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What is Learned from Measuring Aerobic Capacity in Healthy Children and Young Adults with Cystic Fibrosis

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Abstract

Background: In Cystic Fibrosis (CF), low aerobic capacity (VO_2 peak) is a predictor of increased mortality. Lung function has been used to monitor long-term outcomes in patients with CF. Patients with mild CF tend to have normal lung function, hence aerobic capacity may provide an alternative for predicting outcomes. Little is known about predictors of VO_2 peak in patients with mild CF and normal lung function. Recent studies have shown higher mortality in Hispanic CF patients, though data comparing aerobic capacity and physical activity between Hispanic and non-Hispanic CF patients are limited.

Methods: This is a cross-sectional analysis of twenty-one subjects with mild CF, ages 10 to 20 years seen at one Cystic Fibrosis Center between September 2015 and March 2017. VO_2 peak was measured by cardiopulmonary exercise testing on a cycle ergo meter. Physical activity was assessed using a validated questionnaire. Bivariate analyses was used to examine the relationship between VO_2 peak and physical activity, ethnicity, sex, Pseudomonas aeruginosa infection, CFTR mutation class severity, and BMI z-score, age, and lung function. A multivariate model was created to assess predictors of VO_2 peak.

Results: This cohort (mean age 14.4 years) had normal lung function (FEV1 95% predicted) and normal VO_2 peak (96% predicted). Habitual activity and percent-predicted VO_2 peak did not differ significantly by sex. Hispanics with CF had lower VO_2 peak (30.3 ml/kg/min *vs.* 39.5 ml/kg/min, p=0.022) compared to non-Hispanics and reported fewer hours spent in vigorous physical activity (2.4 *vs.* 6.0 h/week, p=0.035). Lung function did not differ by ethnicity. In the multivariate model, significant predictors of aerobic capacity were vigorous physical activity and CFTR mutation severity. Aerobic capacity was reduced in Hispanics (p=0.067) and those with chronic Pseudomonas aeruginosa infection (p=0.053) but results did not reach statistical significance.

Conclusion: In a small cohort of children and young adults with mild CF and normal lung function, we found that vigorous physical activity and CFTR mutation severity were significant predictors of aerobic capacity (VO_2 peak). Twenty-four percent of subjects in this cohort were Hispanic. Hispanics had comparable lung function but lower VO_2 peak, longer recovery time, and lower participation in vigorous physical activity than non-Hispanics. While this study was limited by small sample size, early measurement of aerobic capacity may be clinically important. Larger studies are needed to further understand the relationship between VO_2 peak and mortality, particularly with respect to ethnicity.

Keywords: Cardiopulmonary exercise testing; Aerobic capacity; Cystic fibrosis; Physical activity; Hispanic

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Abbreviation

VO_2 peak: Peak Oxygen Uptake; CPET: Cardiopulmonary Exercise Test CF: Cystic Fibrosis; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; AT: Anaerobic Threshold; HR: Heart Rate; MAQ: Modifiable Activity Questionnaire; MET: Metabolic Equivalent; MVPA: Moderate-to-Vigorous Physical Activity; BMI: Body Mass Index; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator Aerobic Capacity in mild CF

Introduction

Aerobic capacity is determined by measuring peak oxygen uptake (VO_2 peak) during a maximal Cardiopulmonary Exercise Test (CPET) and provides a comprehensive functional assessment of

the body under stress [1]. CPET has been used to tailor exercise prescriptions as pulmonary impairment progresses in various chronic pulmonary conditions [2]. Low VO_2 peak has prognostic significance in adults with chronic heart failure and is used to assess treatment response and to plan optimal timing of heart transplant [2]. In Cystic Fibrosis (CF), low VO_2 peak and high rate of decline of VO_2 peak are associated with decreased survival independent of lung function [3-5]. Recognition of the prognostic significance of aerobic capacity led to a recent consensus statement recommending that individuals with CF regularly perform exercise testing [6]. Studies consistently show that people with CF have a lower aerobic capacity (VO_2 peak) compared to healthy controls [7,8]. VO_2 peak is affected by genetic factors and in CF has been shown to be affected by baseline activity level, chronic inflammation, Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutations, and nutritional status [9-13]. Lung function affects VO_2 peak significantly if Forced Expiratory Volume in one second (FEV1) is abnormal, but is less likely to affect VO_2 peak in mild CF [1,14]. As therapies for CF improve, lung function and survival are also improving. Studies that continue to explore predictors of aerobic capacity are warranted as the CF population becomes healthier. Although overall survival in CF is improving, certain notable disparities exist with respect to sex and ethnicity (separately). Women with CF have a lower median survival than men after adjusting for other risk factors of early mortality, and the cause of this disparity has not been fully elucidated [15]. Hispanics with CF have increased mortality and lower lung function compared to non-Hispanics, even after controlling for CFTR genotype, chronic infection, and socioeconomic factors [16]. The percent of Hispanic patients of any race in the CF Registry is increasing over time (8.7% in 2017), reflective of population trends [17]. In California, 28% of patients in the CF Registry from 1991 to 2010 identified as Hispanic16, and at the time of this study 24% of patients in our pediatric CF Center were Hispanic. This provides an opportunity to study characteristics of this vulnerable group of children and adolescents with CF. Ethnic differences in regular physical activity and aerobic capacity among people with CF are not clearly defined. In this study we assessed aerobic capacity and participation in physical activity among healthy CF patients seen at our Cystic Fibrosis Center. We also compared VO_2 peak and participation in physical activity between males and females as well as between Hispanic and non-Hispanics.

Methods

Subjects

Subjects with CF who qualified for cardiopulmonary exercise testing between September 2015 and March 2017 in the Pediatric Cystic Fibrosis Center at the University of California, San Francisco (UCSF) were recruited to complete the physical activity questionnaire during their exercise-testing visit. Data were excluded if the patient did not perform a maximal CPET, had an acute pulmonary exacerbation, and had an acute drop from baseline FEV1 of 15% or greater. Written informed consent and child assent were obtained as appropriate. This study was approved by the Institutional Review Board at the University of California, San Francisco.

Exercise testing

Subjects performed a CPET on an upright cycle ergo meter using a progressive incremental ramp protocol [18]. Oxygen uptake was continuously measured using breath-by-breath analysis of expired gases with the Ultimate CPXTM metabolic cart (MGC Diagnostics, Saint Paul, MN, USA). A maximal CPET was defined by a plateau of oxygen uptake despite increase in ergo meter resistance, attainment of ≥ 85% of age-predicted maximal heart rate, or a calculated respiratory exchange ratio >1.036. Percent-predicted VO_2 peak was calculated using sex-specific equations developed by Cooper for those under years and by Wasserman for those over [16,19,20]. Data analyzed from the CPET included VO_2 peak (ml/kg/min and percent-predicted), recovery time to 50 percent of VO_2 peak (seconds), maximum power achieved (Watts and Watts/kg), VE/VCO_2 at Anaerobic Threshold (AT) (a measurement of ventilatory efficiency), and oxygen pulse (VO_2/HR) (a proxy for stroke volume and cardiac function).

Spirometry

Spirometry was performed according to American Thoracic Society standards using a Med graphics spirometer (MGC Diagnostics, Saint Paul, MN, USA) [21]. Percent-predicted values for FEV1 and Forced Vital Capacity (FVC) were calculated using the Global Lung Initiative equations adjusting for race [22].

Activity assessments

Physical activity in the last year was ascertained using Kriska's Modifiable Activity Questionnaire (MAQ), which has been previously validated in CF7, [23]. The MAQ assesses past year participation in recreational activity and sports. A past-year questionnaire was used to account for seasonable variability in sports participation that may be lost in a short-term survey. Subjects were also asked, "Did you participate in a sport season or camp in the last year that was organized by your school or city?" Parents could assist in completing the questionnaire for children younger than 18 years. The metabolic cost of each activity was recorded using Metabolic Equivalent Tables (MET) [24,25]. One MET is the energy expenditure during quiet sitting, approximately equal to 3.5 ml/kg/min [26]. Moderate intensity exercise is defined as exercise that accelerates the heart rate and requires 3.0 to 6.0 METs (slow cycling, brisk walking, or swimming). Vigorous exercise requires more than 6.0 METs and causes rapid breathing and a substantial increase in heart rate (running fast, swimming laps, singles tennis). Moderate-to-Vigorous Physical Activity (MVPA) includes all activities ≥ 3 METs [26]. Average hours per week spent in vigorous or moderate activity was recorded from each questionnaire.

Table 1: Baseline characteristics.

Mean (n=21)	
Age, years	14.4 (± 3.3)
Best FVC% predicted in last year	105.8 (± 16.8)
Best FEV1% predicted in last year	94.7 (± 19.9)
BMIz-score	0.002 (± 0.86)
N (%)	
Female	11 (52%)
Hispanic ethnicity	5 (24%)
CFTR mutation class	
Severe CFTR mutation	16 (76%)
Less severe CFTR mutation	5 (24%)
Chronic Pseudomonas aeruginosa infection	5 (24%)
CFTR modulator use	
None	12 (57%)
Ivacaftor	4 (19%)
Ivacaftor/lumacaftor	5 (24%)

Table 2: Self-reported physical activity weekly by Kriska's Modifiable Activity Questionnaire.

	Non-Hispanic (n=16) Median (interquartile range)	Hispanic (n=5) Median (interquartile range)
Vigorous physical activity (hours per week)*	6.0 (1.7 to 12.0)	2.4 (0.3 to 3.0)
Moderate physical activity (hours per week)	3.1 (0.9 to 5.4)	3.2 (2.2 to 3.5)
MVPA** (hours per week)	9.5 (6.0 to 15.4)	3.2 (2.5 to 6.5)

Table 3: Cardiopulmonary exercise test and same day lung function.

	All (n=21) Mean (± SD)	Male (n=10) Mean (± SD)	Female (n=11) Mean (± SD)	P value	Non-Hispanic (n=16) Mean (± SD)	Hispanic (n=5) Mean (± SD)	P value
VO_2 peak (ml/kg/min)	37.3 (± 8.1)	40.8 (± 7.5)	34.2 (± 7.7)	0.06	39.5 (± 7.4)	30.3 (± 6.5)	0.02
VO_2 peak (percent-predicted)	95.7 (± 18.5)	91.5 (± 17.1)	99.5 (± 19.6)	0.34	100.5 (± 17.8)	80.2 (± 11.1)	0.03
Recovery time to 50% VO_2 peak (seconds)	57.9 (± 13.3)	55.4 (± 12.2)	60.1 (± 14.4)	0.43	54.8 (± 11.5)	67.8 (± 14.9)	0.05
Power at VO_2 peak adjusted for body mass (Watts/kg)	2.53 (± 0.58)	2.53 (± 0.66)	2.53 (± 0.52)	0.99	2.66 (± 0.53)	2.12 (± 0.58)	0.07
VE/VCO_2 at anaerobic threshold	27.8 (± 4.6)	26.1 (± 5.5)	29.3 (± 3.1)	0.11	27.4 (± 4.3)	29.0 (± 5.8)	0.5
Oxygen pulse (VO_2/H^+) percent-predicted	111.0 (± 20)	12.1 (± 4.7)	10.1 (± 2.6)	0.24	113.0 (± 21)	105.0 (± 18)	0.44
FVC percent-predicted	105.8 (± 16.8)	104.8 (± 16.2)	106.8 (± 18.1)	0.79	100.8 (± 12.2)	122 (± 20.7)	0.01
FEV1 percent-predicted	94.7 (± 19.9)	91.7 (± 19.5)	97.4 (± 20.9)	0.52	90.7 (± 16.2)	107.3 (± 27.1)	0.1

Subject characteristics

A subject's age, sex, self-reported ethnicity (Hispanic/Latino or not Hispanic/Latino), Body Mass Index (BMI), CFTR genotype, Pseudomonas aeruginosa infection status, pancreatic sufficiency, lung function in the previous year, and use of ivacaftor or lumacaftor/ivacaftor were obtained from the electronic medical record. CFTR genotype was categorized as severe if two alleles were present from class I, II, or III and as less severe if at least one allele was from class IV or V [12].

Statistical analysis

The primary outcome was VO_2 peak (ml/kg/min). Spearman correlation was used to test the association of aerobic capacity and non-parametric activity covariates. Bivariate analyses of categorical and continuous variables with VO_2 peak were conducted by Fisher exact tests, 2-tailed t tests, or K-sample median tests depending on variable type and distribution of the data. Variables that were associated with VO_2 peak at a $p<0.2$ in bivariate analysis were included in multivariate linear regression models. Multivariate analyses were performed using backward stepwise linear regression. The final multivariable model included variables that were significant at $p<0.05$ or that modified the association between ethnicity and VO_2 peak. Age was included because VO_2 peak is known to decrease with increasing age. The final model included ethnicity, hours per week of vigorous activity, sex, Pseudomonas aeruginosa infection, CFTR mutation class severity, BMI z-score, age, and same day FEV1% predicted and FVC% predicted. Analyses were performed using Stata 14.0 (Stata Corp, College Station, TX, USA).

Results

Twenty-one subjects between the ages of 10 to 20 years were enrolled. All subjects performed tests that met criteria for maximal exercise testing. Baseline characteristics of the cohort are presented in Table 1. There was no significant difference in baseline characteristics between males and females or between hispanics and non-hispanics with respect to age, sex, CFTR gene mutation severity, chronic *Pseudomonas aeruginosa* infection, or CFTR modulator use. The best FVC and FEV1 percent-predicted in the last year trended higher in Hispanics compared to non-hispanics, but the difference was not statistically significant. Hispanic subjects had a higher BMI z-score than non-hispanic subjects (p=0.046). No subject had CF- related diabetes.

Physical activity

Median time per week spent in moderate, moderate-to-vigorous, and vigorous physical activity are presented in Table 2. Report of physical activity was not statistically different between males and females. Hispanic subjects reported significantly fewer hours spent in vigorous activities compared to non-hispanics, but similar time spent in moderate activities. Participation in organized sports did not differ by age, sex, lung function, BMI z-score, chronic Pseudomonas infection, or CFTR mutation severity (data not shown). Overall, 11 subjects (52%) reported participating an organized sport for over 6 months of the previous year, and 13 subjects (62%) participated in any organized sport in the prior year. Hispanic subjects were less likely to report participation in any organized sport (p=0.047). Participation in organized sports was associated with a higher aerobic capacity (those participating 6 months or more: 41.4 *vs.* 32.9 ml/kg/min, p=0.01; any organized sport: 40.6 *vs.* 32.1 mL/kg/min, p=0.02).

Exercise capacity

Data on aerobic capacity and lung function stratified by sex and by ethnicity are presented in Table 3. Similar to what has been shown previously, males tended to have a higher VO_2 peak than females (40.8 ml/kg/min *vs.* 34.2 ml/kg/min, p=0.06). This difference was not seen in percent-predicted VO_2 peak using sex-specific predictive equations. Male and female subjects did not have significantly different exercise outcome parameters or lung function. Hispanic subjects had significantly lower VO_2 peak than non-Hispanic subjects (30.3 ml/kg/min *vs.* 39.5 ml/kg/min, p=0.02). Hispanic subjects had a significantly higher percent-predicted FVC on the day of exercise testing. Percent-predicted FEV1 was higher in Hispanics but the difference was not statistically significant. Recovery time was longer in Hispanics compared to non-Hispanic subjects (68 *vs.* 55 seconds, p=0.05). Hispanics and non-hispanics achieved similar unadjusted maximum power (121 Watts *vs.* 136 Watts, p=0.59). There was a trend toward lower maximum power achieved per kg among hispanics compared to non-Hispanics (2.12 Watts/kg *vs.* 2.66 Watts/kg, p=0.07), likely reflective of the higher BMI seen in Hispanic

Table 4: Cardiopulmonary exercise test and same day lung function.

	Bivariate Model		Multivariate Model	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Hispanic/Latino Ethnicity	-9.3 (17.1 to -1.5)	0.02	-6.92 (-14.40 to 0.57)	0.067
Vigorous activity (hrs/week)	0.97 (0.5 to 1.5)	<0.01	0.69 (0.24 to 1.13)	0.006
Female sex	-6.6 (-13.6 to 0.3)	0.06	-0.59 (5.34 to 4.15)	0.788
Chronic Pseudomonas infection Severe CFTR mutation	-6.3 (-14.8 to 2.1)	0.13	-4.99 (-10.07 to 0.08)	0.053
Severe CFTR mutation	-8.5 (0.54 to 16.5)	0.04	-7.56 (-12.54 to -2.58)	0.007
BMI z-score Age (years)	-4.08 (-8.19 to 0.02)	0.05	-1.94 (-4.84 to 0.95)	0.168
Age (years)	-0.15 (-1.34 to 1.05)	0.8	-0.63 (-1.40 to 0.14)	0.098
Same day FVC % pred	-0.10 (-0.33 to 0.12)	0.35	0.13 (-0.20 to 0.45)	0.409
Same day FEV1% pred	-0.04 (-0.23 to 0.16)	0.71	-0.01 (-0.24 to 0.22)	0.908

subjects in this cohort. VE/VCO_2 at Anaerobic Threshold (AT) and oxygen pulse were normal and did not significantly differ between Hispanic and non-Hispanic subjects.

Levels of physical activity and exercise capacity

Spearman correlation was used to assess the strength of the association of activity variables and VO_2 peak. Time spent in vigorous activities (>6 METs) was strongly correlated with VO_2 peak (r=0.71, p=0.0003). Total time spent in MVPA (≥ 3 METs) was moderately correlated (r=0.47, p=0.03), but time spent in moderate activities alone (3 to 6 METs) was not correlated (r= -0.04, p=0.87) with VO_2 peak. This suggests the correlation between total activity (MVPA) and aerobic capacity is driven by time spent in vigorous physical activities. Based on this finding, the activity variable chosen for bivariate and multivariate models was weekly hours of vigorous physical activities. We did examine total weekly hours of moderate and Moderate-to-Vigorous Physical Activity (MVPA) in multivariate models and they were not significant predictors of VO_2 peak (data not shown).

Bivariate and multivariate analyses

Subjects with severe mutations had a lower VO_2 peak compared to those with less severe mutations (35.3 ml/kg/min *vs.* 43.8 ml/kg/min, p=0.038), but similar lung function. Subjects with chronic Pseudomonas aeruginosa infection had similar lung function but lower VO_2 peak compared to those without chronic infection (32.5 ml/kg/min *vs.* 38.8 ml/kg/min, p=0.13). Bivariate and multivariate linear regression models are presented in Table 4. In the multivariate model, hours of vigorous physical activity and CFTR mutation severity remained statistically significant predictors of VO_2 peak. Hispanic ethnicity and chronic Pseudomonas aeruginosa infection demonstrated trends toward association with VO_2 peak but did not reach statistical significance.

Discussion

In this group of CF patients with mild respiratory disease and normal lung function who performed cardiopulmonary exercise testing, vigorous physical activity and CFTR mutation severity are associated with reduced VO_2 peak independent of other factors (female sex, low BMI, and chronic Pseudomonas aeruginosa infection) that have been associated with disease. We also found trends for Hispanic ethnicity and chronic *Pseudomonas aeruginosa* infection as predictors of lower aerobic capacity, though these did not meet the threshold for statistical significance [16,27]. Lower aerobic capacity has been associated with decreased survival in CF, independent of lung function [3,4]. To our knowledge, this is the first study to compare aerobic capacity and physical activity in hispanics and non-hispanics with CF. Despite the small sample size, these results are interesting and suggest that low VO_2 peak may play a role in the increased mortality noted in hispanic individuals with CF. Our study findings are generally consistent with other studies that have documented the separate predictive values of vigorous physical activity, CFTR mutation class severity, and chronic Pseudomonas aeruginosa infection for aerobic capacity. Savi et al. established that higher levels of vigorous physical activity correlated with higher aerobic capacity in adults with CF [28]. Van de Weert and colleagues showed that chronic *Pseudomonas aeruginosa* colonization had a negative association with longitudinally measured aerobic capacity (between 1998 and 2008) in young patients with CF (mean age 13.3), though these subjects had slightly lower lung function than our cohort (FEV1 83% predicted *vs.* 95% predicted in our study) [11]. Studies evaluating the effect of CFTR gene mutation severity on exercise capacity have found conflicting results. Selvadurai and colleagues showed that in 97 young children with CF (mean age 14.1 years) who had at least one copy of delF508, aerobic capacity was significantly lower if the second CFTR mutation was a class I or class II mutation (more severe). A more recent study including 726 subjects from 17 CF centers worldwide found that CFTR genotype was not a predictor of peak aerobic capacity, though BMIz-score and FEV1 % predicted were significant predictors. Subjects in this study were an average of 18.7 years of age with FEV1 of 76.6% predicted. A sub analysis which included only patients with FEV1>80% predicted also found no effect of CFTR genotype on exercise capacity [29]. The authors propose that their finding may be related to the higher lung function in their cohort than in the Selvadurai study, which reported that most patients had percent-predicted FEV1 in the mid-50s. The relationship between severe genotype and aerobic capacity may be confounded by ethnicity; this need to be further elucidated in future studies. FEV1% predicted has been closely associated with both mortality and with aerobic capacity 3, 5, but was not a significant predictor of VO_2 peak in this study, which may be due to the overall normal lung function in our cohort. As average lung function and survival continue to improve in cystic fibrosis, and as new CFTR modulator therapies become available that will likely preserve lung function even longer, it is increasingly relevant to investigate characteristics of aerobic capacity and physical activity in subjects with cystic fibrosis who have normal or only mildly impaired lung function. Low BMI has previously been shown to be a negative predictor of exercise capacity [5,13]. In our study, BMIz-score was negatively associated with aerobic capacity in bivariate analysis, but did not remain significant after adjusting for other factors in the multivariate model. This may be related to small

sample size. Similar to previous studies7, 10, we demonstrate a positive association between baseline activity level and VO_2 peak. Importantly, we found that VO_2 peak is strongly associated with participation in vigorous physical activities, but not moderate activities. In previous of studies of children and teens with CF, females have been shown to have lower levels of habitual physical activity compared to males with CF, especially after the onset of puberty [30]. In our study, we noted a trend toward lower participation in vigorous physical activity for female subjects compared to males, though this difference was not significant. hispanic children in our study reported significantly lower total activity and less time spent in vigorous physical activities than non-hispanics. A low level of physical activity in hispanic children is not consistent with studies that have evaluated activity level and race/ethnicity in healthy children [31]. To our knowledge, studies that have examined physical activity in people with cystic fibrosis in the United States have not included information on ethnicity in baseline demographics. It is possible that our study is affected by reporting bias, with either hispanics under-reporting or non-hispanics over reporting their hours of participation in various physical activities. To reduce potential for reporting bias, we also asked about participation in organized sports, which is easier to recall and report. Hispanics were less likely to report participation in any organized sport (n=1 *vs.* n=12, p=0.047).

Participation in organized sports was also associated with a higher aerobic capacity. Hispanic ethnicity was an independent predictor of aerobic capacity in multivariate model adjusting for vigorous physical activity, although the result did not reach statistical significance likely due to small sample size. Our data suggest that the difference in aerobic capacity by ethnicity is unlikely to be mediated by lung function. The mean lung function measurements were normal and similar between the two ethnic groups, with hispanics having slightly higher mean percent-predicted FEV1 and FVC. We also did not find a correlation between exercise capacity and lung function in our study. This is not unexpected, as previous studies have shown that VO_2 peak tends to drop when FEV1 drops below 80% of the predicted value [14]. In addition to objective measurements of lung function, we estimated ventilatory efficiency during exercise using the VE/VCO_2 at Anaerobic Threshold (AT). The mean VE/VCO_2 at Anaerobic Threshold (AT) was normal in this cohort and did not differ by ethnicity. Similar to lung function, aerobic capacity declines with age. In a recent study, hispanics with CF were found to have a 12 point difference in percent-predicted FEV1 compared to non-Hispanics, but the yearly rate of decline was similar between Hispanics and non-Hispanics [16]. In CF, a higher rate of decline in VO_2 peak is associated with decreased survival [1]. It is not known if the rate of decline of aerobic capacity is different between Hispanic and non-Hispanic individuals with CF. If Hispanics with CF demonstrate both a lower baseline VO_2 peak and a higher rate of decline in VO_2 peak than non-hispanics, this may help explain the increased mortality seen in Hispanics with CF. Alternatively, if the rate of decline is the same between Hispanics and non-hispanics, this would suggest that, similar to lung function, an earlier insult or intrinsic biologic factor may result in low baseline aerobic capacity in Hispanic individuals with CF. Twin studies suggest that genetic factors determine an estimated 55% of an individual VO_2 [9]. However, large studies of adults without cystic fibrosis have not demonstrated a significant difference in aerobic capacity between Hispanics and non-hispanic whites [32,33]. In addition to the pulmonary factors described above, aerobic capacity can be limited by cardiovascular or musculoskeletal factors, which were each considered separately. Cardiac inefficiency or dysfunction is assessed in an exercise test by the oxygen pulse, which is a surrogate for stroke volume. It unlikely that cardiac inefficiency contributes to lower aerobic capacity seen in Hispanic CF subjects, as all subjects in the study had normal oxygen pulse and this did not differ by ethnicity. Musculoskeletal limitations can affect aerobic capacity in CF including abnormal mitochondrial and glycolytic metabolism of skeletal muscle and muscle weakness not fully explained by physical inactivity [34,35]. Although we did not perform strength testing or assess body composition to directly assess the role of muscle strength or a lower exercising muscle mass on exercise capacity, we did look at maximum power achieved. The maximum power which an individual generates to overcome the increasing resistance of the cycle ergo meter reflects exercising muscle mass and muscle fatigability [36]. This was not statistically different between the two ethnic groups. Poor nutritional status, usually assessed in exercise studies by low BMI, has been linked to low aerobic capacity. In our cohort, Hispanic subjects had a higher BMI z-score, which argues against poor nutrition as a contributor. We demonstrated an important finding of the relationship between ethnicity, aerobic capacity and physical activity in a small cohort of individuals with CF. We recognized several limitations to this study, first being the small sample size. Second, the use of a survey instead of objectively measured activity introduces the risk of recall bias. Subjects who participated in structured activities such as seasonal team sports or sports camps of defined seasons and durations had less difficulty completing the questionnaire than those who did not participate in structured activities. Participation in a regularly scheduled activity may result in less recall bias, though it is difficult to predict whether this would over- or underestimate true activity levels. Since Hispanic subjects were less likely to report participation in organized sports, this group may have been at higher risk for recall bias. Third, the study is limited by a lack of a healthy non-CF control group, which may have helped elucidate if Hispanic CF subjects were less active and less aerobically fit than healthy age-matched Hispanic children. Larger studies that specifically target racial and ethnic minority CF subjects will be necessary to corroborate the findings in this study given the small sample size. The CF Foundation Registry could provide an opportunity to study aerobic capacity of healthy patients and of minorities in sufficient numbers if CF centers had the option to enter results of exercise testing when it is performed. Lastly, this is a generally healthy group of young people with CF with very mild lung impairment. This may impact the generalizability of the results, though aerobic capacity was still significantly reduced in Hispanics compared to non-Hispanics despite relatively normal lung function in both groups.

Conclusion

In a small group of children and young adults with mild CF and normal lung function, we found that vigorous physical activity and CFTR mutation severity were significant predictors of maximal aerobic capacity. Hispanics have lower VO_2 peak and longer recovery time than non-Hispanics regardless of hours of participation in vigorous activities and factors that have been associated with disease severity. Reduced aerobic capacity has been associated with increased mortality in CF therefore low aerobic capacity may contribute to higher mortality reported in this subgroup. Larger studies are needed to further understand the relationship between VO_2 peak, ethnicity and mortality.

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