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# Determinants of exercise capacity in cystic fibrosis patients with mild-to-moderate lung disease

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## Abstract

**Background:** Adult patients with cystic fibrosis (CF) frequently have reduced exercise tolerance, which is multifactorial but mainly due to bronchial obstruction. The aim of this retrospective analysis was to determine the mechanisms responsible for exercise intolerance in patients with mild-to-moderate or severe disease.

**Methods:** Cardiopulmonary exercise testing with blood gas analysis at peak exercise was performed in 102 patients aged  $28 \pm 11$  years: 48 patients had severe lung disease ( $FEV_1 < 50\%$ , group 1) and 54 had mild-to-moderate lung disease ( $FEV_1 \geq 50\%$ , group 2).  $VO_2$  peak was measured and correlated with clinical, biological, and functional parameters.

**Results:**  $VO_2$  peak for all patients was  $25 \pm 9$  mL/kg/min ( $65 \pm 21\%$  of the predicted value) and was  $< 84\%$  of predicted in 82% of patients (100% of group 1, 65% of group 2).  $VO_2$  peak was correlated with body mass index, C-reactive protein,  $FEV_1$ , FVC, RV, DLCO,  $V_E/VCO_2$  peak,  $V_D/V_T$ ,  $PaO_2$ ,  $PaCO_2$ ,  $P(A-a)O_2$ , and breathing reserve. In multivariate analysis,  $FEV_1$  and overall hyperventilation during exercise were independent determinants of exercise capacity ( $R^2 = 0.67$ ).  $FEV_1$  was the major significant predictor of  $VO_2$  peak impairment in group 1, accounting for 31% of  $VO_2$  peak alteration, whereas excessive overall hyperventilation (reduced or absent breathing reserve and  $V_E/VCO_2$ ) accounted for 41% of  $VO_2$  alteration in group 2.

**Conclusion:** Exercise limitation in adult patients with CF is largely dependent on  $FEV_1$  in patients with severe lung disease and on the magnitude of the ventilatory response to exercise in patients with mild-to-moderate lung disease.

**Keywords:** Cystic fibrosis, Cardiopulmonary exercise testing, Pulmonary function, Exercise

## Background

Cystic fibrosis (CF) is characterized by deterioration of nutritional status and irreversible loss of lung function [1-3]. Patients with CF often experience exertional dyspnea and have reduced maximal exercise capacity, which is an important predictor of mortality [4-7]. Regular exercise in these patients has been associated with improved aerobic exercise endurance and quality of life [4,8]. Physical exercise requires the cardiopulmonary system to deliver oxygen to muscles in sufficient quantity to generate energy through aerobic glycolysis. There are conflicting data on the precise mechanisms

underlying exercise intolerance in CF, and a number of factors have been implicated [9], including poor nutritional status, peripheral muscle dysfunction [10,11], and especially, ventilatory limitation [12,13]. In other studies, dysfunctional gas exchange has been shown to play a crucial role in limiting exercise performance [14-17].

Only a third of the variability in exercise capacity of CF patients can be explained by  $FEV_1$ , demonstrating that resting pulmonary function tests (PFTs) alone are insufficient to explain the exercise limitation [1,9,13]. By comparison, cardiopulmonary exercise testing (CPET) offers a sensitive evaluation of potential physiological disturbances in cardiovascular, respiratory, peripheral, or neurosensory responses to a standardized exercise protocol [18]. Although it remains underutilized in CF [19], CPET could provide important exercise-related

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measures that might explain the reduced exercise performance and thus assist in CF patient management aimed at improving exercise capacity.

With this in mind, we initiated a study to determine the mechanisms responsible for exercise limitation in 102 adult CF patients with mild-to moderate or severe lung disease. The patients were subjected to CPET with blood gas analysis during exercise and the results were correlated with clinical and functional characteristics.

## Methods

### Patients

A total of 102 adult patients (sex ratio M:F 0.52) with CF were enrolled at four CF centers in France: Lille (75 patients), Rouen (15 patients), Dijon (5 patients), and Grenoble (7 patients). Written informed consent for participation in the study was obtained from participants. Use of the patient data was approved by the local ethics committee, and the study was considered observational and approved as such by the Institutional Review Board of the French Learned Society for Pulmonology (*Société de Pneumologie de Langue Française*, CEPRO 2012 009).

Clinical, nutritional, biological, PFT, and CPET data were obtained on the same day, either at diagnosis or at the routine annual evaluation, and were retrospectively collected. When patients were seen at several follow-up visits, only the data from the first visit were recorded. Hypoxemic patients did not perform CPET and were excluded from the analysis. A diagnosis of CF was obtained by sweat chloride > 60 mmol/L and the presence of CFTR gene mutations by molecular analysis. Additional characteristics recorded at the time of testing were diseases usually associated with CF, bacterial colonization, treatments, and nutritional status, including height and weight measurements and impedance analysis.

### Cardiopulmonary testing

Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV<sub>1</sub>), FEV<sub>1</sub> to FVC ratio, total lung capacity (TLC), and residual volume (RV) were measured by plethysmography (Jaeger-Masterlab<sup>®</sup> cabin). Diffusing capacity of the lung for carbon monoxide (DLCO: mL CO/min/mm Hg) was adjusted for hemoglobin concentration in g/dL according to Cotes' equation: corrected (Hb) DLCO = DLCO × (10.2 + Hb)/(1.7 × Hb). Following ATS/ERS 2005 guidelines, the lower limits of normal were set at the 5th percentile (or predicted minus 1.64 SD) of each reference population. The results are expressed as percentages of the predicted values. Predicted normal values were derived from standard equations [20-22].

PFTs and CPET were performed in an air-conditioned laboratory (22°C constant temperature), using a standardized protocol as previously described [23,24]. The

CPET protocol was the same at each center. Each patient underwent a symptom-limited incremental exercise test on an ergometric bicycle (Ergoline-Ergometrics 800<sup>®</sup>). The protocol included a warm-up period of 3 min at 20 W followed by a progressively increasing work rate (WR) in a ramp fashion and then 3 min recovery. The ramped WR increment was individualized (range, 8–30 W/min). During exercise, heart rate (HR) was monitored continuously by 12-lead ECG, and arterial oxygen saturation (SpO<sub>2</sub>) was measured by pulse oximetry (Nellcor N-395). The expired gases were analyzed with an Ergocard<sup>®</sup>, focusing on oxygen consumption (VO<sub>2</sub>), carbon dioxide production (VCO<sub>2</sub>), minute ventilation (VE), and tidal volume (VT). The oxygen pulse (VO<sub>2</sub>/HR) was calculated. Measurements of PaO<sub>2</sub> and PaCO<sub>2</sub> were performed on room air at rest and at peak exercise. Normal values for PaO<sub>2</sub> were derived from [25]. Lactatemia was determined at maximal exercise. Breathing reserve (BR) was calculated as BR = (predicted maximum minute ventilation [MMV] – V<sub>E</sub> peak)/MMV, with MMV estimated from MMV = FEV<sub>1</sub> × 40. HR peak was expressed as a percentage of maximum predicted HR, calculated as HR max = 210 – (0.65 × age). Dead space (V<sub>D</sub>/V<sub>T</sub>) was calculated according to Bohr's equation corrected for the additional instrument dead space: V<sub>D</sub>/V<sub>T</sub> = (PaCO<sub>2</sub> – PECO<sub>2</sub> mean)/PaCO<sub>2</sub> – (V<sub>D</sub> [machine]/V<sub>T</sub>) where PECO<sub>2</sub> is the partial pressure of expired CO<sub>2</sub>. Predicted values for VO<sub>2</sub> max were calculated from reference equations [26]. Poor motivation appeared not to be an interfering factor in our analysis, as all patients had at least one of the following: BR < 15%, peak HR > 90% of predicted, peak lactate > 7 mmol/L, peak exercise PaO<sub>2</sub> < 55 mm Hg, and peak V<sub>E</sub>/VO<sub>2</sub> > 35 or peak RER > 1.15 [23]. Immediately after exercise, subjects were asked to score their sense of breathlessness and muscle fatigue at peak exercise using Borg scales.

### Statistical analysis

The continuous variables are reported as mean ± SD. Normal distribution of quantitative variables was tested by the Shapiro–Wilk test. Differences in FEV<sub>1</sub> between the groups were determined with the Student's t-test or Mann–Whitney test. Bivariate analyses were performed to study the relationships between each explanatory variable and the VO<sub>2</sub> peak. Pearson's or Spearman's correlation coefficient was used for quantitative variables, and the Student's t-test or Mann–Whitney test for qualitative variables. In addition, a multivariable linear regression with a stepwise selection at the level 0.2 was performed to identify a subset of the most important explanatory variables for the relationship with VO<sub>2</sub> peak. In order to avoid the problem of multicollinearity which happens when the explanatory variables are highly correlated, and to obtain a parsimonious model, we adopt the

following strategy: first, variables with  $p < 0.2$  were selected and included in a Principal Component Analysis (PCA) in order to study their correlations. Then, the variables included in the multivariable regression model were selected by the results of PCA (graphic correlation circle) on the basis of their clinical pertinence. The stability of the model was assessed by a bootstrap method [27]. The bootstrap resampling method was based on 1000 replicates of the initial dataset. Multivariable regression with a stepwise selection at the level 0.2 was performed on each of these replicates. The inclusion of the variable in the final model was confirmed if this candidate variable was selected in at least 70% of these 1000 analyses. In the final model, for each variable we computed the partial R-square, coefficient, 95% confidence intervals and adjusted p-value. Final variables from the multivariate analysis were applied to each group of FEV<sub>1</sub>. All analyses were achieved with SAS software version 9.2 (SAS Institute Inc., Cary, NC). All tests were performed at the significant level at 0.05.

## Results

### Subjects

The demographic and clinical characteristics are shown in Table 1, and the resting PFT results are presented in Table 2. The cohort consisted of 102 CF patients with a mean age of  $28 \pm 11$  years (range 17–67). The time from diagnosis to evaluation was  $16 \pm 10$  years. For data analysis, the cohort was divided into two groups according to

**Table 1 Demographic and clinical characteristics of the CF patients**

ΔF 508 homozygous mutation <sup>a</sup>	31/79 (40%)
Smoker <sup>a</sup>	10/102 (10%)
Oxygen supplementation <sup>a</sup>	11/95 (11%)
ABPA <sup>a</sup>	33/95 (35%)
Exocrine pancreatic insufficiency <sup>a</sup>	78/102 (76%)
Diabetes <sup>a</sup>	21/102 (21%)
Nasal polyposis <sup>a</sup>	25/94 (27%)
BMI, kg/m <sup>2b</sup>	20 (20 ± 3)
Lean body mass, kg <sup>b</sup>	45 (48 ± 9)
<i>Pseudomonas aeruginosa</i> <sup>a</sup>	63/99 (63%)
<i>Staphylococcus aureus</i> MS <sup>a</sup>	36/99 (36%)
<i>Mycobacterium abscess</i> <sup>a</sup>	4/99 (4%)
Blood leukocytes, 10 <sup>12</sup> /mm <sup>3b</sup>	9 (9.7 ± 3.8)
Blood polymorphonuclear neutrophils, 10 <sup>12</sup> /mm <sup>3b</sup>	6 (6.4 ± 3.3)
CRP, mg/L <sup>b</sup>	5.5 (15 ± 30)
Serum albumin, g/L <sup>b</sup>	42 (42 ± 4)

ABPA = allergic bronchopulmonary aspergillosis; BMI = body mass index; CRP = C-reactive protein.

Qualitative variables are given as frequency and percentage.

<sup>a</sup>Results are expressed as number (percentage) of patients.

<sup>b</sup>Results are expressed as median values (mean ± SD).

**Table 2 Resting pulmonary function tests in CF patients classified according to FEV<sub>1</sub>**

	All patients (n = 102)	Group 1 (n = 48)	Group 2 (n = 54)
FEV <sub>1</sub>		< 50%	≥ 50%
FEV <sub>1</sub> <sup>a</sup>	60 ± 28	35 ± 9 <sup>b</sup>	82 ± 18
FVC <sup>a</sup>	75 ± 24	56 ± 14 <sup>b</sup>	93 ± 16
FEV <sub>1</sub> /FVC	65 ± 15	54 ± 11 <sup>b</sup>	75 ± 10
RV <sup>a</sup>	176 ± 65	220 ± 50 <sup>b</sup>	135 ± 48
DLCO <sup>a</sup>	68 ± 18	56 ± 13 <sup>b</sup>	78 ± 14
PaO <sub>2</sub> , mm Hg	80 ± 14	71 ± 10 <sup>b</sup>	87 ± 12
PaCO <sub>2</sub> , mm Hg	38 ± 4	38 ± 5	37 ± 4
P(A-a)O <sub>2</sub> , mm Hg	29 ± 13	38 ± 8 <sup>b</sup>	21 ± 12

<sup>a</sup>Results are expressed as mean ± SD percentage of predicted values.

<sup>b</sup>P < .0001 compared with group 2.

their FEV<sub>1</sub>: group 1 patients with severe lung disease (FEV<sub>1</sub> < 50%, 48 patients) and group 2 patients with mild-to-moderate lung disease (FEV<sub>1</sub> ≥ 50%, 54 patients). Group 1 had a significantly higher frequency of homozygosity for the CFTR ΔF 508 mutation, pancreatic insufficiency, bronchial colonization with *Pseudomonas aeruginosa*, and biological inflammatory syndrome, and significantly lower body mass index (BMI) and longer disease duration (data not shown).

The patients had a range of disease severities and were recruited from four centers in France. Patients from different centers all had characteristics consistent with the French CF Registry 2009 Report [28] and showed equivalent frequencies of key CF characteristics (ΔF508 mutation, exocrine pancreatic insufficiency, and colonization with *P. aeruginosa*), supporting the reproducibility of the results and the potential for extrapolation to other patient populations.

Resting PFT values (Table 2) were significantly more altered in group 1 than in group 2 (Table 2). As expected, three major functional abnormalities were found: obstructive syndrome (FEV<sub>1</sub>/FVC = 65 ± 15% of predicted), altered distension (RV = 176 ± 65% of predicted), and altered DLCO (68 ± 18% of predicted).

### Exercise responses

Exercise cessation was mainly due to leg fatigue in combination with dyspnea (62%), whereas leg fatigue alone or dyspnea alone was observed in 17% and 21% of patients, respectively. The VO<sub>2</sub> peak value (weight-adjusted VO<sub>2</sub>) was decreased to < 84% of predicted in 83/102 (82%) of patients (48/48 [100%] in group 1 and 35/54 [65%] in group 2) and was significantly lower in group 1 than in group 2 (Table 3).

Analysis of the ventilatory response (V<sub>E</sub> peak, BR, respiratory rate (RR), V<sub>T</sub>/FVC peak) highlighted the differences according to FEV<sub>1</sub> impairment (Table 3). Group

**Table 3 Cardiopulmonary exercise tests in CF patients classified according to FEV<sub>1</sub>**

	All patients (n = 102)	Group 1 (n = 48)	Group 2 (n = 54)
FEV <sub>1</sub>		< 50%	≥ 50%
VO <sub>2</sub> peak, mL/kg/min	25 ± 9	20 ± 5 <sup>d</sup>	30 ± 8.5
VO <sub>2</sub> peak <sup>a</sup>	65 ± 21	51 ± 13 <sup>d</sup>	77 ± 20
Borg dyspnea	4.7 ± 1.9	5.6 ± 2 <sup>b</sup>	4.1 ± 1.5
Borg Leg fatigue	4.5 ± 1.8	5.2 ± 1.8 <sup>b</sup>	4.4 ± 1.7
VE peak, L/min	58 ± 22	44 ± 11 <sup>d</sup>	70 ± 21
RR peak, min	41 ± 9	43 ± 9 <sup>b</sup>	39 ± 8
V <sub>T</sub> /FVC peak, %	48 ± 11	47 ± 13	48.6 ± 8
V <sub>E</sub> /VO <sub>2</sub> peak	41 ± 7	42 ± 7	41 ± 7
V <sub>E</sub> /VCO <sub>2</sub> peak	36 ± 6	37 ± 6	35 ± 5
BR, %	24 ± 20	8 ± 11 <sup>d</sup>	37.5 ± 16
V <sub>D</sub> /V <sub>T</sub> peak	0.32 ± 0.11	0.39 ± 0.07 <sup>d</sup>	0.25 ± 0.10
pH peak	7.34 ± 0.04	7.34 ± 0.04	7.35 ± 0.04
PaO <sub>2</sub> peak, mm Hg	76 ± 16	63 ± 10 <sup>d</sup>	89 ± 12
PaCO <sub>2</sub> peak, mm Hg	40 ± 7	44 ± 6 <sup>d</sup>	36 ± 4
P(A-a)O <sub>2</sub> peak, mm Hg	37 ± 13	46 ± 8 <sup>d</sup>	28 ± 10
Lactatemia peak, mmol/L	7 ± 2.6	6 ± 2 <sup>d</sup>	7.9 ± 3
HR peak <sup>a</sup>	82 ± 10	79 ± 8 <sup>d</sup>	86 ± 9
VO <sub>2</sub> /HR peak <sup>a</sup>	79 ± 22	67 ± 16 <sup>d</sup>	90 ± 21

<sup>a</sup>Results are expressed as mean ± SD percentage of predicted values.

<sup>b</sup>P < .01 compared with group 2.

<sup>c</sup>P < .001 compared with group 2.

<sup>d</sup>P < .0001 compared with group 2.

1 had a lower absolute value of V<sub>E</sub> at peak exercise, and a depletion of BR. Hyperventilation was due to simultaneous increases in RR and tidal volume. Impairment in pulmonary gas exchange was more severe in group 1, as shown by higher values of P(A-a)O<sub>2</sub>, V<sub>D</sub>/V<sub>T</sub> peak, and PaCO<sub>2</sub>, and lower values of PaO<sub>2</sub>. Cardiocirculatory responses were normal in group 2, but patients in group 1 showed low VO<sub>2</sub>/HR values and a significant decrease in peak HR. Four patients experienced ECG abnormalities but continued with the exercise test.

#### Determinants of exercise capacity

Significant correlations were observed between VO<sub>2</sub> peak and nutritional status (BMI, lean body mass), inflammation markers (C-reactive protein [CRP], leukocytosis), resting PFT (FVC, FEV<sub>1</sub>, RV, DLCO, P(A-a)O<sub>2</sub>), and quantifiable parameters of CPET (V<sub>E</sub> peak, V<sub>E</sub>/VO<sub>2</sub> peak, V<sub>E</sub>/VCO<sub>2</sub> peak, BR, V<sub>D</sub>/V<sub>T</sub> peak, PaO<sub>2</sub> peak, P(A-a)O<sub>2</sub> peak, and HR (Table 4 and Figure 1).

The results of the stepwise multiple regression analysis for determinants of exercise capacity are shown in Table 5. Of the variables entered into the model (BMI, FEV<sub>1</sub>, FVC, DLCO, PaO<sub>2</sub>, V<sub>E</sub>/VCO<sub>2</sub> peak, BR, V<sub>D</sub>/V<sub>T</sub> peak, PaO<sub>2</sub> peak, PaCO<sub>2</sub> peak, P(A-a)O<sub>2</sub> peak, and lactatemia peak),

**Table 4 Correlation of clinical and functional variables with VO<sub>2</sub> peak in CF patients**

Qualitative variables	n	P value	
Female	102	.22	
ΔF508 homozygous mutation	79	.02	
Exocrine pancreatic insufficiency	102	.55	
<i>Pseudomonas aeruginosa</i>	99	.36	
Quantitative variables	n	Correlation (r)	
Age, years	102	-0.11	.29
BMI, kg/m <sup>2*</sup>	102	0.26	.009
Leukocytosis, 10 <sup>9</sup> /mm <sup>3</sup>	70	-0.42	.0003
CRP, mg/L	64	-0.34	.006
Serum albumin, g/L	43	0.34	.02
FEV <sub>1</sub> <sup>*</sup>	102	0.71	< .0001
FVC <sup>a*</sup>	102	0.69	< .0001
RV <sup>a</sup>	79	-0.58	< .0001
DLCO <sup>a</sup>	68	0.56	< .0001
PaO <sub>2</sub> , mm Hg	98	0.43	< .0001
PaCO <sub>2</sub> , mm Hg	98	0.11	.29
Cardiopulmonary exercise parameters	n	Correlation (r)	
V <sub>E</sub> peak, L	102	0.64	< .0001
V <sub>E</sub> /VCO <sub>2</sub> peak <sup>*</sup>	98	-0.35	< .0001
BR, % <sup>*</sup>	102	0.37	.0001
V <sub>D</sub> /V <sub>T</sub> peak <sup>*</sup>	96	-0.64	< .0001
PaCO <sub>2</sub> peak, mm Hg <sup>*</sup>	97	-0.45	< .0001
P(A-a)O <sub>2</sub> peak, mm Hg <sup>*</sup>	97	-0.54	< .0001
Lactatemia peak, mmol/L <sup>*</sup>	86	0.59	< .0001
HR peak <sup>a</sup>	102	0.40	< .0001

<sup>a</sup>Correlations based on percentage of predicted values.

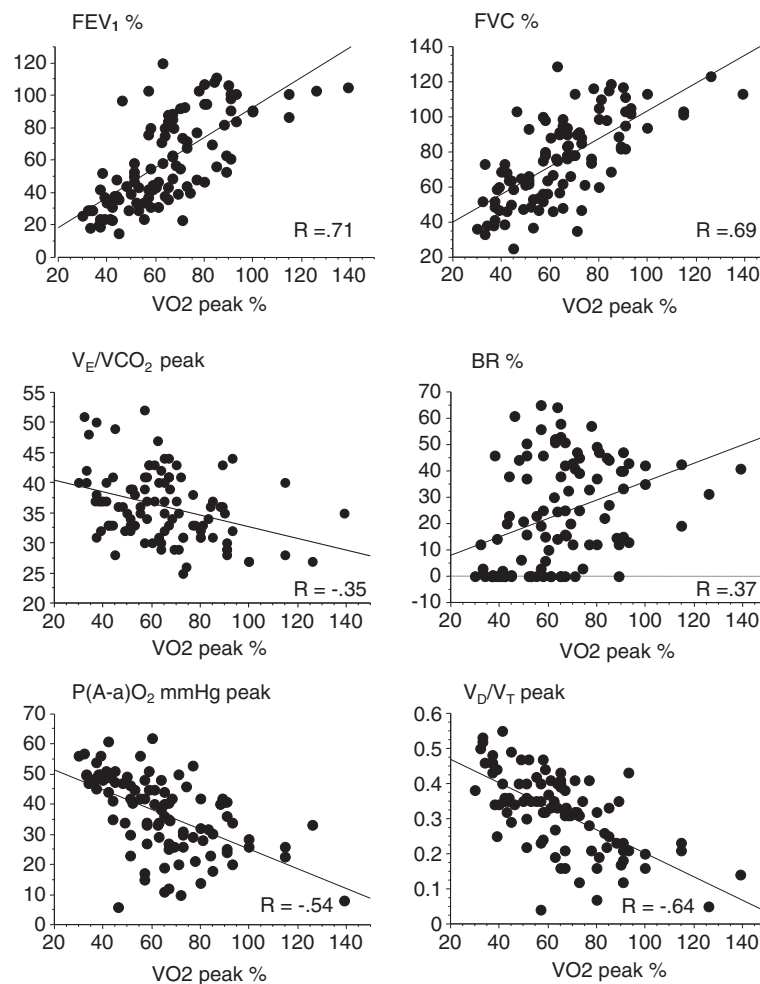
\*Selected variables for multivariate stepwise analysis.

only FEV<sub>1</sub>, V<sub>E</sub>/VCO<sub>2</sub> peak, and BR were found to be independent predictors of exercise capacity (r<sup>2</sup> = 0.67). Analysis of these three variables showed that, for group 1, 31% of the VO<sub>2</sub> peak was explained by FEV<sub>1</sub>, whereas the major determinants of the VO<sub>2</sub> peak in group 2 were BR, FEV<sub>1</sub> and V<sub>E</sub>/VCO<sub>2</sub> peak (Table 5).

Separate analysis in the cohort of Lille (75 out of the 102 patients) showed the same results: FEV<sub>1</sub>, BR and V<sub>E</sub>/VCO<sub>2</sub> were independent predictors of exercise capacity (r<sup>2</sup> = 0.65) (data not shown).

#### Discussion

Our study focused on a population of 102 adults with CF who underwent CPET with blood gas analysis at peak exercise. Maximal oxygen uptake was impaired in 82% of patients and was more pronounced in patients with low FEV<sub>1</sub>. We noted a high prevalence of abnormal exercise responses in our population, including abnormal gas exchange, ventilatory and cardiocirculatory



**Figure 1** Correlation between  $VO_2$  peak and  $FEV_1$ , FVC,  $VE/CO_2$  peak, BR,  $P(A-a)O_2$  peak, and  $V_D/V_T$  peak in CF patients.  $VO_2$  peak,  $FEV_1$ , FVC, and BR are expressed as percentage of predicted values.  $P(A-a)O_2$  peak is expressed as mm Hg.

responses, and peripheral limitation. The main findings from this study are that exercise intolerance in CF is multifactorial and is correlated mainly with resting pulmonary function, nutritional status, and inflammatory status, but is also affected by the magnitude of the overall ventilatory response during exercise. Multivariate analysis revealed that bronchial obstruction plays a dominant role in patients with severe disease, whereas

excessive hyperventilation during exercise was the major determinant of exercise limitation in patients with mild-to-moderate disease.

CF can be associated with abnormal gas exchange, ventilatory, cardiocirculatory, and muscular responses to exercise [3,9,13,29]. In our study, these abnormalities were responsible for limiting the aerobic capacity of 82% of patients, a proportion consistent with previous studies

**Table 5** Determinants of  $VO_2$  peak in CF patients

Variable	All patients (n = 102)	Group 1 (n = 48)	Group 2 (n = 54)
$FEV_1$	50 (0.84 [0.70;0.98]) <sup>a</sup>	31 (1.08 [0.70;1.45]) <sup>a</sup>	18 (0.67 [0.46;0.88]) <sup>a</sup>
BR	12 (-0.62 [-0.82;-0.42]) <sup>a</sup>	6 (-0.36 [-0.68;-0.04]) <sup>b</sup>	35 (-0.85 [-1.10;-0.59]) <sup>a</sup>
$VE/CO_2$ peak	5 (-1.13 [-1.56;-0.69]) <sup>a</sup>	15 (-0.95 [-1.41;-0.48]) <sup>c</sup>	6 (-1.52 [-2.22;-0.82]) <sup>a</sup>

Results are expressed as the partial r-square ( $r^2$ ), i.e. the percentage of  $VO_2$  alteration explained by the variable. Coefficient and 95% confidence intervals are shown between parentheses.  $FEV_1$ ,  $VE/CO_2$  peak, and BR were independent predictors explaining 67% of exercise capacity ( $r^2 = 0.67$ ). In group 1, 31% of the  $VO_2$  peak was explained by  $FEV_1$ , whereas, in group 2, BR was the major determinant explaining 35% of the  $VO_2$  peak.

Results are derived from multivariable analysis.

<sup>a</sup>Adjusted p value < .0001; <sup>b</sup>p = .027; <sup>c</sup>p = .0002.

of adult CF patients [5,12,30]. We did not observe a single exercise profile common to all patients, reflecting the complexity of mechanisms involved in exercise limitation in CF patients. Some patients showed abnormalities predominantly in gas exchange, others in the ventilatory response. Still others experienced exercise intolerance despite the absence of ventilatory limitation. The relative contribution of these factors differed between the two groups.

In our study, BMI and CRP levels were strongly correlated with exercise limitation, which is consistent with several studies indicating the importance of inflammatory and nutritional status in exercise limitation. Nutritional status plays a well-established role in CF exercise intolerance [31] and prognosis [32], and may be linked to the chronic inflammation observed in CF patients, which is mainly due to respiratory colonization [33]. Inflammatory markers such as CRP are also negatively associated with exercise capacity in patients with CF [7]. Moreover, inflammation is experimentally correlated with loss of muscle mass [34] and skeletal muscle weakness [10] and could explain the association observed here between CRP, lean body mass, and reduced maximal oxygen uptake.

Multivariate analysis showed that FEV<sub>1</sub> was the most significant predictor of VO<sub>2</sub> peak in patients with severe lung disease. This result is consistent with data from earlier studies [3,35] and demonstrates the predominant role of ventilatory disorders in exercise limitation in severe CF patients. Additional functional parameters, such as distension, obstruction, and CO diffusion also correlated with VO<sub>2</sub> peak, but were not independent predictors. The low BR exhibited by our population is another characteristic of the exercise response in severe CF patients. Tantisira *et al.* showed that the BR index (V<sub>E</sub>/maximal voluntary ventilation calculated at ventilatory threshold) was the most powerful predictor of mortality in CF patients awaiting lung transplantation [36]. This has also been observed in COPD [37] but is not common to all obstructive lung diseases. For example, McNicholl *et al.* reported that only 18% of severe asthma patients had ventilatory limitation due to obstructive lung function [38].

In contrast, the VO<sub>2</sub> peak was not fully explained by FEV<sub>1</sub> in patients with mild-to-moderate lung disease, and some patients exhibited impaired aerobic capacity despite having normal resting lung function (Figure 1). Indeed, multivariate analysis showed that two CPET parameters were the major independent determinants of VO<sub>2</sub> peak in group 2: hyperventilation due to abnormal ventilatory control, resulting in high ventilatory equivalents (as demonstrated by V<sub>E</sub>/VO<sub>2</sub> and V<sub>E</sub>/VCO<sub>2</sub> peaks), and BR depletion. Exercise ventilation is regulated by numerous mechanisms, most of which remain

incompletely understood [39]. Hyperventilation during exercise reflects a nonspecific response to one or more dysfunctional links in the respiratory chain, but the main cause is not known [40]. In some diseases, such as heart failure, hyperventilation is recognized as a more relevant prognostic factor than VO<sub>2</sub> peak. The hyperventilatory response may be due to several factors, including inefficient gas exchange as reflected by P(A-a)O<sub>2</sub> and the V<sub>D</sub>/V<sub>T</sub> ratio. Although hyperventilation is difficult to relate to other abnormalities, the strong correlation of hyperventilation with oxygen pulse and peak lactatemia suggests that central (cardiovascular) and peripheral (muscle) determinants play a role [10].

In our study, all patients underwent blood gas analysis at peak effort and we noted a high prevalence of gas exchange abnormalities during exercise. It is interesting to note that patients with identical lung function did not all show gas exchange abnormalities. This could be explained by an inadequate ventilatory response in some patients or by a high degree of ventilation-perfusion mismatch. Exercise-induced hypoxemia was common in our study and correlated with VO<sub>2</sub> peak, workload, peak V<sub>D</sub>/V<sub>T</sub>, and dyspnea assessed by the Borg scale (results not shown). We found that P(A-a)O<sub>2</sub> correlated well with peak VO<sub>2</sub>, highlighting the relevance of this parameter in gas exchange analysis. Other studies have examined impairment of gas exchange during exercise in CF patients. Nixon *et al.* showed that P<sub>ET</sub>CO<sub>2</sub> > 41 mm Hg at peak exercise is associated with a twofold higher relative risk of mortality [4]. However, P<sub>ET</sub>CO<sub>2</sub> is not a reliable marker for PaCO<sub>2</sub> during exercise and does not allow accurate calculation of dead space [41]. Compared with PFT, CPET with blood gas analysis at peak exercise is better able to assess gas exchange abnormalities and highlight exercise hypoxemia, a recognized prognosis marker, and thus gauge the need for oxygen supplementation.

The primary limitation of our study is its retrospective nature and the possibility of missing data. Peripheral muscle strength was not assessed and might be a significant contributing factor [10]. These results should be confirmed by a prospective study.

## Conclusion

In conclusion, exercise limitation in adult patients with CF correlates with respiratory function as well as nutritional and inflammatory status. This limitation is dependent on FEV<sub>1</sub> in patients with severe disease but is mainly affected by the magnitude of the ventilatory response to exercise in patients with mild-to-moderate lung disease. CPET thus contributes to a more comprehensive understanding of exercise limitation and can assist in patient management aimed at improving exercise capacity.

### Competing interests

For each author, no significant competing interest exists with any companies or organisations whose products or services are mentioned in this article. The authors declare that they have no competing interests.

### Authors' contributions

Conception and design: BW, JP and AP; Analysis and interpretation: BW, JP, AP, CT, CL and AD; Drafting the manuscript for important intellectual content: BW, JP, AP, and CL. All authors read and approved the final manuscript.

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