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# 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 ( $Q_1$ ) was measured using acetylene rebreathe and oxygen uptake (VO<sub>2</sub>) breath-by-breath. Forced expiratory volume in 1-second (FEV<sub>1</sub>) was performed at rest.

*Results*: Peak Q<sub>I</sub> was 6.7  $\pm$  0.5 vs. 9.1  $\pm$  0.3 mL/min/m<sup>2</sup>, CF vs. controls, respectively (P < 0.05). Linear regressions between Q<sub>I</sub> ( $R^2 = 0.63$  and 0.51) and exercise duration or PW were stronger than VO<sub>2</sub> ( $R^2 = 0.35$  and 0.37) or FEV<sub>1</sub> ( $R^2 = 0.34$  and 0.36) in CF, respectively (P < 0.05).

*Conclusion:* These data are clinically relevant suggesting attenuated cardiac function in addition to low airway function relate to exercise tolerance in CF.

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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.<sup>1,2</sup> This disease is caused by gene mutations leading to absent or misplaced CF conductance transmembrane regulator (CFTR) that affects chloride (Cl<sup>-</sup>) transport as well as attenuated inhibition of

epithelial Na<sup>+</sup> channels (ENaC) at the apical epithelial membrane layer of airway, intestinal, and exocrine cells.<sup>1,3,4</sup> 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.<sup>2,4</sup> This reduction in airway function has been traditionally suggested to be the primary contributor to reduced exercise tolerance in these individuals.<sup>5–7</sup>

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.<sup>5,6,8–13</sup> For example, it has been observed that dysregulated movement of Cl<sup>-</sup> and Na<sup>+</sup> within lung epithelial tissue leads to airway obstruction and increased work of breathing caused by inadequate ventilation and oxygen reaching the alveoli.<sup>8–12</sup> 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.<sup>14</sup> Thus, it is through reductions in gastransfer and ventilatory function that the pathophysiology of low exercise tolerance has been traditionally viewed in CF.



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<sup>-</sup>, chloride; DBP, diastolic blood pressure; ENaC, epithelial Na<sup>+</sup> channel; FEV<sub>1</sub>, forced expiratory volume in 1-second; FVC, forced vital capacity; HR, heart rate; MAP, mean arterial pressure; Na<sup>+</sup>, sodium; P<sub>ET</sub>CO<sub>2</sub>, end-tidal carbon dioxide; PW, peak workload; Q, cardiac output; Q<sub>1</sub>, cardiac index; RPE, rate of perceived exertion; RR, respiratory rate; SaO<sub>2</sub>, oxygen saturation; SBP, systolic blood pressure; SD, standard deviation; SV, stroke volume; SV<sub>1</sub>, stroke volume index; VO<sub>2</sub>, oxygen uptake; VCO<sub>2</sub>, carbon dioxide production; V<sub>E</sub>, minute ventilation; V<sub>T</sub>, tidal volume.

Conflicts of interest: None.

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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<sub>1</sub>]<sup>2,4</sup>); whereas, to a lesser extent, it is becoming more recognized that low exercise tolerance is also related to prognosis in these individuals.<sup>5–7</sup> 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<sup>-</sup> 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.<sup>15,16</sup> 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 endstage heart failure patients compared to individuals with nonfailing hearts.<sup>17</sup> 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)<sup>18</sup> and cardiac hemodynamic responsiveness to inhalation of the selective  $\beta_2$ -agonist albuterol are attenuated in CF.<sup>19</sup> 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.<sup>14–24</sup> 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,<sup>25</sup> whereas there is an increased cardiovascular and heart disease risk in adults >40 years, which can be predicted by exercise tolerance.<sup>26–28</sup>

Therefore, because decreased myocardial contractility in CF cannot be predicted by the magnitude of resting pulmonary dysfunction,<sup>18,23</sup> 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<sub>2</sub>) and cardiac function in cardiovascular patients.<sup>29,30</sup> Greater relative change in VO<sub>2</sub> 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<sup>-</sup> sweat test

 $(\geq 60.0 \text{ mmol/L Cl}^{-})$  and genotyping of the  $\Delta$ F508 mutation of CFTR, which is the most common genotype (  $\sim$  70% of CF population) of the 1000+ possible genotypes associated with this disease.<sup>31,32</sup> 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<sub>2</sub> for healthy individuals.<sup>33</sup> Additional exclusion criteria for CF, while also applying to CTLs included: 1) history of hypertension, cardiac, metabolic, neurologic, orthopedic, 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.<sup>8,11,18,20,21</sup> 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<sup>34</sup> 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.

Table 1			
Participant	characteristics	at	rest

	CTL	CF	Р			
	N = 25	<i>N</i> = 17	0.22			
Gender, male/female	15/10	13/4	0.27			
Height, cm	$174\pm2$	$168 \pm 2$	0.04			
Weight, kg	$72\pm3$	$62\pm3$	0.01			
BMI, kg/m <sup>2</sup>	$24\pm1$	$22\pm1$	0.12			
Hemoglobin, g/dL	$14.7\pm0.3$	$14.7\pm0.5$	0.76			
Peak VO <sub>2</sub> , % predicted	$96\pm5$	$55\pm 6$	< 0.01			
Pulmonary function test parameters						
FVC, L	$\textbf{4.8} \pm \textbf{0.2}$	$\textbf{3.6} \pm \textbf{0.3}$	< 0.01			
FVC, % predicted	$96 \pm 2$	$80\pm5$	0.01			
FEV <sub>1</sub> , L	$\textbf{3.8} \pm \textbf{0.2}$	$2.6\pm0.2$	< 0.01			
FEV <sub>1</sub> , % predicted	$94\pm3$	$69\pm 6$	< 0.01			
FEV <sub>1</sub> /FVC	$\textbf{0.8}\pm\textbf{0.0}$	$\textbf{0.7} \pm \textbf{0.0}$	< 0.01			
FEF <sub>25-75</sub> , L/s	$\textbf{3.8} \pm \textbf{0.2}$	$\textbf{2.0} \pm \textbf{0.3}$	<0.01			
FEF <sub>25-75</sub> , % predicted	$90\pm 5$	$51\pm 8$	< 0.01			

Data are mean  $\pm$  SEM or as *n*. CTL, healthy controls; CF, cystic fibrosis; BMI, body mass index; VO<sub>2</sub>, oxygen uptake; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1-second; FEF<sub>25-75</sub>, 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  $\chi^2$  tests.

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