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Physiological Markers of Exercise Capacity and Lung Disease Severity in Cystic Fibrosis

Laurie Smith[1] MSc, Charles C Reilly[1,2] PhD, Victoria MacBean[1] PhD, Caroline J Jolley[1.3] PhD, Caroline Elston[2] MBBS, John Moxham[1] MD & Gerrard F Rafferty[1] PhD

[1]King's College London, Division of Asthma, Allergy and Lung Biology, London UK.

[2]King's College Hospital NHS Foundation Trust, London UK.

[3]King's College London, Centre for Human and Aerospace Physiological Sciences.

Correspondence:

Dr Gerrard Rafferty

Department of Respiratory Medicine (Chest Unit), 2nd Floor Cheyne Wing, King's College Hospital, Denmark Hill, London SE5 9RS, UK

Email gerrard.rafferty@kcl.ac.uk

Summary at a glance

A novel marker of cystic fibrosis (CF) lung disease severity, inspiratory muscle electromyogram activity was investigated in 20 adult CF patients. Both T_LCO %predicted and inspiratory muscle electromyogram activity related strongly to exercise performance and therefore may be useful in CF lung disease management.

ABSTRACT

Background and objective

Peak aerobic capacity (VO_2peak) is an important outcome measure in cystic fibrosis (CF) but measurement is not widely available and can be influenced by patient motivation, pain and fatigue. Alternative markers of disease severity would be helpful. Neural respiratory drive, measured using parasternal intercostal muscle electromyography (EMGpara) reflects the load to capacity balance of the respiratory system and provides a composite measure of pulmonary function impairment in CF. The aim of the study was to investigate the relationship between exercise capacity, EMGpara and established measures of pulmonary function in clinically stable adult CF patients.

Methods

Twenty CF patients (12 male, median (range) age 22.3 (17.0-43.1) years) performed the 10m incremental shuttle walk test (ISWT) with contemporaneous measures of aerobic metabolism. EMGpara was recorded from second intercostal space at rest and normalised using the peak EMG obtained during maximum respiratory manoeuvres and expressed as EMGpara%max.

Results

VO_2peak was strongly correlated with ISWT distance (r=0.864, p<0.0001). T_LCO %predicted was best correlated with VO_2peak (r=0.842, p<0.0001) and ISWT distance (r=0.788, p<0.0001). EMGpara%max also correlated with VO_2peak (-0.757, p<0.0001), while the relationships between exercise outcome measures and FEV_1 %predicted and FVC %predicted were less strong. A T_LCO %predicted of <70.5%was the strongest predictor of VO_2peak <32ml/min/kg, (AUC 0.96, 100% sensitivity, 83.3% specificity).

ISWT distance and EMGpara%max also performed well, with other pulmonary function variables demonstrating poorer predictive ability.

Conclusion

T_LCO% predicted and EMGpara%max relate strongly to exercise performance markers in CF and may provide alternative predictors of lung disease progression.

Keywords: cystic fibrosis, disease management, electromyography, exercise, intercostal muscles, respiratory function

Short title: Disease severity in Cystic Fibrosis

INTRODUCTION

Forced expiratory volume in one second (FEV_1) and the rate of its decline are the most commonly used clinical predictors of survival in cystic fibrosis (CF)[1-3]. FEV_1 is, however, effort and technique dependent, relatively insensitive to small treatment responses[4] and poorly related to symptoms[5]. Recent advances in CF care, have highlighted the prognostic insensitivity of FEV_1[6]. Lung clearance index (LCI) is more sensitive to changes in CF lung disease severity than FEV_1[7], but measurement remains limited primarily to the research setting.

The significant load imposed on the cardiovascular and respiratory systems during exercise testing can reveal pathophysiological changes associated with disease progression that are not detected using spirometry. Peak aerobic capacity (VO_{2peak}) is related to quality of life[8], and is a strong predictor of hospitalisation[9] and mortality[10, 11] in adult CF patients. Exercise testing, however, not only requires specialist equipment and personnel, but also significant patient motivation. Some individuals are unable to exercise maximally due to pain and fatigue.

Indices which reflect both the airways obstruction and lung hyperinflation that occur in CF lung disease may provide more accurate markers of disease severity. Measurement of neural respiratory drive (NRD), obtained during resting tidal breathing using the parasternal intercostal electromyogram (EMGpara), has been shown to provide a sensitive, easily applied indicator of load on the respiratory system that reflects lung disease severity in CF[12, 13]. We wished, therefore, to test the hypothesis that indices

which reflect the overall impact of the pathophysiological changes that occur in CF lung disease would most strongly relate to exercise performance as assessed by the 10m incremental shuttle walk test (ISWT), in clinically stable adult CF patients and could, therefore, provide more robust markers of disease severity in CF.

METHODS

Clinically stable adult CF patients were recruited from Kings College Hospital, London, between January-July 2014. The study received local research ethics committee approval (South London (Dulwich) LREC Ref No 05/Q0703/82) and written informed consent was obtained.

Measurements

Spirometry, lung gas transfer (T_LCO) and its components (transfer coefficient (KCO) and alveolar volume (Va)) and lung volumes using body plethysmography were measured (Jaeger Masterscreen, CareFusion, Germany). Height and weight were measured and body mass index (BMI) calculated. Fat free mass (FFM) was determined by bioelectrical impedance (Bodystat 1500, Bodystat Ltd., Isle of Man, UK).

Surface EMGpara was recorded from the second intercostal space as previously described [12]. Resting EMGpara was measured during five minutes of relaxed breathing and the average value per breath calculated from the final minute. EMGpara was expressed as a percentage of the maximum value (EMGpara%max) achieved during a maximal volitional inspiratory manoeuvre. Three manoeuvres were performed at least five times; inhalation to total lung capacity (TLC) from functional residual capacity (FRC), maximal inspiratory pressure (PImax) and maximal sniff nasal pressure (SNIP). Maximal pressures were recorded for Pimax and SNIP. The greatest peak EMGpara regardless of the manoeuvre performed was selected to normalise EMGpara[12, 14]. For more details, see Supplementary Appendix S1.

Exercise capacity was assessed using the incremental shuttle walking test (ISWT) as previously described[15] with the distance achieved recorded. During the ISWT, ventilatory and metabolic variables were measured using a portable exercise system (Metamax 3b, Cortex Medical, Germany) and oxygen saturation recorded using pulse oximetry.

Protocol

All measurements were made during a single visit. EMGpara was measured initially followed by the maximal inspiratory manoeuvres, then pulmonary function followed by the ISWT.

Data analysis

All data expressed as median (range). Relationships between variables were assessed using Spearman correlation analysis. Change from rest to end exercise assessed using Wilcoxon matched pairs signed rank test. Mann-Whitney was used to compare variables between patients with a VO_2peak >32ml/min/kg to those with a VO_2peak <32ml/min/kg. Receiver operator characteristic (ROC) analysis was used to evaluate the predictive power of variables with respect to VO_2peak<32ml/min/kg, using thresholds demonstrating optimum balance between sensitivity and specificity. Statistical analysis performed using Prism version 6.0 (GraphPad Software Inc., California, USA). A p value <0.05 was considered statistically significant, except for correlation analysis for which a p value <0.01 was used to allow for the number of comparisons performed.

Mean (SD) EMGpara%max was 13.4 (7) in 15 patients with CF[12]. Studying 20 patients would provide a representative sample with a 5% margin of error at the 10% level.

RESULTS

Twenty adult patients, median (range) age 22.3 (17.0 - 43.1) years (12 male), with stable CF were studied (Table 1). The patients had a range of disease severity as classified using FEV_1 z-score. Five had mild (median (range) FEV_1 %predicted 95.2% (89.7 – 101.3)), three moderate (median (range) FEV_1 %predicted 66.2% (65.0 - 68.8)), two severe (median (range) FEV_1 %predicted 55.0% (48.3 – 61.6)) and 10 very severe airflow obstruction (median (range) FEV_1 %predicted 38.1% (16 – 50.3)). Gas trapping and hyperinflation were also present as indicated by RV/TLC >25% and TGV/TLC >50% (Table 1).

All patients performed a maximal shuttle walk test as indicated by either a respiratory exchange ratio (RER) >1.1 (n=14), a max HR >80% predicted (n=4) or a maximum minute ventilation (Vemax) >80% predicted (Predicted from FEV_1 x 40) (n=2). Median (range) ISWT distance was 645m (280 – 880). All physiological variables changed significantly from baseline to end exercise (Table 2) ($p<0.001$).

Median (range) VO_2peak 23.9 ml/min/kg (16.8 – 38.7)) and VO_2 at AT (15.2 ml/min/kg (10.3 – 29.5)) indicated markedly reduced exercise capacity in this patient group overall. A strong correlation was observed between ISWT distance and VO_2peak ($r=0.864$, $p<0.0001$). The relationship between VO_2peak and ISWT distance was described by the regression equation and 95% confidence intervals VO_2peak = 1.789 (-4.91 to 8.49) + 0.0401 (0.03 to 0.05) x ISWT distance (Fig 1).

EMGpara%max reflected CF lung disease severity and was significantly correlated with T_LCO %predicted, RV/TLC, FEV_1 % predicted and FVC % predicted and Va %predicted (Table 3).

T_LCO %predicted showed the strongest relationship with exercise outcome measures, correlating significantly with VO_2peak (r=0.842, p<0.0001), VO_2 at AT (r=0.671, p=0.0012) and ISWT distance (r=0.788, p<0.0001) (Table 4). T_LCO %predicted showed the best correlation with end exercise SpO_2 (r=0.64, p<0.01). EMGpara%max was also significantly correlated with VO_2peak, VO_2 at AT and ISWT distance walked (Table 4). The relationships between exercise capacity and other lung function and respiratory muscle parameters including FEV_1 %predicted and FVC %predicted were less strong (Table 4). Fat free mass correlated with ISWT distance.

Using the variables that correlated with VO_2peak, patients with a VO_2peak <32ml/min/kg had significantly higher EMGpara%max at rest and lower T_LCO %predicted, ISWT distance and FVC %predicted than those with VO_2peak >32ml/min/kg (Fig 2). Thresholds for predicting VO_2peak <32ml/min/kg, together with sensitivity and specificity values and area under the ROC curve for each measured variable are shown in Table 5. A T_LCO %predicted of <70.5%was the strongest predictor of VO_2peak <32ml/min/kg, (AUC 0.96, 100% sensitivity, 83.3% specificity). ISWT and EMGpara%max also performed well, with other variables demonstrating poorer predictive ability (Table 5).

DISCUSSION

The study examined the relationship between exercise capacity, EMGpara activity and pulmonary function in adult CF patients. EMGpara%max and T_LCO %predicted were more strongly related to measures of exercise performance than FEV_1. T_LCO %predicted was most strongly related to VO_2peak and ISWT distance and most accurately predicted VO_2peak.

Exercise capacity was assessed using the ISWT with contemporaneous measurements of respiratory and metabolic variables. The ISWT has been shown to provide a valid assessment of maximal exercise capacity in individuals with chronic respiratory diseases[16, 17]. Patients performed the ISWT maximally and each test was conducted by an experienced practitioner. Although the ISWT was performed once only, all participants were accustomed to the test as part of their routine clinical assessment. Contemporaneous measurement of metabolic variables avoided comparison between results of exercise tests performed on two separate occasions. Exercise limitation in CF is multifactorial hence not all patients will demonstrate respiratory limitation at end exercise, however each patient was deemed to have reached limitation by at least one of the described criteria: RER >1.1 representing metabolic limitation, HR >80%predicted representing cardiac limitation or Vemax >80%predicted representing ventilatory limitation.

To reduce contamination from adjacent postural muscles and ensure good quality EMGpara signals were acquired, patients adopted a relaxed seated position with arms supported and adaptive mains filtering and post-acquisition digital band-pass filtering were applied to minimise background electrical noise. Standardised electrode position and good electrical contact were adopted to minimise poor between-subject and between-occasion reproducibility[18]. EMG signal attenuation due to subcutaneous fat was not considered important as none of the patients were obese.

As expected, a strong correlation between ISWT distance and VO_2peak was observed and the data broadly comparable to those obtained by Bradley et al[19] ($r=0.95$, $p<0.01$) using a modified ISWT[19]. When compared in percentage terms to these data[19], the steeper slope and lower intercept of the regression equation derived from the current data resulted in slightly lower values for VO_2peak at the shorter ISWT distances (90% at 300m) and higher values at the longer ISWT distances (118% at 900m). These differences probably reflect the use of the modified ISWT by Bradley et al and the inclusion of patients with greater exercise tolerance and higher VO_2peak.

Measures of exercise capacity were also strongly correlated with a number of pulmonary function variables and EMGpara%max. Overall, VO_2peak, VO_2 at AT and ISWT distance were most strongly correlated with T_LCO %predicted. The strength of the relationship between T_LCO %predicted and VO_2peak ($r=0.842$) was similar to that observed between ISWT distance and VO_2peak ($r=0.864$), suggesting T_LCO could be a useful marker of lung disease severity in CF patients particularly in those that are unable

or unwilling to exercise maximally. Similar, albeit less strong relationships were observed between EMGpara%max, VO_2peak, VO_2 at AT and ISWT distance. Interestingly FEV_1 and RV/TLC were only moderately well correlated with markers of exercise capacity, reflecting previous findings on the strength of the relationships observed between pulmonary function and exercise performance [6, 19]..

Pianosi *et al* demonstrated that a VO_2peak <32ml/min/kg was associated with a 60% eight-year mortality in CF[10]. Our data indicated that patients with a VO_2peak <32ml/min/kg had significantly lower levels of T_LCO %predicted and higher levels of EMGpara%max as well as decreased ISWT distance, FEV_1 %predicted and FVC %predicted. Receiver operator curve analysis indicated T_LCO %predicted <70.2% was the strongest predictor of a VO_2peak <32ml/min/kg. Both ISWT distance and EMGpara%max also had good positive predictive accuracy, while FVC %predicted and FEV_1%predicted performed less well. The relatively poorer predictive capacity of spirometric variables was most likely due to such measures only representing one aspect of the pathophysiological changes that occur in CF lung disease and hence do not fully reflect the range of factors which limit exercise in this patient group.

There are few data available concerning the relationship between exercise performance and T_LCO in CF. Pastre et al[20] demonstrated that T_LCO and FEV_1 correlated with VO_2peak, but that FEV_1 demonstrated the strongest relationship. The study did, however, involve bootstrapping to account for missing data for some variables including

T_LCO. Our results are similar in that FEV_1 did correlate with VO_2peak, but that T_LCO %predicted had the strongest relationship.

Exercise tolerance in CF is multifactorial, only 30% of the variability in exercise performance has been attributed to airways obstruction[20-23]. Gas exchange abnormalities have also been shown to affect exercise performance[24-26]. Small airway dysfunction leading to ventilation heterogeneity and ventilation perfusion mismatch alongside elevated venous admixture, intrapulmonary shunting and alveolar hypoventilation[7, 27, 28] have been implicated. T_LCO reflects the lung volume available for gas exchange, gas diffusion and exchange across the alveolar membrane. In worsening CF lung disease, accessible alveolar volume decreases due to ventilation heterogeneity and gas diffusion is impaired by suboptimal ventilation/perfusion relationships. By contrast gas exchange across the alveolar membrane is not substantially reduced, as demonstrated in the current cohort by the relatively well preserved KCO. When considered alongside the measured reductions in alveolar volume and the relationship of Va %predicted to VO_2peak and VO_2 at AT and the relationship between TLCO% predicted and end exercise SpO_2, the current data suggest that it is the decreased accessible lung volume and impaired gas diffusion as measured using T_LCO that contributed mostly to exercise impairment in this cohort of CF patients rather than airways obstruction.

The parasternal intercostal muscles are obligate inspiratory muscles recruited in tandem with the diaphragm, acting to prevent rib cage distortion and ventilatory

inefficiency. EMGpara increases progressively alongside diaphragm EMG during exercise[12]. EMGpara provides a measure of NRD which, unlike measures such as spirometry which only measures a single aspect of respiratory function, reflects the combined effects of mechanical and metabolic load on the respiratory system. In CF, airways obstruction and lung hyperinflation increase the load on the respiratory muscles. Lung hyperinflation increases the elastic work of breathing and the development of intrinsic positive end-expiratory pressure which imposes a threshold load on each breath. Hyperinflation also reduces inspiratory muscle length leading to functional inspiratory muscle weakness[29]. NRD as measured by EMGpara increases to maintain ventilation at the appropriate level for blood gas homeostasis. The current data confirm our previous findings that EMGpara%max provides a sensitive indicator of load on the respiratory system which is related to disease severity in CF[12, 13] and demonstrate that this index provides an effort independent measure of exercise capacity which could be helpful in disease management.

EMGpara%max and T_LCO %predicted were also strongly correlated with each other. As median KCO %predicted for the group was 99% and not significantly related to EMGpara%max, the current data suggest that the significant relationship between T_LCO %predicted and EMGpara%max was primarily due to decrements in alveolar volume available for gas exchange. A significant correlation between EMGpara%max and Va %predicted was observed.

Although exercise limitation in CF has a large ventilatory component, it is also influenced by peripheral muscle function[30-32] and nutritional status [21] as indicated by the significant correlation between FFM and ISWT distance. Suboptimal peripheral muscle function results in decreased aerobic metabolism and early lactic acidaemia[23, 31], resulting in reduced exercise capacity. Although T_LCO and EMGpara%max were strongly correlated with physiological measures of exercise capacity, such measurements were performed at rest and therefore do not reflect both the influence of peripheral muscle dysfunction and the changes in lung function such as dynamic hyperinflation [12] that occur during exercise which influence exercise performance.

T_LCO is not routinely measured in CF and is not part of CF care standards [33]. There is conflicting evidence as to the benefit of measuring T_LCO in patients with CF. T_LCO has been shown to be maintained until lung disease becomes more advanced[34] and hence is unhelpful prognostically[35]. Conversely, serial measurements have been shown to correlate with clinical severity in patients with advanced lung disease, unlike routine lung function tests such as FEV_1[36, 37]. Although lung function indices such as FEV_1 and FVC are commonly used to assess CF lung disease severity, assessment of exercise performance is a key clinical and trial outcome tool in CF [33, 38] and measurement of VO_2peak has been shown to better predict both mortality [10, 11, 39] and the risk of hospitalisation[9]. Exercise testing with the aim of measuring VO_2peak is, however, expensive and demanding on patients and therefore not always utilised in CF centres. This study has shown that measurements of T_LCO %predicted, as well EMGpara%max were strongly related to exercise performance.

In conclusion, measurement of peak aerobic capacity is an important assessment tool in CF management. It is, however, not widely available and such testing can be negatively influenced by poor patient motivation, pain, fatigue as well as shortness of breath. Integrated measures of pulmonary function such as T_LCO %predicted and EMGpara%max were related strongly to exercise performance in adult patients with CF and therefore may be of benefit in the assessment of CF lung disease severity.

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Table 1. Patient characteristics, pulmonary function and exercise performance in 20 adult patients with CF.

	Median (range)
Age (years)	22.3(17.0 - 43.2)
Height (cm)	169.9 (150.1 - 178.4)
Weight (kg)	56.6 (47.3 - 73.3)
BMI (kg/m^2)	19.9 (18.0 - 27.2)
FFM (%)	80.0 (59.4 – 91.9)
FEV_1 %predicted	49.3(16.0 - 101.3)
FVC %predicted	76.5 (23.8 - 111.9)
RV/TLC (%)	44.0 (22.0 - 74.0)
TGV/TLC (%)	61.0 (43.0 - 79.0)
T_LCO %predicted	70.5 (41.1 - 104.1)
KCO %predicted	98.8 (70.6 - 127.4)
Va %predicted	75.7 (33.2 – 126.8)
Pimax (cmH_2O)	99.9 (61.1 – 130.0)
SNIP (cmH_2O)	94.0 (40.61 – 128.6)

BMI body mass index, FFM fat free mass, FEV1, forced expired volume in 1 second, FVC forced vital capacity, RV residual volume, TLC total lung capacity, TGV thoracic gas volume, T_LCO lung gas transfer, KCO transfer coefficient, Va alveolar volume, Pimax maximal inspiratory pressure, SNIP sniff nasal inspiratory pressure)

Table 2. Median (range) rest and end exercise data for ISWT, VO_2peak, VCO_2peak, RER, Ve/VO_2, Ve/VCO_2, Ve %predicted, heart rate, SpO_2 and EMGpara%max.

Variable	Resting	End Exercise	p
ISWT distance (m)		645m (280 – 880)	
VO_2~~peak~~(ml/min/kg)	5.8 (4.3 - 8.1)	24.4 (16.8 - 38.7)	<0.001
VCO_2~~peak~~(ml/min/kg)	4.7 (3.1 - 7.1)	24.9 (14.1 - 42.5)	<0.001
RER	0.83 (0.62 - 0.94)	1.09 (0.8 - 1.46)	<0.001
Ve/VO_2		35.15 (25.1 – 45.6)	
Ve/VCO_2		32.7 (24.6 – 48.8)	
Ve (%pred.)	12.0 (4.9 - 41.9)	63.7 (43.0 - 114.0)	<0.001
HR (bpm)	86.5(60 - 110)	161 (125 – 175)	<0.001
SpO_2	96 (88 – 100)	93 (70 – 97)	< 0.001
EMGpara%max (%)	7.8 (2.0 - 34.5)		

ISWT incremental shuttle walk test, VO_2peak peak oxygen consumption, VCO_2peak peak carbon dioxide production, RER respiratory exchange ratio, Ve minute ventilation, HR heart rate, SpO_2 pulse oximetry derived oxygen saturation, EMGpara%max parasternal intercostal muscle EMG expressed as a percentage of maximum)

Table 3. Spearman's correlation analysis examining the relationships between resting EMGpara%max and T_LCO %predicted, RV/TLC, FEV1 % predicted, FVC % predicted and Va %predicted.

	EMGpara%max	
	r	P
T_LCO %predicted	-0.78	<0.0001
RV/TLC %predicted	0.69	0.001
FEV_1 %predicted	-0.65	0.002
Va %predicted	-0.62	0.004
FVC %predicted	-0.61	0.004

T_LCO lung gas transfer, RV residual volume, TLC total lung capacity, FEV1, forced expired volume in 1 second, Va alveolar volume, FVC forced vital capacity

Table 4. Spearman's correlation analysis examining the relationships of VO_2peak, AT and ISWT distance with T_LCO % predicted, resting EMGpara%max, FEV_1 % predicted, FVC %predicted and FFM.

	VO_2peak (ml/min/kg)		VO_2 at AT (ml/min/kg)		ISWT Distance Walked (m)	
	r	p	r	P	r	p
T_LCO % predicted	0.842	<0.0001	0.671	0.0012	0.788	<0.0001
EMGpara%max	-0.757	<0.0001	-0.669	0.0012	-0.720	<0.0001
FVC %predicted	0.593	0.0058	0.666	0.0013	0.551	0.011
FEV_1 % predicted	0.558	0.011*	0.549	0.012*	0.581	0.007
Va %predicted	0.572	0.008	0.592	0.006	0.509	0.022*
FFM (%)	0.524	0.018*	0.295	0.207	0.628	0.003

*p values less than 0.01 used to define significance due to the number of comparisons performed. T_LCO lung gas transfer, EMGpara%max parasternal intercostal muscle EMG expressed as a percentage of maximum, FVC forced vital capacity, FEV1, forced expired volume in 1 second, Va alveolar volume, FFM fat free mass

Table 5. Results of ROC analysis to predict VO_2peak <32 ml/min/kg. Area under curve, sensitivity and specificity for T_LCO %predicted, ISWT distance, EMGpara%max, FVC %predicted and FEV1 %predicted.

Variable	Threshold	Area	Sensitivity	Specificity
T_LCO %predicted	<70.5%	0.96	100	83.3
ISWT	<670 m	0.93	100	84.6
EMGpara%max	>10.20%	0.92	100	76.9
FVC	<77.7%	0.87	85.71	76.9
FEV_1 %predicted	<63.30%	0.86	85.71	84.6
Va %predicted	<70.15	0.86	100	53.9

T_LCO lung gas transfer, ISWT incremental shuttle walk distance, EMGpara%max parasternal intercostal muscle EMG expressed as a percentage of maximum, FVC forced vital capacity, FEV1, forced expired volume in 1 second, Va alveolar volume)

Figure legends

Figure 1. Regression analysis describing the relationship between VO_2peak and ISWT distance. Dashed line lines represent 95% confidence intervals. Regression equation (95%CI) VO2peak = 1.789 (-4.91 to 8.49) + 0.0401 (0.03 to 0.05) x ISWT distance

Figure 2. Comparison of EMGpara%max, T_LCO, ISWT and FVC %predicted and FEV1 %predicted in patients achieving a VO2peak <32ml/min/kg with those of >32ml/min/kg. Horizontal lines indicate median