this difference in GX_{CAP} was driven primarily by differences in SV. This offers evidence that there may be weaknesses within the

technique and that it may not provide accurate results in patients with CF. It has been suggested previously that P_{ETCO2} may provide insight into pulmonary vascular constriction or, inversely, dilation, and this provides the rationale behind the use of P_{ETCO2} as an estimate of pulmonary vascular conductance (17, 38). P_{ETCO2} has been shown here to be a poor predictor of pulmonary vascular pressure as well as shown no significant difference from peak to rest between healthy and CF subjects as well as provide no correlation to GX_{CAP}.

Despite our finding that there was no difference in GX_{CAP} it is clear that chronic inflammation leads to the remodeling of the pulmonary tissue, most notably the small blood vessels of the lung (4, 14) highlighting the need for more sensitive measures of pulmonary vascular function in patients with CF. The cycle of chronic inflammation coupled with infection, parenchymal fibrosis and bronchiectasis lead to the inevitable destruction of the lung tissue. Destruction and subsequent vascular remodeling is also compounded by hypoxic pulmonary vasoconstriction leading to increasing vascular resistance and ultimately irreversible PH (1, 3, 12, 38). However, why the venous portion of the pulmonary vasculature seems immune to this remodeling and why some patients develop PH and others do not have yet to be explained. Studies in other disease states with progressive respiratory failure have demonstrated that right HF is inevitable; this too may be true of CF as the patient's life expectancy lengthens. Although not a focus of this study, previous work has shown an abnormal hemodynamic

response apparent in CF during exercise, as well as an increase in mean pulmonary artery pressure and decreased EF (3, 18).

The GX_{CAP} estimate of pulmonary vascular pressure assumes that the pulmonary vasculature dilates in response to increases in SV. However, in patients who experience chronic hypoxic pulmonary vasoconstriction, there may be an opposing mechanistic narrowing of the pulmonary vascular bed in response to hypoxia. Therefore, the GX_{CAP} equation may not be reliable in CF as the equation may be confounded by this vasoconstriction. The need for a more comprehensive equation may be warranted that accounts for variables. An equation that accounts for Q, SV and perhaps diffusion for carbon dioxide to ascertain membrane conductance (Dm) and pulmonary capillary blood volume (Vc).

Potential limitations of the following study are due to the size and disease severity of our CF population. CF subjects were on the healthy end of the disease spectrum representing a wide variety of disease severity; that coupled with the small sample size left no room for stratification of the disease (i.e. mild, moderate and severe disease states). It has been shown that central hemodynamic dysfunction may only be apparent in end stage CF, warranting further study into central hemodynamic changes in different stages of the disease progression.

CHAPTER 6. CONCLUSION

This is the first known study of healthy, stable, CF central hemodynamics utilizing inert gas exchange to estimate pulmonary capacitance. We initially found that GX_{CAP} was reduced at rest and at peak exercise; it was however evident that this difference was driven by differences in SV between healthy subjects and CF patients. We sought to match subjects and patients via workload and therefore SV; when matched the apparent difference in GX_{CAP} was ameliorated. The GX_{CAP} equation was found to poorly predict pulmonary vascular pressure, leading to the realization that there may be better predictors of central hemodynamic dysfunction. Weakness in the equation not previously identified in other diseased populations may be elucidated in CF. Future work is required in developing simplistic, reliable, valid and non-invasive clinical measures for the assessment for PV_{CAP}. Work is also warranted to shed light on cardiac and pulmonary vascular dysfunction in multiple stages of disease progression in CF as patients experience increased longevity.

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CHAPTER 8. TABLES AND FIGURES

Table 1. Demographic Characteristics: Unmatched

	Rest		Peak	
	Healthy	CF	Healthy	CF
Sample Size	17	19		
Age (yrs.)	22 ± .585	22 ± 1.7		
Height (cm)	171 ± 2	167 ± 2		
Body Mass (kg)	68 ± 2	63 ± 4		
BMI ($kg \cdot m^2$)	23 ± .5	23 ± 1		
VO_2 (mL/Kg/min)	6 ± 2	6 ± 2	35 ± 11	24 ± 9*
Peak Power (W)			185 ± 65	101 ± 35
% of Max (W)			96 ± 31	52 ± 15
FVC (%)	93 ± 3	83 ± 5	4 ± 1	3 ± 1
FEV_1 (%)	89 ± 2	72 ± 6	4 ± 1	3 ± 1
FEV_1/FVC	.81 ± .02	.72 ± .03*	1 ± .07	1 ± .09

(mean ± standard error of the mean)

BMI (body mass index), VO_2 (oxygen consumption), FVC (forced vital capacity), FEV_1 (forced expiratory volume in one second).

* demonstrates significance differences between healthy and CF subjects at $\alpha <$ .05

Table 2. Demographic Characteristics: Matched

	Healthy	CF
Sample Size	13	9
Age (yrs.)	28 ± 10	22 ± 9
Height (cm)	168 ± 10	170 ± 7
Body Mass (kg)	70 ± 16	66 ± 17
BMI ($kg \cdot m^2$)	25 ± 5	23 ± 4
FEV_1 (%)	93 ± 11	85 ± 19 *
FVC % Predicted	92 ± 8	95 ± 13
FEF_{25-75} % Predicted	94 ± 17	68 ± 31

(mean ± standard error of the mean)

FEF_{25-75} (forced expiratory at 25-75% of volume)

* demonstrates significance differences between healthy and CF subjects at $\alpha <$ .05

Table 3. Exercise Performance: Matched

	Healthy	CF
Sample Size	13	9
Work (W)	90 ± 16	72 ± 18 *
% of Max (W)	66 ± 18	63 ± 13
VO_2 (L/min)	5 ± 2	7 ± 2
VO_2 (ml/kg/min)	23 ± 6	19 ± 3
VO_2 % Predicted	83 ± 22	53 ± 27
VCO_2 (mL)	1276 ± 345	1227 ± 454
SV (mL)	90 ± 4	89 ± 4
P_{ETCO2} (mmHg)	36 ± 3	34 ± 3
$GX_{CAP\ (mL/BEAT \cdot mmHg)}$	18 ± 5	21 ± 7

(mean ± standard error of the mean)\

W (watts)

* demonstrates significance differences between healthy and CF subjects at α< .05

Figure 1. Stroke Volume at Rest & Peak Exercise: Unmatched

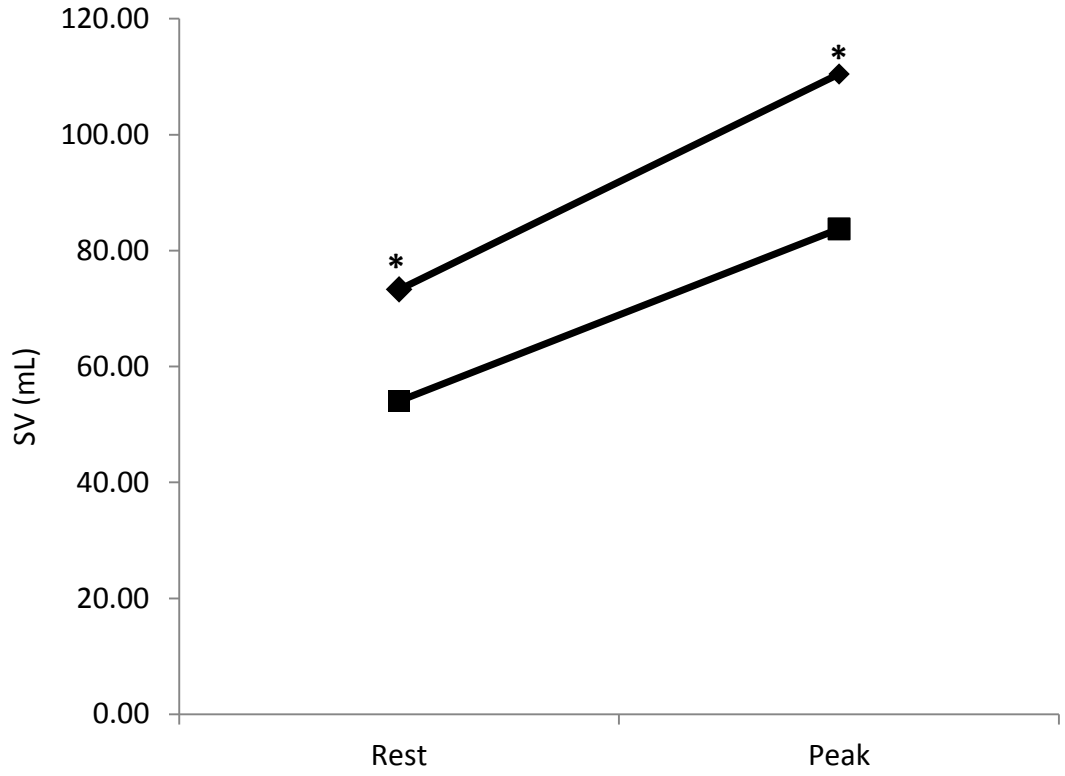


Figure 1 Shows similar decrease in SV in CF as well compared to healthy counterparts; significant at α=.05

* demonstrates significance differences between healthy and CF subjects at α< .05

Figure 2. GX_{CAP} at Rest & Peak Exercise: Unmatched

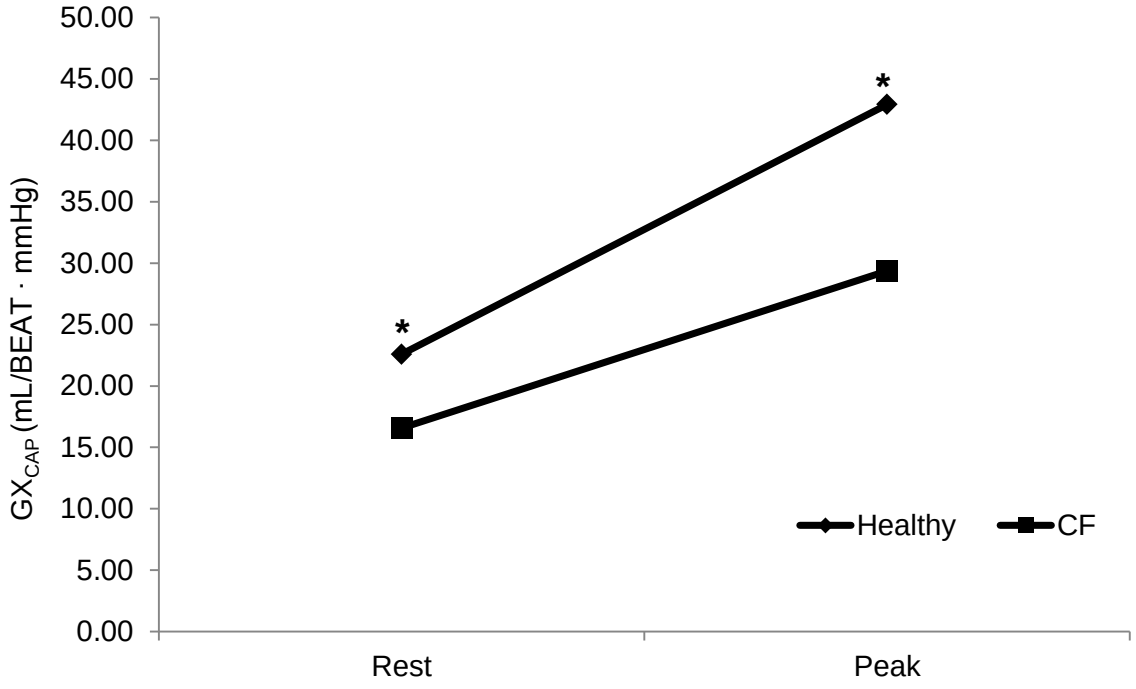
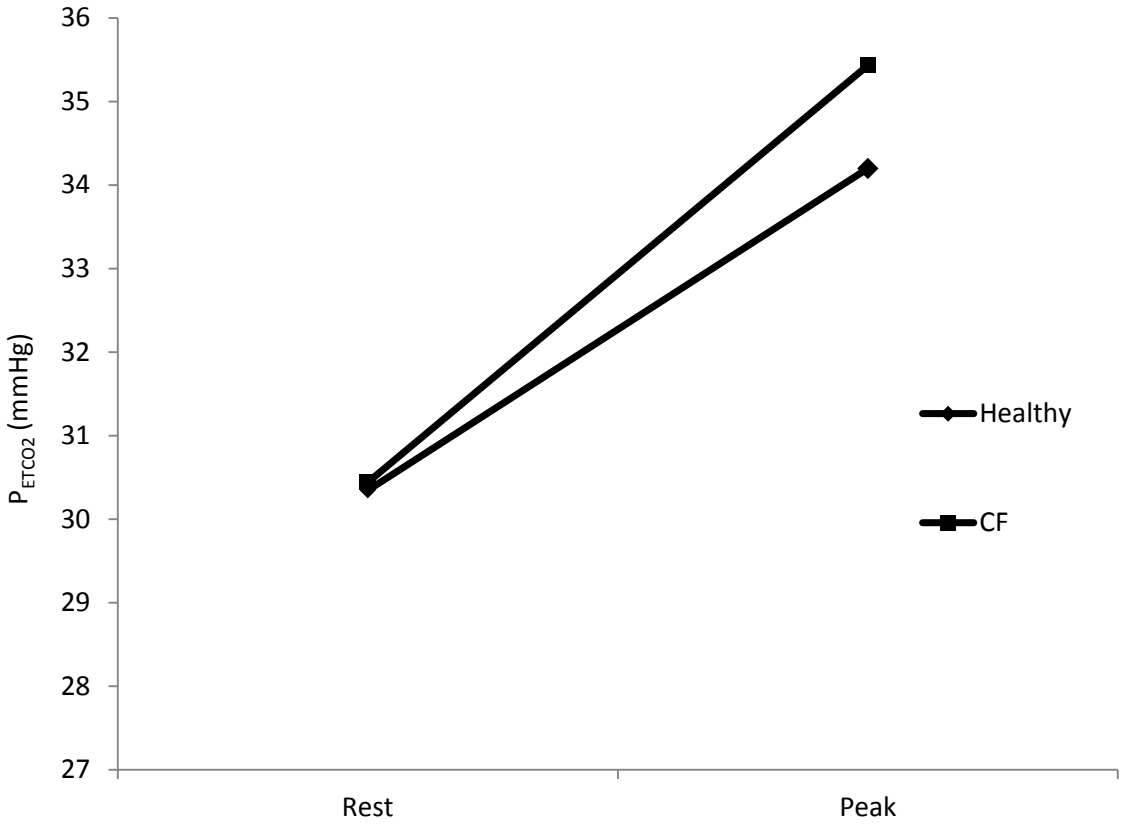


Figure 2 Shows decreased GX_{CAP} in CF compared to healthy subjects.

* demonstrates significance differences between healthy and CF subjects at α< .05

Figure 3. P_{ETCO2} at Rest & Peak Exercise: Unmatched



There was no significant difference between Healthy and CF P_{ETCO2} (30 and 30 mmHg) at α=.05.

Figure 4. Healthy and CF SV to GX_{CAP} Correlations: Unmatched

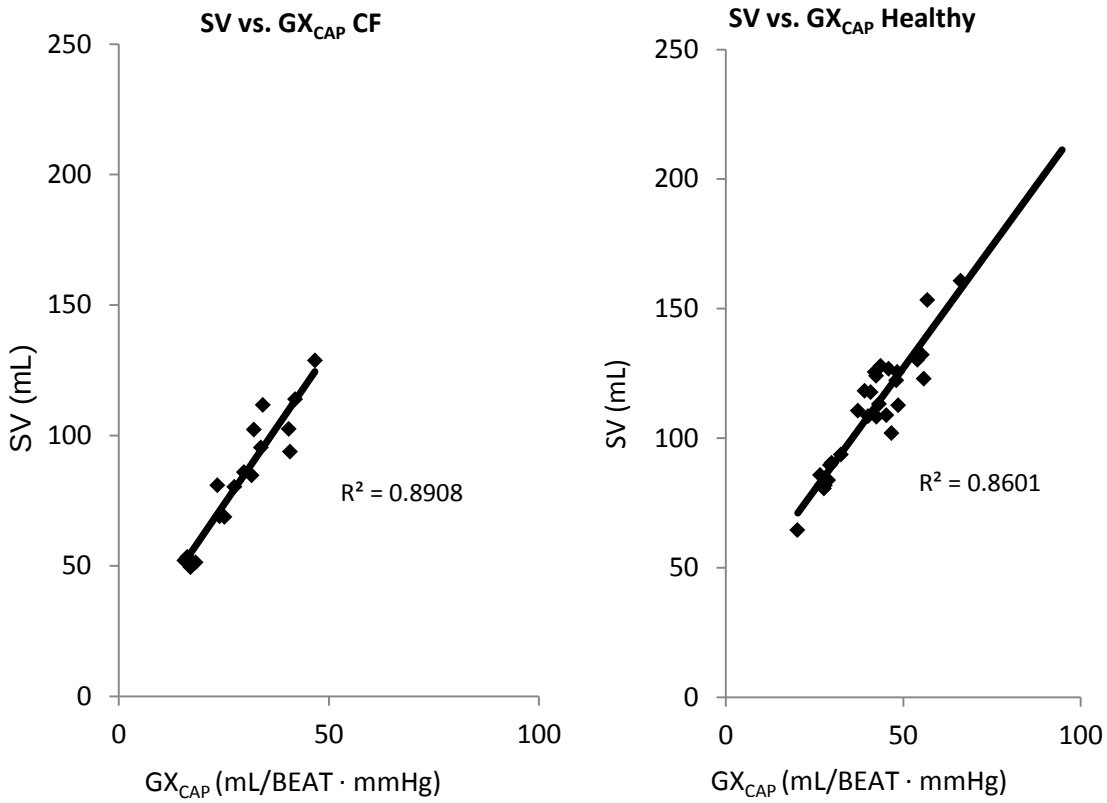
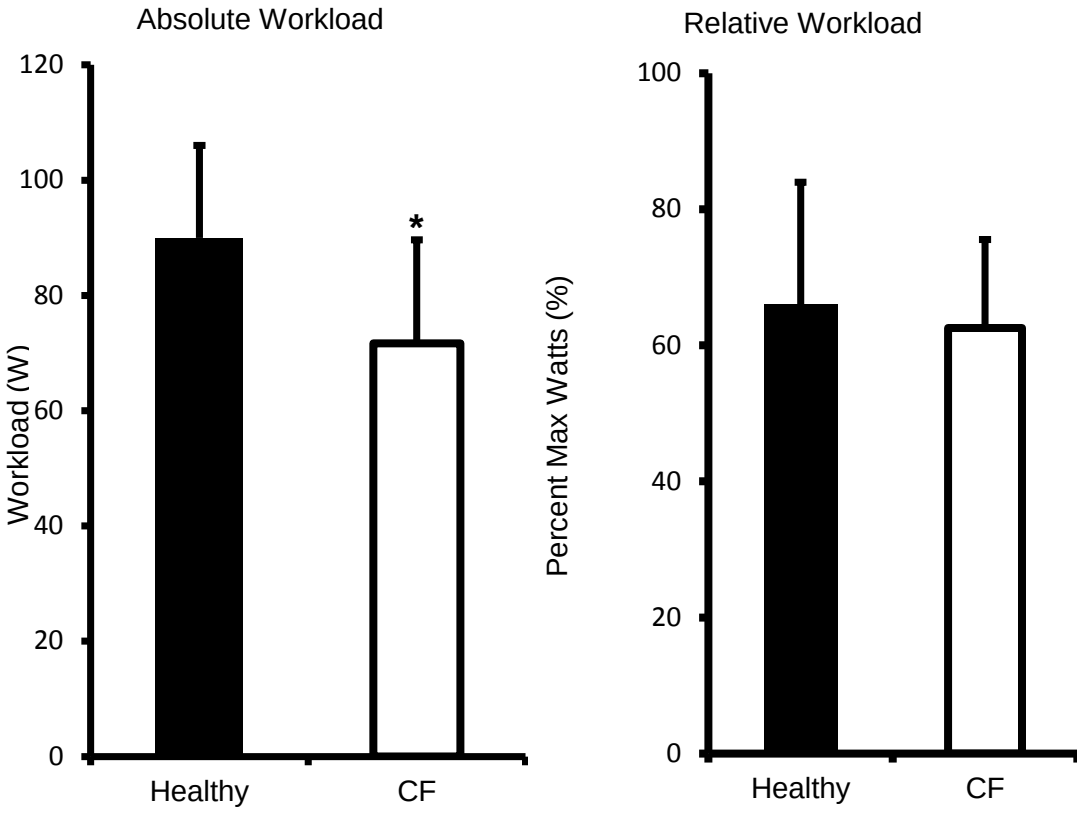


Figure 3: SV and GX_{CAP} were highly correlated at an R^2 of .89 and .86 for CF and healthy subjects respectively.

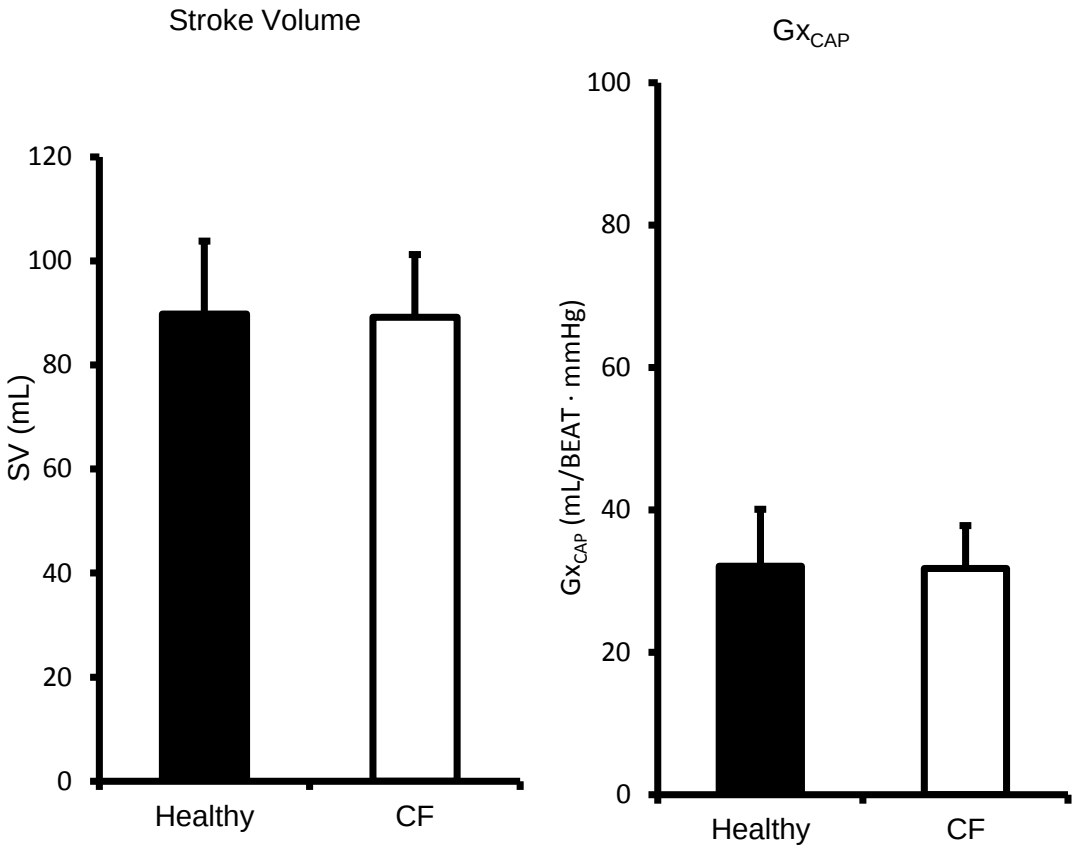
Figure 5. Absolute & Relative Workload for Healthy & CF: Matched



When matched for relative workload (~65% peak workload), CF subjects worked at a significantly lower absolute workload.

* demonstrates significance differences between healthy and CF subjects at α< .05

Figure 6. Stroke Volume & GX_{CAP}: Matched



When matched for relative workload and therefore stroke volume, GX_{CAP} was statistically similar between healthy and CF subjects.