Associations between peak oxygen uptake, lung function and bronchiectasis in children with cystic fibrosis in the era of CFTR modulators

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Associations between peak oxygen uptake, lung function and bronchiectasis in children with cystic fibrosis in the era of CFTR modulators

Abstract

Background
With the emergence of cystic fibrosis transmembrane conductance regulator (CFTR) modulators, FEV₁ may become a less sensitive measure of pulmonary disease progression in children with cystic fibrosis (CF). Increasing evidence shows that peak oxygen uptake (Vo₂peak) is a strong predictor of prognosis in CF. The primary aim of this study was to describe the associations between peak oxygen uptake, lung function and bronchiectasis in children with CF in the era of CFTR modulators.

Methods
Spirometry and a maximal cardiopulmonary exercise test (CPET) were performed on the same day and compared to markers of disease severity. Markers of disease severity included number of pulmonary exacerbations resulting in a hospital admission within the preceding 12 months, BMI, Pseudomonas aeruginosa (PsA) infection and bronchiectasis.

Results
52 subjects (24 female) with CF participated in the study with a mean (SD) age of 13.8 (2.4) years, range 8-18y. 49 participants met satisfactory criteria for a maximal CPET. A significant correlation was found between Relative Vo₂peak % predicted and FEV₁ % predicted ($r = 0.546, p < 0.001$). 4/49 children demonstrated an impaired aerobic capacity despite normal spirometry. Participants who had experienced one or more pulmonary exacerbations in the previous 12 months had a significantly lower Relative Vo₂peak % predicted ($p = 0.02$).
Conclusions
In children with CF who have mild pulmonary disease there is significant correlation between FEV1 and Vo2peak. 8.2% of participants had an abnormal CPET result despite normal spirometry, and preceding pulmonary exacerbations were associated with poorer CPET outcomes. CPET may offer important prognostic information for clinical decision making in this new era of CFTR modulators.

Key words: cystic fibrosis, cardiopulmonary exercise test, peak oxygen uptake, pulmonary exacerbation

Introduction
Cystic fibrosis (CF) is a severe life limiting disease, associated with multi organ impairment that affects exercise capacity. Though cardiopulmonary exercise testing (CPET) in children with CF is recognized as an important prognostic tool due to the association between peak oxygen consumption (Vo2peak) and mortality rates [1-5], it remains an underutilised test despite being recommended as the gold standard for assessment of exercise capacity in Australia and New Zealand [6-8].

With the emergence of Cystic fibrosis transmembrane regulator (CFTR) modulators, forced expiratory volume in 1 s (FEV1) may become a less sensitive measure of pulmonary disease progression in coming years. An improved understanding of CPET derived parameters may provide CF care teams with the information required to better recognise clinical deterioration and response to treatment, thereby improving overall clinical management. Other CPET derived measurements strongly associated with mortality in CF include peak power output (Wattmax), ventilatory equivalent for oxygen (VE/Vo2) and the ventilatory equivalent for carbon dioxide (VE/VCo2) [2].

The primary aim of this study was to describe the associations between peak oxygen uptake, lung function and bronchiectasis in children in the era of CFTR modulators.
Secondary aims involved investigating factors present in CF that may influence $\text{VO}_{2}\text{peak}$ outcomes such as CF related co-morbidities, genotype and microbiological infection.

**Materials and Methods**

**Study Participants**

In June 2019, The Royal Children’s Hospital (RCH), Melbourne implemented CPET as part of annual CF assessments for all age appropriate children and adolescents. A retrospective analysis was performed on the data of participants who performed a CPET in conjunction with spirometry as part of their annual review at RCH, Melbourne between June 2019 and February 2020. The review obtained ethics approval from the hospital institutional review board. Children were required to be $>135\text{cms}$ in height to allow for sufficient pedalling on the cycle ergometer. We collected anthropometric data, pulmonary function and CPET derived outcomes, radiological findings, pulmonary exacerbation data, CF-related markers of disease severity including pancreatic insufficiency, microbiological infection, cystic fibrosis-related diabetes (CFRD), CFTR genotype and modulator data. All participants were clinically stable on the day of testing. The bronchiectasis status of the patient was confirmed by their most recent chest computed tomography (CT) scan. A pulmonary exacerbation was defined as a significant decline in lung function within the previous 12 months that required a hospital admission. *PsA* infection was detected from a sputum sample taken on the day of the CPET. If it was not possible to obtain a sputum sample on the same day of the CPET, the participant’s most recent sputum sample was used provided it was obtained within a two month period prior to date of CPET.
Anthropometry

Height was recorded without shoes to the nearest 0.1cm and weight to the nearest 0.1kg using an ultrasonic stadiometer with digital scales (Seca 285, Seca Gmbh & Co, Germany).

Pulmonary Function Testing

All spirometry testing was performed in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines and conducted by two experienced paediatric respiratory scientists [9]. Spirometry was measured via a Jaeger MS Pneumo (Carefusion, Germany) using the Global Lung Initiative prediction equations [10].

Cardiopulmonary Exercise Testing

Participants performed a symptom-limited peak exercise test on an electronically braked cycle ergometer (Ergoselect, Via Sprint 150p, Germany) using an incremental ramp protocol. Wasserman & Hansen (2005) prediction equations were used to calculate CPET parameters [11]. Participants were interfaced to the metabolic cart (Vyntus CPX, Carefusion, Germany) via facemask. Watt protocol was selected on the basis of age, activity level, lung function and BMI. Resting data was collected for one minute which was then followed by a three minute phase of unloaded pedalling before the incremental exercise phase was initiated. The test was terminated if the participant could no longer maintain a cadence of > 60rpm despite verbal encouragement. A two minute recovery phase consisting of unloaded pedalling followed the incremental exercise phase. Maximum voluntary ventilation (MVV) was estimated as 35 x FEV₁. Peak exercise values were averaged over the final 30 seconds of maximal work. The gas exchange threshold was identified using a combination of the V’slope method and ventilatory equivalents [12, 13]. We considered criteria for maximal effort achieved if

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one of the following was met: (1) $\text{VO}_2\text{peak}$ increased less than 2.0ml/min/kg despite an increase of 5-10% in workload, (2) a breathing reserve < 15%, (3) RER > 1.05, or (4) if a heart rate > 90% predicted was achieved [14]. Borg scale for shortness of breath and leg fatigue was used in conjunction to assess subject effort.

**Data management and Analysis**

Patient demographic data (sex, age and genotype) were expressed as means and SDs. Statistical analysis was performed using Stata Version 16.0 (Stata Corporation, College Station, Texas, USA). Results were expressed in absolute terms for $\text{FEV}_1$ (L) as well as % predicted and z-score to adjust for age and height. In a similar fashion, $\text{VO}_2\text{peak}$ was expressed in absolute terms (mL/min) and % predicted to adjust for age and height, and relative terms (mL/min/kg) to adjust for weight. The relationship between $\text{VO}_2\text{peak}$, $\text{FEV}_1$, peak workload, BMI z-score and age was investigated using Pearson’s correlation coefficient. A two-sample t-test used to investigate statistical difference between $\text{VO}_2\text{peak}$, $\text{FEV}_1$, number of pulmonary exacerbations within the previous 12 months, presence of bronchiectasis, PsA, use of CFTR modulators and effect of genotype.

**Results**

A technically satisfactory CPET was obtained from 49/52 (94.2%) of the participants. Two of the participants did not meet satisfactory criteria for CPET due to submaximal effort. One CPET was terminated early due to excessive coughing at submaximal workloads. Mean $\text{FEV}_1$ % predicted and BMI z-scores were within normal ranges, however 16 participants had mild to severe airway obstruction in accordance to ATS/ERS guidelines. Twelve (24.5%) participants demonstrated an impaired aerobic capacity (Relative $\text{VO}_2\text{peak} < 82\%$). Ventilatory limitation, defined as a breathing reserve < 15%, was observed in 20 (40.8%) of participants. However on
average, the cohort demonstrated normal aerobic capacity with a mean \( \text{Vo}_2\text{peak} > 82\% \). No ECG abnormalities were observed at rest, during or post exercise, though three participants had significant desaturations (\( \text{SpO}_2 < 95\% \)) during CPET.

Significant correlations were observed between \( \text{FEV}_1 \% \text{ predicted} \) and Relative \( \text{Vo}_2\text{peak} \% \text{ predicted} \) \((r = 0.546, \ p < 0.001)\) and \( \text{FEV}_1 \% \text{ predicted} \) and \( \text{Watt}_{\text{max}} \% \text{ predicted} \) \((r = 0.529, \ p = 0.001)\). A modest but significant inverse correlation was observed between Relative \( \text{Vo}_2\text{peak} \% \text{ predicted} \) and age at CPET \((r=-0.407, \ p=0.004)\).

No correlation was observed between Relative \( \text{Vo}_2\text{peak} \% \text{ predicted} \) and BMI z-score. 4/49 (8.2%) of participants had an abnormal aerobic capacity despite normal spirometry. Participants who had one or more pulmonary exacerbation in the previous 12 months had significantly lower Relative \( \text{Vo}_2\text{peak} \% \text{ predicted} \) when compared to those that had not \((\text{mean difference} = 14.22\%, \ p = 0.002)\). Homozygous \( \Delta F508 \) had lower Relative \( \text{Vo}_2\text{peak} \% \text{ predicted} \) outcomes than those were heterozygous \( \Delta F508/\text{other} \) \((\text{mean difference} = 8.82\%, \ p = 0.022)\). Sex \((p=0.41)\), bronchiectasis status \((p = 0.46)\), \( PsA \) infection \((p = 0.61)\) or CFTR modulator use \((p=0.26)\) did not influence Relative \( \text{Vo}_2\text{peak} \% \text{ predicted} \) results.

**Discussion**

A significant moderate correlation between \( \text{FEV}_1 \) and \( \text{Vo}_2\text{peak} \) demonstrates the role pulmonary function plays in maintaining aerobic fitness in CF. In our cohort, 4/49 (8.2%) children with normal lung function \((\text{FEV}_1 \geq 80\%)\), demonstrated an impaired aerobic capacity \((\text{Vo}_2\text{peak} \leq 82\%)\), indicating aerobic deconditioning. A further 8 children had reduced \( \text{Vo}_2\text{peak} \) as well as impaired lung function. Deconditioning results in reduced peripheral muscle power, the number of capillaries within skeletal muscle, mitochondrial density and cardiac function implications such as a reduced stroke volume [15]. Our findings identified those with poor aerobic fitness, thereby allowing
physiotherapists to implement a more targeted approach to exercise prescription. We postulate that similar findings may become more common in the future as more children with CF benefit from preserved lung function via CFTR modulators. Accordingly, if the sensitivity of FEV$_1$ continues to weaken, CPET may enable ‘at risk’ children to be identified despite having normal lung function. Regular exercise training has been linked to reduced mortality rates, greater aerobic fitness, improved pulmonary function, enhanced sputum expectoration, greater bone mineral density and quality of life [16-18]. Therefore, it is particularly important to maintain and monitor fitness levels as children progress into adolescence as participation in exercise often declines during this transition. We observed a stronger inverse correlation between Vo$_{2peak}$ and age compared with FEV$_1$ and age. While it is recognized that Vo$_{2peak}$ declines with age in CF [3, 19], it is also plausible that this decline is accelerated by poor exercise adherence in CF even in those with persevered lung function.

Interestingly the use of CFTR modulators did not have a difference on Spirometry or CPET outcomes. Due to the novelty of CFTR modulator therapy, and because CPET is only conducted routinely in a small number of specialised centres, research on the effect that CFTR modulators have on exercise capacity is very limited. However recent advances in the availability and access of CFTR modulators will enable future studies to investigate the effects that modulators have on exercise capacity in greater detail. Edgeworth et al conducted a double blind cross over study investigating the effects of ivacaftor on exercise capacity in an adult population with CF over a 28 day period. Despite increased mean exercise time during the repeat CPET, improved physical activity and increased FEV$_1$ values, there was no subsequent increase in Vo$_{2peak}$ or other ventilatory parameters [20]. Advancements in CFTR modulator
therapy over the coming decade may lead to significant increases in lung function, as evident from the recent results of randomised clinical trials investigating the efficiency of elexacafor-tezacaftor-ivacaftor triple therapy [21]. As CPET can identify ventilatory abnormalities which may still exist in the presence of normal lung function, CPET may prove to be an important prognostic tool to measure disease progression in CF.

Vo2peak outcomes were significantly lower in participants who had experienced one or more pulmonary exacerbation in the previous 12 months of the CPET in comparison to those who did not; this finding was irrespective of the age of the participant. Given the difference in Vo2peak outcomes observed in our cohort for this sub group it shows that results obtained from CPET may identify those at higher risk of pulmonary exacerbation. These findings highlight the potential for better identification of patients who are at risk of a pulmonary exacerbation and may aid in the development of tailored interventions that aim to prevent onset of pulmonary exacerbation in children with a lower Vo2peak. Perez et al investigated the association between aerobic fitness and rate of hospitalization in children with CF over a three year period and also found a significant association between higher Vo2peak outcomes and lower risk of hospitalization [22]. A decline in lung function as a result of a chest infection which leads to a hospital admission may greatly impact and interfere on a child’s physical activity level and participation in exercise [23]. Lack of exercise during a hospital admission is likely due to pulmonary symptoms and fatigue experienced during an exacerbation. Number of hospitalizations due to pulmonary exacerbation is an important prognostic factor in CF due to the implications it has on long term morbidity and mortality [24, 25]. Repeat serial measurements are needed to
investigate if a decline in Vo$_{2peak}$ by a particular amount over a 12 month period can predict the likelihood of an exacerbation occurring.

There is conflicting evidence between the association of Vo$_{2peak}$ and FEV$_1$, particularly amongst paediatric CF cohorts. Weir et al investigated the CPET results in 38 children and adolescents with CF but failed to demonstrate a relationship between FEV$_1$ and Vo$_{2peak}$ [19]. However, positive correlations between aerobic fitness and pulmonary disease severity have been demonstrated in previous landmark studies [1, 3]. We postulate that differing associations within the literature may be due to variations in disease severity, and sample size. It remains unclear if the method in which CPET is conducted on the cycle ergometer, such as chosen procedure (e.g. ramp versus minute-by-minute workload increments), or selection of work rate increment, influences Vo$_{2peak}$ outcomes in CF populations. It may be plausible that heterogeneous approaches in how CPET has been conducted has contributed to differing associations, however more studies are required to determine this [14].

The spirometry and CPET results obtained from this study show that our cohort had mild pulmonary disease and were aerobically fit. Aerobic fitness is often normal in children with CF who have well persevered lung function. An impairment of exercise capacity may not be seen until FEV$_1$ declines to less than 60-80% predicted, with bronchial obstruction becoming the primary determinant of exercise intolerance in patients with more severe disease [3, 26-28]. This may explain the weak correlations between FEV$_1$ and Vo$_{2peak}$ typically seen in CF paediatric cohorts given that an accelerated decline in lung function often does not occur until later adolescence to young adulthood [25, 29]. Our observed correlation strength is likely due to the varying degrees of pulmonary disease severity that was included in our dataset, with
participant FEV1 results ranging from less than 35% predicted to over 120% predicted.

A significant difference between genotype was observed, with those who were homozygous for ΔF508 having lower Vo2peak outcomes than those were heterozygous ΔF508/other. This finding was irrespective of the age of the patient at the time they underwent the CPET. These results conflict with a landmark study by Radtke et al who reviewed Vo2peak outcomes and genotype in 726 patients with CF and found that CFTR genotype had no association with exercise outcomes [30]. The differing results from our study is likely due to our low sample size.

There was no discernible difference in Vo2peak outcomes between those with or without CF related bronchiectasis. Interestingly, a significant difference was found between FEV1 results between the two groups. Associations between CF related bronchiectasis and FEV1 has been well documented [31], however this has not been the case for Vo2peak. Similarities have been found between the exercise capacity in individuals with CF bronchiectasis and non-CF bronchiectasis, with normal response to exercise being unrelated to the aetiology of the bronchiectasis [32]. Our findings indicate that CF related bronchiectasis in children with mild disease does not impact on exercise capacity.

With various methods, protocols and equipment available to investigate aerobic capacity, the standardisation of CPET remains difficult. This has been particularly evident amongst a recent multicentre retrospective study by Hebestreit et al (2015) [2]. The group reviewed the CPET results of 433 CF patients from 10 different international centres and cited heterogeneous diagnostic approaches being a primary limitation to the study. Issues of test standardisation have recently been highlighted by the ERS [14]. Their statement has proposed new predictive equations for watt
protocol selection for CF and other chronic lung diseases. A limiting factor of our study is that these guidelines and equations were published after our data collection period had begun. However we are confident that an accurate watt protocol was selected for each participant. This is evident by the mean time to \( \text{Vo}_{2\text{peak}} \) for our cohort (see table 2) which is in line with ERS guidelines for maximal effort in an incremental exercise test [14]. We acknowledge that recent ERS statements on cardiopulmonary exercise testing recommends \( \text{FEV}_1 \times 40 \) for MVV prediction. However there is still much debate on this topic with no standard consensus yet available. Other limitations to this study include a relatively small sample size and absence of longitudinal data. In addition to this we were unable to investigate the effect of elexacafor-tezacaftor-ivacaftor triple therapy on exercise capacity as during the time of data collection it had not been approved for use by the Therapeutic Goods Administration of Australia.

We were unable to demonstrate a significant correlation between BMI and \( \text{Vo}_{2\text{peak}} \) outcomes. Associations between nutritional status and exercise capacity has been established in previous studies with a mean sample population above the age of 18 and therefore involving those with more advanced lung disease [18, 33]. However in the absence of abnormal BMI, \( \text{Vo}_{2\text{peak}} \) outcomes appear to be unaffected, similar findings has also been observed in studies investigating the relationship between BMI and CPET outcomes in a paediatric cohort [19].

**Conclusion**

In children with CF who have mild pulmonary disease there is significant moderate correlation between \( \text{FEV}_1 \) and \( \text{Vo}_{2\text{peak}} \). Annual CPET detected a reduced aerobic capacity in 8.2% of children despite normal spirometry. Participants had significantly worse CPET outcomes if they had one or more pulmonary exacerbation within the
previous 12 months prior to undergoing the CPET. Given the association between VO$_{2}^{\text{peak}}$ and pulmonary exacerbations, in addition to the ability of CPET to discern ventilatory abnormalities and physical deconditioning in the presence of normal lung function, parameters derived from CPET in conjunction with Spirometry may offer important prognostic information for clinical decision making in this new era of CFTR modulators.

**References**


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**TABLE 1 – Study Population Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>49</td>
</tr>
<tr>
<td>Female</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>13.8 (8.9, 18.5)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.5 (±13.3)</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Height (Z-Score)</td>
<td>0.04 (±0.83)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>51.1 (±12.3)</td>
</tr>
<tr>
<td>Weight (Z-Score)</td>
<td>0.09 (±0.76)</td>
</tr>
<tr>
<td>BMI (Z-score)</td>
<td>0.1 (±0.78)</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
</tr>
<tr>
<td>Homozygous ΔF508</td>
<td>26 (53.1%)</td>
</tr>
<tr>
<td>Heterozygous ΔF508</td>
<td>22 (44.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Cystic Fibrosis Transmembrane Regulator</td>
<td>27 (55%)</td>
</tr>
<tr>
<td>Modulator</td>
<td></td>
</tr>
<tr>
<td>Orkambi</td>
<td>19 (38.8%)</td>
</tr>
<tr>
<td>Kalydeco</td>
<td>6 (14.3%)</td>
</tr>
<tr>
<td>Symdeko</td>
<td>2 (4.1%)</td>
</tr>
<tr>
<td>Bronchiectasis present</td>
<td>32 (64%)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa infection</td>
<td>7 (14.6%)</td>
</tr>
<tr>
<td>Pulmonary exacerbations (≥1 in previous 12 months)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>45 (90%)</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.65 (0.92; 0.91, 4.66)</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>86.6 (19.76; 34.7, 123.4)</td>
</tr>
<tr>
<td>FEV₁ (Z-score)</td>
<td>-1.12 (1.66; -5.24, 2.05)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.30 (1.11; 1.72, 5.94)</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>93.12 (17.33; 50.2, 134)</td>
</tr>
<tr>
<td>FVC (Z-score)</td>
<td>-0.59 (1.48; -4.39, 2.72)</td>
</tr>
<tr>
<td>FEV₁/FVC Ratio</td>
<td>80.78 (8.28; 57.1, 90.20)</td>
</tr>
</tbody>
</table>
FEV₁/FVC Ratio (Z-score)  -1.12 (1.03; -3.67, 0.96)

Data presented as n (%), mean (SD), mean (range) or mean (SD; min, max).
BMI., Body mass index
FEV₁., Forced expiratory volume in 1 s.
FVC., Forced vital capacity.

**TABLE 2 – Cardiopulmonary Exercise Test Results**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Mean</th>
<th>SD</th>
<th>Min, Max</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absolute Vo₂peak (mL/min)</strong></td>
<td>1816.91</td>
<td>538.19</td>
<td>1059, 3192</td>
</tr>
<tr>
<td><strong>Relative Vo₂peak (mL/min/kg)</strong></td>
<td>35.98</td>
<td>7.91</td>
<td>21.8, 54.3</td>
</tr>
<tr>
<td><strong>Relative Vo₂peak (%) predicted</strong></td>
<td>89.81</td>
<td>13.70</td>
<td>60, 125</td>
</tr>
<tr>
<td><strong>Protocol (watt)</strong></td>
<td>14.74</td>
<td>3.54</td>
<td>10, 20</td>
</tr>
<tr>
<td><strong>Time to Vo₂peak (min)</strong></td>
<td>12.17</td>
<td>2.39</td>
<td>6.31, 17.1</td>
</tr>
<tr>
<td><strong>Peak Power Output (watt)</strong></td>
<td>134.04</td>
<td>46.28</td>
<td>70, 285</td>
</tr>
<tr>
<td><strong>Peak Power Output (%) predicted</strong></td>
<td>87.12</td>
<td>14.27</td>
<td>56, 123</td>
</tr>
<tr>
<td><strong>VE/Vo₂</strong></td>
<td>38.18</td>
<td>6.32</td>
<td>24.8, 57.3</td>
</tr>
<tr>
<td><strong>VE/VCo₂</strong></td>
<td>32.01</td>
<td>3.96</td>
<td>25.7, 44.9</td>
</tr>
<tr>
<td><strong>V'E (L/min)</strong></td>
<td>75.93</td>
<td>26.70</td>
<td>38, 146</td>
</tr>
<tr>
<td><strong>Breathing reserve (%)</strong></td>
<td>14.26</td>
<td>19.21</td>
<td>-43, 43</td>
</tr>
<tr>
<td><strong>Oxygen Pulse (ml/beat)</strong></td>
<td>10.03</td>
<td>2.77</td>
<td>6, 16.7</td>
</tr>
<tr>
<td><strong>Heart Rate (BPM)</strong></td>
<td>185.32</td>
<td>10.42</td>
<td>157, 208</td>
</tr>
<tr>
<td><strong>Vo₂ at GET (ml/min/kg)</strong></td>
<td>17.3</td>
<td>3.5</td>
<td>9.6, 24.2</td>
</tr>
<tr>
<td><strong>GET (% of Vo₂peak)</strong></td>
<td>48.71</td>
<td>7.65</td>
<td>33, 65</td>
</tr>
<tr>
<td><strong>VE/VCo₂ Slope</strong></td>
<td>25.53</td>
<td>6.6</td>
<td>21, 44</td>
</tr>
</tbody>
</table>

Vo₂peak., Peak oxygen uptake.
VE/Vo$_2$, Ventilatory equivalent for oxygen.
VE/VCo$_2$, Ventilatory equivalent for carbon dioxide.
V'E, Minute ventilation.
GET, Gas exchange threshold.
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