The Relationship between Cardiac Hemodynamics and Exercise Tolerance in Cystic Fibrosis

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Abstract

Background—Individuals with cystic fibrosis (CF) have reduced pulmonary function and exercise tolerance. Additionally, these individuals may develop abnormal cardiac function. The implications of abnormal cardiac function on exercise tolerance are unclear in CF.

Objective—Study relationships between exercise cardiac hemodynamics and exercise tolerance in CF.

Methods—17 CF and 25 controls participated in cardiopulmonary exercise testing to measure exercise duration and peak workload (PW). Cardiac index (Q_I) was measured using acetylene rebreathe and oxygen uptake (VO_2) breath-by-breath. Forced expiratory volume 1-second (FEV_1) was performed at rest.

Results—Peak Q_I was 6.7 ± 0.5 vs. 9.1 ± 0.3 mL/min/m^2, CF vs. controls, respectively ($p < 0.05$). Linear regressions between Q_I ($R^2 = 0.63$ and 0.51) and exercise duration or PW were stronger than VO_2 ($R^2 = 0.35$ and 0.37) or FEV_1 ($R^2 = 0.34$ and 0.36) in CF, respectively ($p < 0.05$).

Conclusion—These data are clinically relevant as they suggest attenuated cardiac function in addition to low airway function relate to exercise tolerance in CF.

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Keywords

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Introduction

Cystic fibrosis (CF) is an autosomal recessive disease affecting >30,000 individuals in the United States with an estimated median survival age of 37 and 40 years in females and males, respectively.[1, 2] This disease is caused by gene mutations leading to absent or misplaced CF conductance transmembrane regulator (CFTR) that affects chloride (Cl^-) transport as well as attenuated inhibition of epithelial Na^+ channels (ENaC) at the apical epithelial membrane layer of airway, intestinal, and exocrine cells.[1, 3, 4] The most commonly recognized location of abnormal CFTR and ENaC in CF is the pulmonary system that eventually gives way to diminished global airway function.[2, 4] This reduction in airway function has been traditionally suggested to be the primary contributor to reduced exercise tolerance in these individuals.[5-7]

Several studies suggest attenuated exercise tolerance in CF occurs because of central mechanisms related to abnormal airway function that causes an inability to deliver oxygen-rich blood to metabolically active muscle.[5, 6, 8-13] For example, it has been observed that dysregulated movement of Cl^- and Na^+ within lung epithelial tissue leads to airway obstruction and increased work of breathing caused by inadequate ventilation and oxygen reaching the alveoli.[8-12] Further exacerbating this condition, it is suggested that of the ventilated alveoli, reduced structural integrity of the alveoli-capillary membrane layer may attenuate free diffusion of oxygen into perfused pulmonary capillaries resulting in ventilation—perfusion mismatch and dead space perfusion.[14] Thus, it is through reductions in gas-transfer and ventilatory function that the pathophysiology of low exercise tolerance has been traditionally viewed in CF.

A large body of evidence in CF suggest disease severity is most closely linked to performance on resting pulmonary function tests (e.g., forced vital capacity [FVC] or forced expiratory volume in 1-second [FEV_1][2, 4]); whereas, to a lesser extent, it is becoming more recognized that low exercise tolerance is also related to prognosis in these individuals.[5-7] However, despite the knowledge of both poor airway function and low exercise tolerance in CF, there is no clearly established direct mechanistic link between reduced airway function and low exercise tolerance in this population. Therefore, it remains possible that pathology in addition to airway dysfunction may contribute to reduced exercise tolerance in CF.

A small number of studies have examined the possibility of abnormal cardiac function with respect the implications this could have in individuals with CF. Among those studies, it has been demonstrated that Cl^- movement associated with functional CFTR in cardiac myocytes may directly contribute to increased myocardial contractility resulting from stimulation (e.g., via isoproterenol) of linked β-adrenergic receptor and cyclic adenosine monophosphate pathways in mouse models.[15, 16] Whereas, others demonstrate from results of histochemical analyses of human myocardial tissue that CFTR represented by transport protein ABCC7 is

nearly completely absent in left ventricular tissue of end-stage heart failure patients compared to individuals with non-failing hearts.[17] The relevance of those data are noteworthy as it has been observed in human studies of CF that left ventricular strain using echocardiography (i.e., inotropy)[18] and cardiac hemodynamic responsiveness to inhalation of the selective β_2-agonist albuterol are attenuated in CF.[19] However, despite these and several other findings in CF, to date, it is unclear what clinical implication abnormal cardiac function in the setting of known airway dysfunction is in CF.[14-24] Comprehensive clinical phenotyping of CF to include an integrative cardiopulmonary understanding of this disease should enhance approaches to develop and deliver targeted novel therapeutic care for these individuals. The consideration of abnormal cardiac function in CF could be important since the lifespan of these individuals is increasing,[25] whereas there is an increased cardiovascular and heart disease risk in adults >40 years, which can be predicted by exercise tolerance.[26-28]

Therefore, because decreased myocardial contractility in CF cannot be predicted by the magnitude of resting pulmonary dysfunction,[18, 23] measures more closely reflecting the physiologic response to exercise, such as exercise cardiac hemodynamics, may demonstrate stronger relationships with exercise tolerance compared to resting pulmonary function in CF. The aim of this study was to test the hypothesis that there is a direct relationship between cardiac hemodynamics and exercise tolerance in CF. Changes in total exercise duration and peak exercise workload (PW) (measures of exercise tolerance) are known to be influenced by adjustments in both oxygen uptake (VO_2) and cardiac function in cardiovascular patients.[29, 30] Greater relative change in VO_2 compared to cardiac hemodynamics from rest to peak exercise would further support our hypothesis that low exercise tolerance in individuals with CF is related to an attenuated rise in cardiac hemodynamics relative to the total duration of exercise and PW.

Material and Methods

Participants

Individuals with CF or healthy individuals serving as controls (CTLs) who volunteered for this study were part of a convenience sample (characteristics, Table 1). Participation of individuals with CF mainly came from provider referrals from a nearby clinic that provided care for individuals with CF. Individuals with CF had mild- to- moderate disease, confirmed by a positive Cl⁻ sweat test (60.0 millimole/L Cl⁻) and genotyping of the F508 mutation of CFTR, which is the most common genotype (∼70% of CF population) of the 1000+ possible genotypes associated with this disease.[31, 32] Exclusion criteria included: 1) experienced a pulmonary exacerbation within the last two weeks or pulmonary hemorrhage within six months resulting in greater than 50 cc of blood in the sputum, 2) taking any antibiotics for pulmonary exacerbation, or 3) taking any experimental drugs related to CF. Participation from CTLs came from word of mouth and flyers posted around the University campus. Controls were of moderate fitness, suggested by percent of predicted peak VO_2 for healthy individuals[33]. Additional exclusion criteria for CF, while also applying to CTLs included: 1) history of hypertension, cardiac, metabolic, neurologic, orthopaedic, or other diseases affecting the neuromuscular system, 2) history of smoking, or 3) those who were not able to engage in exercise (e.g., known orthopedic limitations or musculoskeletal

disorders). The protocol was reviewed and approved by the University Institutional Review Board. All participants provided written informed consent prior to study.

The use of a convenience sample in this study that was not matched on body anthropometry is consistent with previous studies in CF, as these individuals are recognized to demonstrate smaller body stature (e.g., weight, body mass index, body surface area) due to nutritional deficiency associated with this disease.[8, 11, 18, 20, 21] Moreover, matching groups on pulmonary function tests generally cannot be accomplished as healthy individuals serving as CTLs would not be expected to demonstrate airway function similar to CF at any age. However, with regard to testing our primary study outcome, the N for each group based on computed effect sizes[34] met appropriate power calculations >0.80 and >0.70 for testing relationships between cardiovascular or airway function with exercise tolerance in both CF and CTLs, respectively.

Overall Protocol

The following procedures were performed before and/or during incremental cardiopulmonary exercise testing (CPET) on a stationary upright cycle ergometer (Corival Lode B.V., Netherlands) on a single testing day in an environmentally controlled physiological laboratory.

Upon arrival to the testing lab, participants were fitted with a 12-lead electrocardiogram (Marquette Electronics, Milwaukee, WI) to continuously monitor heart rate (HR) and rhythm, while resting pulmonary function tests according to American Thoracic Society standards were performed.[35] Next, participants performed resting measures of cardiac output (Q), VO_2, carbon dioxide production (VCO_2), respiratory rate (RR), tidal volume (V_T), minute ventilation (V_E), and end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$).

Cardiopulmonary exercise testing—Peak exercise VO_2, total exercise duration, and PW were determined from symptom limited CPET performed according to guidelines of the American Thoracic Society.[30, 36] This test consisted of 3 minute stages whereby the increment of workload increase ranged from 15 to 40 watts (mean initial workload was 24±1 vs. 33±1 watts for CF vs. CTLs, respectively; p<0.05) determined using each individual's body surface area (BSA) and type and intensity of the individual's typical pattern of physical activity recorded using an exercise vital sign questionnaire instrument.[30, 36, 37] Participants were asked to maintain a pedal rate between 60 and 80 revolutions/minute until volitional fatigue.

During CPET, breath-by-breath ventilation (Medical Graphics CPX/D, St. Paul, MN) was continuously monitored and averaged every three seconds at rest and throughout exercise. For analyses, indices were calculated as averages of 30 second intervals at the end of each exercise stage. Cardiac output was measured within the final 30 seconds of each exercise stage. Pulse oximetry via finger sensor (Nellcor N-600 Pulse Oximeter, Boulder, CO) was used to estimate peripheral oxygen saturation percentage. At rest and near the end of each exercise stage, manual sphygmomanometry was used to assess systolic (SBP) and diastolic (DBP) blood pressures, and rate of perceived exertion (RPE, 6 to 20 Borg scale) was also assessed.

The following were calculated at rest and at peak exercise: mean arterial pressure (MAP=DBP+1/3(SBP−DBP)); arterio-venous oxygen content difference ($C_{a-v}O_2$=(VO$_2$/Q$_I$)/10); stroke volume (SV=Q/HR). Cardiac output and SV were indexed to BSA because abnormal deviations in overall body size are known to influence comparisons of exercise measurements of cardiac hemodynamics (Q$_I$ and SV$_I$, respectively),[38] which is relevant to this study since CF are known to have abnormally low body size.[39] Reserve measures for Q$_I$, SV$_I$, and VO$_2$ were calculated as the percent (%) change at peak exercise from resting values.

Measurement of cardiac output using inert gas breathing

Inert gas breathing using the CO_2 rebreathe method during exercise has been previously validated in CF,[21] whereas nitrous oxide rebreathing has been validated in other patients with lung disease.[21, 40] These gases have lower blood solubility and, hence, are less sensitive to pulmonary blood flow (i.e., Q) compared to acetylene gas that is used in this study.[41]

Measurement of Q occurred near the end of each exercise workload using the acetylene rebreathe technique as described by our group in a separate study design.[42] Briefly, participants breathed through a pneumotachometer (Hans Rudolph, Kansas City, MO) that was connected to a non-rebreathing automatic pneumatic switching Y-valve (Hans Rudolph, Kansas City, MO), which was integrated to a mass spectrometer (Perkin Elmer MGA-1100, Wesley, MA) for continuous gas sampling analysis. The inspiratory port of the switching Y-valve allowed for rapid switching between breathing room air and the 5.0 L anesthesia rebreathe bag (Hans Rudolph, Kansas City, MO) containing 1.0 to 3.5 L of test gas (0.65% acetylene [C_2H_2], 9.0% helium [He], 55.0% nitrogen, and 35.0% O$_2$ depending on initial V$_T$ of the subject as described previously.[42]

High blood solubility acetylene disappears in mixed venous blood in a direct relationship with the rate of pulmonary capillary blood flow.[42, 43] Therefore, Q can be calculated via the rate of disappearance of acetylene with each breath determined from the slope of the exponential disappearance of acetylene with respect to the insoluble gas He.[42, 43]

Statistical analyses

Parametric data are presented as mean ± standard error of the mean (SEM). Homogeneity of data variance was assessed using Levene's test. Wilcoxon rank-sum tests were used to compare continuous variables between groups, whereas categorical variables were compared using χ^2-tests. Within group differences rest to peak exercise were assessed using paired Student's t-tests, or one-way ANOVA with Bonferroni post-hoc correction for comparisons of reserves.

Ordinary least squares regressions with coefficient of determination (R^2) and 95% confidence limits (CL) via univariate modeling were used to explain variance between FVC (rest), FEV$_1$ (rest), VO$_2$ (peak exercise), SV$_I$ (peak exercise), or Q$_I$ (peak exercise) with total exercise duration or PW. Interpretation of R^2 from regression models were based on calculated power and effect size standards of Cohen equal to:[34] modest = 0.02, moderate = 0.15, and strong 0.25. Step-wise linear regression model analyses were also used to assess which variables out of FVC (rest), FEV$_1$ (rest), VO$_2$ (peak exercise), HR (peak exercise),

SV_I (peak exercise), or Q_I (peak exercise) predicted total exercise duration or PW best. Entrance into the step-wise model required variables to reach an alpha set at 0.15, whereas to remain in the model, variables had to reach an alpha set at <0.05. For all other testing, two-tailed significance was determined using an alpha set at 0.05. Computations were made using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, North Carolina).

Results

Participants

All 42 participants in this study completed CPET without adverse events. Shown in Table 1, the sample size for CF compared to CTLs did not differ significantly (N = 17 vs. 25, $P =$ 0.22). Individuals with CF were of similar age compared to CTLs (mean: 23±2 vs. 27±2 years, respectively; $P =$ 0.17). Sex distribution between CF and CTLs did not differ significantly (male/female: 13/4 vs. 15/10, respectively, $P =$ 0.27). Individuals with CF had lower body weight and BSA (CF = 1.7±0.0 vs CTLs = 1.9±0.0 m^2, $P =$ 0.01) compared to CTLs. Airway function was significantly lower in CF compared to CTL. Percent achieved of predicted peak VO_2 was significantly lower in CF compared to CTLs.[33]

Resting and CPET cardiovascular and ventilatory responses

Table 2 shows that individuals with CF demonstrated significantly lower HR, SV_I, Q_I, and SaO_2 compared to CTLs at rest. In contrast, RPE, VO_2 (adjusted for body weight), VO_2, VCO_2, RR, V_E, V_T, $P_{ET}CO_2$, $C_{a-v}O_2$, SBP, DBP, and MAP were similar between groups.

At peak exercise, individuals with CF demonstrated significantly lower PW and total exercise duration compared to CTLs (Table 2). However, RPE in CF was equivalent to CTLs. Additionally, out of all the cardiovascular and ventilatory variables measured at peak exercise, Q_I, VO_2 (adjusted for body weight), VO_2, VCO_2, V_E, V_T, and SBP were significantly lower in CF compared to CTLs.

Reserve cardiovascular and ventilatory responses

Illustrated in Figure 1 are SV_I, Q_I, and VO_2 reserves (% increase from rest to peak exercise). Between group differences were not significant for SV_I ($P =$ 0.16), whereas CTLs had higher Q_I ($P =$ 0.01) and VO_2 ($P <$ 0.001) reserves compared to CF. In both CF and CTLs, there were within group differences between SV_I, Q_I, and VO_2 reserves. In particular, there were significant differences between SV_I and VO_2 (CF, $P <$ 0.001; CTLs, $P <$ 0.001), SV_I and Q_I (CF, $P <$ 0.001; CTLs, $P <$ 0.001), and Q_I and VO_2 (CF, $P <$ 0.001; CTLs, $P <$ 0.001).

Predictors of exercise tolerance

Presented in Figure 2, there were significant relationships for FVC and FEV_1 with both total exercise duration and PW in CF, which were stronger in CTLs. Power for each relationship test exceeded 0.80 for both CF and CTLs.

Illustrated in Figure 3, there were strong relationships between total exercise duration or PW and VO_2 (peak exercise), SV_I (peak exercise), or Q_I (peak exercise) in CF. In contrast, these

same relationships ranged from moderate to strong in CTLs. The power for all relationships in CF were >0.80, and >0.70 in CTLs.

All univariate linear regressions (R^2 values) in Figures 2 and 3 remained within the 95% CL of one another for both groups. Therefore, upon further testing, step-wise linear regression analyses considering FVC (rest), FEV_1 (rest), VO_2 (peak exercise), HR (peak exercise), SV_I (peak exercise), or Q_I (peak exercise) for each group was performed (Table 3 and 4 for CF and CTLs, respectively). The step-wise model for total exercise duration for CF resulted in a single step where Q_I entered and stayed in the final model. In contrast, the exercise duration step-wise model for CTLs included seven steps, which resulted in the greatest amount of the model variance being explained by FVC, SV_I, and Q_I.

The step-wise model for PW in CF resulted in two steps resulting in a final model that included SV_I and HR as significant predictors. In contrast, the step-wise model for PW in CTLs included three steps, with FVC, VO_2, and HR remaining as the strongest predictors of PW.

Discussion

In this study our group demonstrates for the first time that Q_I and SV_I responses at peak exercise directly relate with total exercise duration and PW associated with CPET in individuals with CF. Traditional resting measures of FVC and FEV_1, which are commonly used to assess CF prognosis,[2, 4] did not show relationships with total exercise duration or PW that exceeded the strength of peak exercise Q_I and SV_I in individuals with CF. Additionally, despite peak VO_2 relating to prognosis and commonly used to estimate exercise tolerance in CF,[5-7] peak VO_2 in this study did not predict either total exercise duration or PW when considered in parallel with cardiac hemodynamics and pulmonary function measures in CF.

The relationships observed between peak exercise Q_I and SV_I with both total exercise duration and PW in this study supports results from previous studies showing that abnormal cardiac function is present at rest in individuals with CF.[18-20, 22, 23] However, in extending those observations, this study demonstrates abnormal cardiac function persists during exercise and is strongly related to exercise tolerance in CF. These data provide critical insight concerning the potential importance of evaluating cardiac function during exercise to improve the pathophysiologic understanding of low exercise tolerance in individuals with CF. This is relevant because as the lifespan of individuals with CF increases, with the median age of survival estimated at 37 and 40 years in men and women, respectively,[1, 2, 25] it is also important to recognize that the risk for cardiovascular and heart disease increases at ages >40 years, with exercise tolerance serving as a primary factor in predicting disease prognosis.[26-28]

Cardiac hemodynamics and exercise tolerance in CF

Cystic fibrosis is a genetic disease impairing the normal expression of CFTR while affecting multiple organ system function.[1, 3, 9] This disease is traditionally associated with deranged ion regulation within the pulmonary system, leading to a phenotype of perpetual ventilation

and gas exchange dysfunction with hallmark signs and symptoms, including low FEV_1 and reduced exercise tolerance.[1, 4, 8, 10, 14] In this light, although the underlying mechanisms remain unclear, FEV_1 has been demonstrated to be a strong correlate of exercise tolerance in CF, and therefore the traditional paradigm for low exercise tolerance in CF has centered on understanding pathophysiology related to airway dysfunction.[8, 10, 11] However, in considering only low airway function as an explanation for attenuated exercise tolerance, this may greatly underestimate the overall integrated influence that cardiac and pulmonary systems share during exercise (e.g., ventilation—perfusion matching). Despite showing in this study the presence of pulmonary dysfunction in CF that is consistent with the findings of others,[8, 10, 11] these data underscore the need to assess both pulmonary and cardiac function to determine exercise tolerance meaningfully. The present study further demonstrates that peak exercise cardiac performance, but not VO_2, is a strong determinant of total exercise duration and PW in individuals with CF. This is also an important finding because it demonstrates that a high or low VO_2 in addition to abnormal airway function do not necessarily imply exercise tolerance in CF.

Our observation that peak Q_I and SV_I are lower in CF compared to healthy individuals is consistent with Koelling et al.[20] who also shows abnormal cardiac function is present during exercise in individuals with CF. Furthermore, and although studied at rest, Sellers et al.[18] demonstrates that left ventricular strain (i.e., inotropy) is reduced in individuals with CF. Whereas Van Iterson et al.[19] shows stimulation of β_2-adrenergic receptors (i.e., inotropy) via inhalation of the selective β_2-agonist albuterol results in attenuated increases in Q_I, SV_I, cardiac power, and stroke work in CF compared to healthy individuals. It is therefore not surprising that while also demonstrating evidence of impaired cardiac function in CF, Ionescu et al.[22] suggests there may be a link between cardiac and pulmonary function in CF. Those authors present evidence suggesting that the magnitude of right ventricular dysfunction is associated with disease severity measured by airway function in CF.[22] Lastly, in a separate clinical population who are known to demonstrate concurrent cardiac and pulmonary impairment (i.e., heart failure), Solbach et al.[17] for the first time observed that expression of protein transporter ABCC7 (representing CFTR) in left ventricular tissue of end-stage heart failure patients is nearly entirely absent compared to expression of ABCC7 in left ventricular tissue of healthy individuals. The connection of those findings in heart failure patients with individuals with CF is unknown, but suggests a potentially critical role for the expression of myocardial CFTR in contributing to normal cardiac function in CF.

Clinical implications

Cystic fibrosis is well-recognized to have debilitating effects on pulmonary function and exercise tolerance.[4-7, 9-11] The measurement of airway function at rest to predict prognosis is an extremely useful tool in this population.[2, 4] However, although smaller in number, a growing body of evidence suggests cardiac function as it relates to hemodynamically challenging settings such as exercise, may also be indicative of CF disease severity.[14, 19-23] The abnormal rise and reduced Q reserve may reflect the severity of integrated cardiopulmonary dysfunction, which is likely to coincide with poor performance on other traditional assessments that are already used in the clinical setting (i.e., pulmonary function tests). The quantification of Q at rest and/or during exercise does not need to take on an

invasive and technically challenging approach in the clinical setting. Several studies in patients with pulmonary diseases show Q can be measured using noninvasive techniques that agree with direct measurement standards.[21, 40, 44] This study in addition to others show inert gas breathing may be an efficacious option for Q measurement in patients with obstructive lung diseases (e.g., CF and chronic obstructive pulmonary disease), whereas others show that imaging techniques such as echocardiography may also be used to assess several aspects of cardiac function in addition to Q in CF (e.g., myocardial strain).[14, 18-23, 40, 44] These and other (e.g., arterial waveform analysis[45]) technical approaches for the non-invasive measurement of Q can be readily available in the clinical setting without the need for intensive external expertise and training such as is needed for thermodilution or direct Fick measurements of Q. Additionally, implementation of CPET can be performed efficaciously using several approaches that have been well-studied and may be more practical than walking tests for individuals with CF who may demonstrate abnormal gait during walking due to skeletal muscle weakness.[30] Thus, because of the new findings in this study, in addition to those previously showing the importance of exercise tolerance and abnormal cardiac function in CF,[5-7, 14, 18-23] assessment of cardiac function during CPET may be an important clinical care aspect that should be considered in the therapeutic approach for individuals with CF.

Limitations

Individuals participating in this study were of a convenience sample that did not include a balanced comparison of participants across groups. However, the imbalanced sample size of groups and comparisons performed in this study are consistent with other studies in CF.[8, 11, 18, 20, 21] To match body anthropometry and airway function between CF and CTLs is challenging as the phenotype of CF inherently includes abnormally low body size due to nutritional deficiencies associated with this disease, in addition to the well-known airway limitations.[39] Therefore, it is uncommon to find healthy individuals to serve as CTLs that could readily match CF on baseline demographics and airway function. Moreover, had groups been matched according to absolute workload for CPET, the CTL group would have been performing cycling at much lower exercise intensities leading to long duration tests not reflective of a true CPET.[30] Nevertheless, our assessment of cardiovascular reserve function between groups reflects the relative changes in VO_2, SV_I, and Q_I within group and supports the attenuated absolute responses of these variables during CPET in CF. The primary aim of this study was to assess within group relationships between cardiac function and exercise tolerance. Thus, the CF sample size and relationships that were observed met acceptable power and effect sizes for interpretability.[34] The calculated post-hoc power exceeded 0.80 at an alpha of 0.05 suggesting the possibility of both Type I and II errors were minimal for these tests of relationships within CF.

Measurement of cardiac hemodynamics did not occur using the invasive direct Fick method, and therefore unknown bias in hemodynamic measurements using the acetylene rebreathe technique, particularly related to potential changes in ventilation, cannot be ruled out. However, inert gas rebreathing is non-invasive and relates with direct Fick measurements of cardiac hemodynamics at rest and during exercise in healthy individuals or in cardiac (e.g., heart failure) or obstructive pulmonary (e.g., CF and chronic obstructive pulmonary disease)

patients.[21, 40, 43, 44, 46] Further, our group has previously demonstrated that the variance in lung diffusion[47] does not influence relationships between acetylene rebreathe measured Q_I during CPET in CF. Nevertheless, in an alternative method to inert gas breathing, it has been demonstrated in detail that newer methodological approaches associated with echocardiography can be used effectively with high reliability during exercise to estimate cardiac hemodynamics.[48-50] However, in the absence of highly trained expertise by both sonographer and reader, this technique may be subject to well-known limitations (e.g., high user-dependence relating to image-acquisition and skill of the echocardiographic reader) that are recognized to introduce measurement bias, particularly during exercise.[51-53] Thus, inert gas breathing using the highly blood soluble acetylene-gas[41] rebreathe technique may provide a more favorable estimation of cardiac hemodynamics during exercise in CF compared to echocardiography, CO_2 rebreathing, or nitrous oxide rebreathing. Finally, it should be note that cardiac function measures in the present study have not been conferred with a comprehensive examination by a cardiologist, and therefore interpretability of our assessment of cardiac function in individuals with CF is hypothesis generating for future studies of invasive measurement of cardiac hemodynamics during exercise in this population.

Conclusions

These data suggest that individuals with CF demonstrate shorter total exercise duration and lower PW compared to CTLs, which may be related to abnormal cardiac function. Although the prognostic potential of abnormal cardiac function during CPET is relevant in CF, there is no consensus recommendation for this assessment in the clinical setting as there has not been an extensive examination in this field concerning the influence of CF on abnormal cardiac function as it relates to exercise tolerance. Nevertheless, this study has shown that in moderate severity CF, attenuated Q_I and SV_I appear equally responsible for the shortened total exercise duration and low PW compared to low FVC and FEV_1. Our observations may provide critical insight concerning the nature of the integrative pathophysiology of low exercise tolerance in CF, while adding novel information for an improved understanding of the CF phenotype that extends beyond the pulmonary system. Future studies examining the relationship between low exercise tolerance and low cardiac hemodynamics should look to investigate the role of abnormal integrated cardiopulmonary function relating to ventilation —perfusion mismatch at the central circulation and reduced perfusion and oxygen delivery at the peripheral circulation.

Acknowledgments

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Abbreviations

BSA   body surface area

Ca^{2+}	calcium
$C_{a-v}O_2$	arterio-venous oxygen content difference
CF	cystic fibrosis
CFTR	cystic fibrosis conductance regulator
Cl^-	chloride
DBP	diastolic blood pressure
ENaC	epithelial Na^+ channel
FEV_1	forced expiratory volume in 1-second
FVC	forced vital capacity
HR	heart rate
MAP	mean arterial pressure
Na^+	sodium; $P_{ET}CO_2$; end-tidal carbon dioxide
PW	peak workload
Q	cardiac output
Q_I	cardiac index
RPE	rate of perceived exertion
RR	respiratory rate
SaO_2	oxygen saturation
SBP	systolic blood pressure
SD	standard deviation
SV	stroke volume
SV_I	stroke volume index
VO_2	oxygen uptake
VCO_2	carbon dioxide production
V_E	minute ventilation
V_T	tidal volume
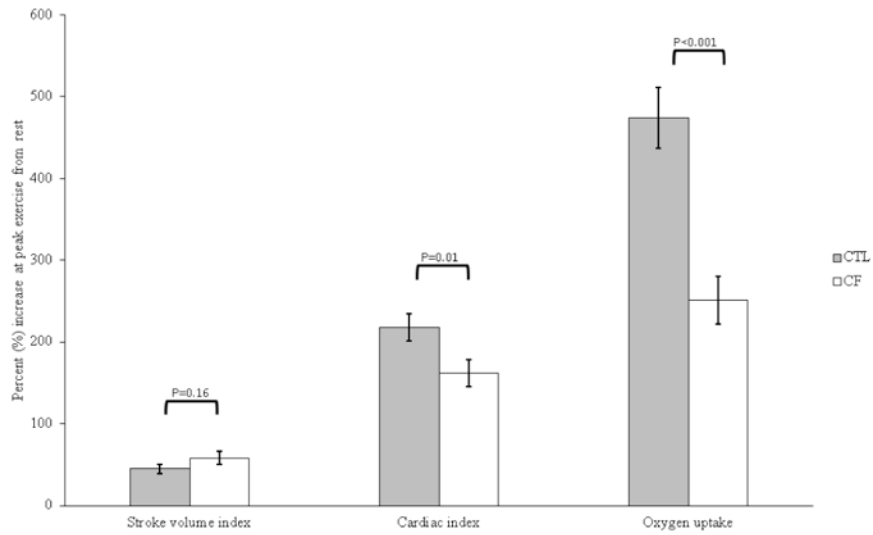
Figure 1.
Cardiac hemodynamic and oxygen uptake reserve. Data presented as mean ± standard error of the mean representing stroke volume index (SV_I), cardiac index (Q_I), or oxygen uptake (VO_2) reserve calculated as the percent (%) increase at peak exercise from rest. CTL = healthy controls; CF = cystic fibrosis.
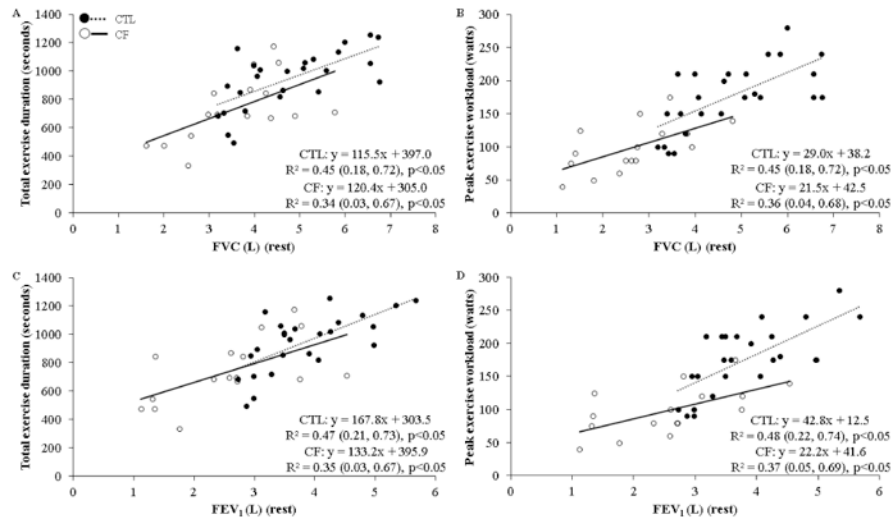
Figure 2.
Pulmonary function at rest and exercise tolerance relationships. Data represents results of univariate linear regressions (coefficient of determination [R^2] with 95% confidence limits) between total exercise duration or peak exercise workload with either, **A and B**) forced vital capacity (FVC) (rest), **C and D**) forced expiratory volume in 1-second (FEV_1) (rest), respectively. CTL = healthy controls; CF = cystic fibrosis.
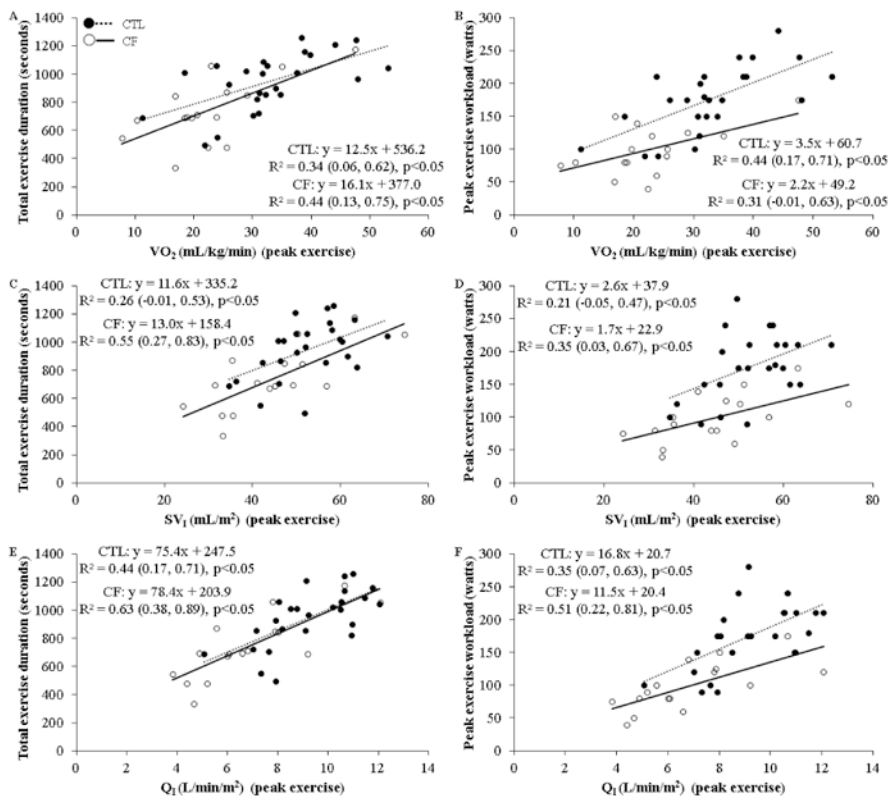
Figure 3.
Peak exercise oxygen uptake and cardiac hemodynamic exercise tolerance relationships.
Data represents results of univariate linear regressions (coefficient of determination [R^2]
with 95% confidence limits) between total exercise duration or peak exercise workload with
either, **A and B**) oxygen uptake (VO_2) (peak exercise), **C and D**) stroke volume index (SV_I)
(peak exercise), or **E and F**) cardiac index (Q_I) (peak exercise), respectively. CTL = healthy
controls; CF = cystic fibrosis.

Table 1

Participant characteristics at rest

	CTL	CF	*P*
	N = 25	N = 17	0.22
Gender, male/female	15/10	13/4	0.27
Height, cm	174 ± 2	168 ± 2	0.04
Weight, kg	72 ± 3	62 ± 3	0.01
BMI, kg/m^2	24 ± 1	22 ± 1	0.12
Hemoglobin, g/dL	14.7 ± 0.3	14.7 ± 0.5	0.76
Peak VO$_2$, %predicted	96 ± 5	55 ± 6	<0.01
Pulmonary function test parameters			
FVC, L	4.8 ± 0.2	3.6 ± 0.3	<0.01
FVC, %predicted	96 ± 2	80 ± 5	0.01
FEV$_1$, L	3.8 ± 0.2	2.6 ± 0.2	<0.01
FEV$_1$, %predicted	94 ± 3	69 ± 6	<0.01
FEV$_1$/FVC	0.8 ± 0.0	0.7 ± 0.0	<0.01
FEF$_{25-75}$, L/sec	3.8 ± 0.2	2.0 ± 0.3	<0.01
FEF$_{25-75}$, %predicted	90 ± 5	51 ± 8	<0.01

Data are mean ± SEM or as n. CTL, healthy controls; CF, cystic fibrosis; BMI, body mass index; VO$_2$, oxygen uptake; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in one second; FEF$_{25-75}$, forced expiratory flow at 25.0 – 75.0% of forced vital capacity. Group comparisons were performed using Wilcoxon rank-sum tests for all variables except n and gender, which were compared by using χ^2 tests.

Table 2

Between group comparisons for cardiopulmonary exercise test variables at rest and peak exercise

	Rest		Peak Exercise	
	CTL	CF	CTL	CF
Total exercise duration, seconds	-	-	960 ± 41	729 ± 48 [*]
Workload, watts	-	-	179 ± 11	100 ± 9 [*]
RPE (6-20, Borg)	6.0 ± 0.0	6.0 ± 0.0	17.5 ± 0.2 [†]	16.8 ± 0.3 [†]
Cardiac hemodynamics				
SV_I, mL/m^2	40 ± 3	31 ± 3 [*]	51 ± 2 [†]	45 ± 3
Q_I, L/min/m	3.1 ± 0.2	2.6 ± 0.2 [*]	9.1 ± 0.3 [†]	6.7 ± 0.5 [*†]
Ventilation or gas exchange				
VO_2, mL/kg/min	5.9 ± 0.3	6.5 ± 0.4	33.2 ± 2.0 [†]	22.6 ± 2.2 [*†]
VO_2, L/min	0.4 ± 0.0	0.4 ± 0.0	2.3 ± 0.1 [†]	1.4 ± 0.1 [*†]
VCO_2, L/min	0.3 ± 0.0	0.4 ± 0.0	26 ± 0.2 [†]	1.6 ± 0.2 [*†]
RR, breaths/min	19 ± 2	22 ± 1	38 ± 2 [†]	36 ± 2
V_E, L/min	14 ± 1	16 ± 1	82 ± 4	56 ± 3 [*†]
V_T, L	0.8 ± 0.05	0.8 ± 0.07	2.2 ± 1.2	1.6 ± 1.2 [*]
$P_{ET}CO_2$, mm Hg	30 ± 1	30 ± 1	35 ± 1	36 ± 1
$C_{a-v}O_2$, mL/100 mL/m^2	5.8 ± 0.7	6.4 ± 1.1	15.7 ± 1.0 [†]	13.3 ± 1.8 [†]
SaO_2, %	97.8 ± 0.3	95.7 ± 0.4 [*]	96.9 ± 0.3	93.8 ± 1.2 [*]
Heart rate or blood pressure				
HR, beats/min	81 ± 3	93 ± 4 [*]	177 ± 2 [†]	145 ± 7 [*†]
SBP, mm Hg	110 ± 2	106 ± 2	158 ± 4 [†]	142 ± 6 [*†]
DBP, mm Hg	71 ± 1	70 ± 2	61 ± 4	67 ± 4
MAP, mm Hg	84 ± 1	82 ± 2	93 ± 3 [†]	92 ± 4

Data are presented as mean ± SEM. CTL, control (n = 25); CF, cystic fibrosis (n = 17); RPE, rate of perceived exertion; SV_I, stroke volume index; Q_I, cardiac index; VO_2, oxygen uptake; VCO_2, carbon dioxide output; RR, respiratory rate; V_E, minute ventilation; V_T, tidal volume; $P_{ET}CO_2$, end-tidal partial-pressure carbon dioxide; $C_{a-v}O_2$, arterial-mixed venous oxygen content difference; SaO_2, peripheral oxygen saturation; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure. Between group comparisons were performed using Wilcoxon rank-sum tests for all variables. Within group comparisons were performed using paired Student's t-tests.

[*] $p < 0.05$, CTL vs. CF.

[†] $p < 0.05$, rest vs. peak exercise.

Table 3

Cystic fibrosis, step-wise regression models for predicting total exercise duration or peak exercise workload

	R^2	Semi-partial R^2	Intercept	b	β	P-value
Total exercise duration (sec)						
Step 1 (final step-wise model)						
Q_I	0.63*	-	204	78	0.79	<0.001
Peak exercise workload (watts)						
Step 1						
HR	0.63*	-	-255	2.3	-	<0.001
Step 2 (final step-wise model)						
HR	0.74*	0.39	-244	2.0	0.67	<0.001
SV_I	-	0.35	-	1.0	0.36	0.01

Data presented as step-wise linear regressions. Variables entered the model upon reaching an alpha set at 0.15, whereas variables remained in the final model upon reaching an alpha set at <0.05. Independent variables used for entry into step-wise regressions were FVC, forced vital capacity (rest); FEV_1, forced expiratory volume in 1-second (rest); VO$_2$, oxygen uptake (peak exercise); HR, heart rate (peak exercise); Q_I cardiac index (peak exercise); or SV_I, stroke volume index (peak exercise). Dependent variables were total exercise duration or peak exercise workload. Coefficient of determination (R^2) is for the overall model at each step. β, standardized slope. *P-value* = alpha value for each parameter in regression models.

*
p<0.05, for the model at each step.

Table 4

Controls, step-wise regression models for predicting total exercise duration or peak exercise workload

	R^2	Semi-partial R^2	Intercept	b	β	*P-value*
Total exercise duration (sec)						
Step 1						
FEV$_1$	0.52*	-	268	175	-	<0.001
Step 2						
FEV$_1$	0.66*	0.52	12.8	128	-	<0.01
Q$_I$	-	0.14	-	47	-	<0.01
Step 3						
FEV$_1$	0.72*	0.52	173	123	-	<0.001
SV$_I$	-	0.06	-	-15	-	0.04
Q$_I$	-	0.14	-	118	-	<0.01
Step 4						
FEV$_1$	0.76*	0.52	131	19	-	0.77
SV$_I$	-	0.06	-	-14.9	-	0.04
Q$_I$	-	0.14	-	125	-	<0.01
FVC	-	0.04	-	76	-	0.09
Step 5 (FEV$_1$ removed)						
SV$_I$	0.76*	0.08	133	-14.9	-	0.03
Q$_I$	-	0.44	-	127	-	<0.001
FVC	-	0.23	-	87	-	<0.001
Step 6						
SV$_I$	0.79*	0.08	2674	-65	-	0.04
Q$_I$	-	0.44	-	419	-	0.02
FVC	-	0.23	-	88	-	<0.001
HR	-	0.03	-	-14.7	-	0.10
Step 7 (final step-wise model)						
SV$_I$	0.76*	0.08	133	-14.9	-0.65	0.03

	R^2	Semi-partial R^2	Intercept	b	β	P-value
Q_I	-	0.44	-	127	1.12	<0.001
FVC	-	0.23	-	87	0.51	<0.001
Peak exercise workload (watts)						
Step 1						
FVC	0.45*	-	38	29	-	<0.001
Step 2						
FVC	0.67*	0.45	-15	22	-	<0.001
VO_2	-	0.22	-	2.6	-	<0.001
Step 3 (final step-wise model)						
FVC	0.73*	0.24	-161	21	0.48	<0.01
VO_2	-	0.44	-	2.2	0.42	<0.01
HR	-	0.06	-	0.9	0.26	0.05

Data presented as step-wise linear regressions. Variables entered the model upon reaching an alpha set at 0.15, whereas variables remained in the final model upon reaching an alpha set at <0.05. Independent variables used for entry into step-wise regressions were FVC, forced vital capacity (rest); FEV_1, forced expiratory volume in 1-second (rest); VO_2, oxygen uptake (peak exercise); HR, heart rate (peak exercise); Q_I, cardiac index (peak exercise); or SV_I, stroke volume index (peak exercise). Dependent variables were total exercise duration or peak exercise workload. Coefficient of determination (R^2) is for the overall model at each step. β, standardized slope. *P-value* = alpha value for each parameter in regression models.

*
p<0.05, for the model at each step.