Role of arterial hypoxemia and pulmonary mechanics in exercise limitation in adults with cystic fibrosis

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We hypothesized that maximal exercise in cystic fibrosis (CF) patients is limited by respiratory factors. We subsequently examined whether respiratory mechanics or arterial hypoxemia limits maximal exercise performance. In study 1, patients completed two maximal exercise tests, a control and a test with 400 ml of added dead space. Maximal O₂ consumption was significantly lower in the added dead space study vs. control (1.04±0.15 vs. 1.20±0.11 l/min; P < 0.05), with no difference in peak ventilation. There was significant O₂ desaturation during exercise that was equal in both control and added dead space studies. The decrease in maximal O₂ consumption with added dead space suggests that maximal exercise in cystic fibrosis is limited by respiratory factors. We subsequently examined whether pulmonary mechanics or arterial hypoxemia limits maximal exercise performance. In study 2, patients completed two maximal exercise tests, a control and a test with 400 ml of added dead space while also breathing 38% O₂. Added dead space was used to overcome the suppressive effects of hyperoxia on minute ventilation. Maximal O₂ consumption was significantly higher with added dead space and 38% O₂ vs. control (1.62±0.16 vs. 1.43±0.14 l/min; P < 0.05). Peak ventilation and O₂ saturation were significantly greater in the added dead space and 38% O₂ test vs. control. The increase in maximal O₂ consumption and peak ventilation with added dead space and 38% O₂ suggests that maximal exercise in cystic fibrosis is limited by arterial hypoxemia.

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All patients were diagnosed with CF based on established criteria (39). The study was approved by the Ethics Committee of St. Vincent’s University Hospital. All patients gave informed consent to the procedures.

Pulmonary function testing was carried out on each patient before and after each exercise test using recommended techniques (1) and predicted normal values (47) were used to calculate percentage predicted values.

All exercise testing was performed on an electrically braked cycle ergometer (Excalibur, Lode, Groningen, The Netherlands). Each exercise test was a maximal test carried out until exhaustion. Our laboratory previously showed that maximal exercise testing in this population is reproducible with no learning effect (30). Exercise was performed at the same time of day on each occasion. Subjects were asked to avoid strenuous activity for at least 24 h before exercise testing as well as food or caffeinated drinks in the preceding 2 h. All patients were instructed to take all of their maintenance medications as usual.

For the exercise tests, after mounting the cycle ergometer, each patient put on a nose clip, inserted the mouthpiece, and breathed comfortably for at least 6 min (see below). Baseline measurements were then taken over 2 min. The initial exercise workload was 15 W and was increased by 15 W/min in a ramp fashion until exhaustion. With the use of speedometer feedback, each subject chose the pedaling rate within a range of 50–70 rpm. All subjects were instructed in an identical manner by the same operator for all exercise studies. The subjects were told that they should continue to exercise until they could exercise no more. No other type of encouragement was offered and no communication was made with the subjects during the testing to ensure consistency of the protocol.

Electrocardiographic leads attached to the chest enabled continuous monitoring of the heart rate (HR) and electrocardiogram. Arterial O₂ saturation (SaO₂) was monitored by pulse oximetry (SAT-TRAK, Sensor Medics, Yorba Linda, CA). The nonrebreathing valve was connected via wide-bore tubing to a 2.6-liter mixing chamber with a heated wire flow sensor at the entrance to the mixing chamber (Mass Flow Meter, Sensor Medics). Respired gases were sampled by rapidly passing through a sampling port at the patient’s mouth. V˙E and VT were expressed at STPD.

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A sampling port in the Douglas bag.

Data analyses. V˙E, tidal volume (VT), respiratory frequency, HR, V˙O₂, and CO₂ output were measured every 20 s using standard formula (21, 45). End-tidal CO₂ was measured every minute through a sampling port at the patient’s mouth. V˙E and VT were expressed at STPD and V˙O₂ and CO₂ output were expressed at STPD. Predicted peak V˙O₂ during exercise was calculated as (21)

\[
\text{Peak V˙O}_2 = 0.83ht^{0.66} \times (1 - 0.007age) \times (1 - 0.25S)
\]

where height (ht) is in meters and S is a factor taking account of gender (S = 0 for men and 1 for women). Predicted peak HR was calculated as (21)

\[
\text{Peak HR} = 210 - 0.66age (yr)
\]

MVV was predicted using the equation (8) forced expiratory volume in 1 s × 40.

The magnitude of dyspnea was assessed using the Borg scale in response to the question “How breathless do you feel?” with the subject pointing to the appropriate number on the scale. Leg discomfort was assessed using the Borg scale as above in response to the question “How much leg discomfort do you feel?” Each patient was also asked the reason for stopping exercise immediately after each exercise test.

Statistical significance of group mean data at end exercise from the two experimental days was determined by paired t-testing. Group mean data at matched submaximal work rates were compared by ANOVA for repeated measures (11). Analysis of the Borg scale was performed using Wilcoxon’s signed rank test. The results are shown as means ± SE. Linear regression was used to determine an association between outcomes of interest and various physiological measures during exercise. P < 0.05 was considered significant.

RESULTS

Characteristics of the population in each study group are shown in Table 1. There were no statistically significant differences between baseline characteristics for subjects in study group 1 compared with study group 2. Fifteen subjects were enrolled, with nine subjects participating in each study section. For logistical reasons, some patients were unable to complete the second study, with three subjects participating in both study sections. As expected, CF patients with airflow obstruction and a low body mass index had impaired exercise capacity.

Study 1. Table 2 shows the group mean ± SE data for control and added VD values collected at end exercise. Maximal V˙O₂ (V˙O₂ max), peak exercise workload, and HR were all significantly lower with added VD compared with the control study. End-tidal P shutter CO₂ was significantly higher in the added VD study at end exercise. There was a significant increase in Borg dyspnea score in the added VD study. There was no significant difference in Borg leg discomfort between
Table 1. Characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
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</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>26.7±3.1</td>
<td>23.7±1.5</td>
</tr>
<tr>
<td>Sex</td>
<td>6 male; 3 female</td>
<td>7 male; 2 female</td>
</tr>
<tr>
<td>FEV₁, liters</td>
<td>1.47±0.23 (39% predicted)</td>
<td>1.61±0.20 (41% predicted)</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>56±3</td>
<td>54±4</td>
</tr>
<tr>
<td>Maximum V̇O₂, l/min</td>
<td>1.20±0.1 (49% predicted)</td>
<td>1.43±0.1 (53% predicted)</td>
</tr>
<tr>
<td>Maximum HR, %predicted</td>
<td>82±3</td>
<td>85±2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>20.3±0.6</td>
<td>19.6±0.6</td>
</tr>
</tbody>
</table>

Values are means ± SE. FEV₁, forced expired volume in 1 s; FVC, forced vital capacity; maximum V̇O₂, maximum O₂ consumption at end exercise; maximum HR, maximum heart rate at end exercise; BMI, body mass index.

DISCUSSION

The major findings of this study of adults with CF are 1) stressing the respiratory system with added VD impairs exercise capacity with no change in peak exercise ventilation or SaO₂, but with a significant fall in peak HR. This indicates that ventilatory limitation or arterial hypoxemia contribute to exercise limitation. And 2) added VD with supplemental O₂ causes an improvement in exercise capacity with an increase in peak exercise ventilation. This indicates that arterial hypoxemia is a significant limiting factor during maximal exercise in these adult patients with CF.

Table 2. Study 1: values obtained at end exercise

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Added VD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>V̇O₂max, l/min</td>
<td>1.20±0.11</td>
<td>1.04±0.15</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Exercise workload, W</td>
<td>101±11</td>
<td>84±13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>V̇CO₂max, l/min</td>
<td>1.25±0.14</td>
<td>0.98±0.18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PetCO₂, Torr*</td>
<td>36.7±2.2</td>
<td>44.0±3.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>V̇E, l/min</td>
<td>52.1±6</td>
<td>55.6±6</td>
<td>NS</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>45.6±4.0</td>
<td>42.6±3.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>V̇̇, l/min</td>
<td>1.18±0.16</td>
<td>1.32±0.16</td>
<td>1.47&lt;0.01</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>162±6</td>
<td>155±7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Borg-dyspnea</td>
<td>4.0±0.5</td>
<td>5.0±0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>89±1</td>
<td>89±3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 9). NS, not significant; V̇O₂max, maximal oxygen consumption; V̇CO₂max, maximal carbon dioxide production; PetCO₂, end tidal CO₂; V̇E, ventilation; V̇̇, tidal volume; f, respiratory frequency; HR, heart rate; SaO₂, oxygen saturation; VD, dead space. *PetCO₂ data only available on 7 patients.
Patients with moderate to severe CF have reduced exercise capacity (6, 9, 10, 16, 22, 28). It has been suggested that this is due to a combination of lung disease, poor nutrition, and peripheral muscle dysfunction. Recently, there has been increasing focus on the role of nutritional status and peripheral muscle dysfunction during exercise, suggesting that these factors, rather than respiratory function, limit maximal exercise capacity (4, 13, 14, 17, 23). Although these factors may influence exercise capacity, it is possible that pulmonary dysfunction, either abnormal mechanics or gas exchange, contributes to exercise limitation in CF. It is not known whether patients with moderate to severe CF are limited by respiratory factors. If maximal exercise in patients with CF is limited by ventilatory function, then at end exercise they should approach or reach their maximum ventilatory capacity. Use of resting measurements, and in particular the MVV, to predict maximum ventilatory capacity may be problematic and may not be reliable in predicting the presence of ventilatory limitation (2, 3, 15, 20). Apart from theoretical concerns about the MVV, the observation that in CF patients peak $\dot{V}_{E}$ exceeds MVV (6, 16, 28) indicates that MVV may underestimate the true maximum ventilatory capacity. These results support the findings that caution must be undertaken when ventilatory limitation during exercise is predicted using measurements such as MVV.

To determine whether exercise is limited by respiratory factors, we applied a selective stress to the respiratory system during exercise with added VD as used in previous studies of normal subjects (42, 44) and in patients with lung disease (5, 26). The addition of VD in normal subjects results in an increased $\dot{V}_{E}$, which is maintained throughout exercise but has no effect on exercise duration. In patients with ILD, added VD results in a significant reduction in exercise duration, peak $V_{O2}$, and peak work rate with no difference in $\dot{V}_{E}$ at end exercise (26). This reduction in maximal exercise capacity with added VD is also seen in patients with CAL (5); however, unlike patients with ILD, patients with CAL are capable of reaching a significantly higher $\dot{V}_{E}$ with added VD. The reduction in maximal exercise capacity seen with added VD suggests that maximal exercise performance in ILD and CAL is limited by respiratory factors.

In CF patients, added VD during exercise results in a significant reduction in exercise tolerance, suggesting that maximal exercise performance is limited by respiratory factors. In contrast to normal subjects (42, 44), our patients did not...
have sufficient reserve to overcome the additional stress of added VD, and this resulted in a significant reduction in maximal exercise capacity. This suggests that CF patients are unable to continue exercise beyond a certain level of ventilation and that, in some cases, the maximum ventilatory capacity may have been reached. In addition, our patients also demonstrated a significant fall in SaO2 during both control and added VD studies, suggesting that arterial hypoxemia may also have limited maximal exercise performance.

To further evaluate whether arterial hypoxemia limits maximal exercise in CF patients, we examined the effects of supplemental O2 on maximal exercise capacity. If patients with CF are limited by arterial hypoxemia, then exercising with supplemental O2 should improve exercise capacity. Nixon et al. (34) found that supplemental O2 was of no benefit during maximal exercise in a patient that desaturated to 92% and found that VO2 max at maximal workloads was identical, suggesting that measurement error due to increased inspired O2 fraction was unlikely to have been the cause for the differences in VO2 max observed with supplemental O2 (data not shown). There are also concerns about whether factors limiting maximal exercise were the same in the two study populations. Although this would not change the overall conclusions, Table 1 shows that baseline characteristics were very similar between the two study groups. Absolute V̇O2 max was higher at end exercise in the control arm of study 2 compared with study 1, although this was not statistically significant. Also, when O2 study was lower than that during the control study. This suppression of V̇E associated with hyperoxia could explain the improved exercise capacity, since patients with ventilatory limitation should take longer to reach their maximum ventilatory capacity and so increase exercise duration. This is an important mechanism previously described in studies of supplemental O2 during exercise in patients with CAL and ILD (18, 25, 40).

To overcome the suppressive effects of hyperoxia on V̇E, we added VD during the exercise test on supplemental O2. With supplemental O2, CF patients reached a higher V̇E at end exercise and greater exercise workload than on room air. The ability to increase maximal V̇E in the presence of sufficient supplemental O2 to prevent significant arterial desaturation leads to the conclusion that maximal exercise in this patient group is primarily limited by arterial hypoxemia rather than pulmonary mechanics.

It is important to note that preventing arterial hypoxemia only resulted in a small increase in maximal exercise capacity, indicating that additional factors also limit maximal exercise capacity in CF patients. At end exercise with supplemental O2 and added VD, subjects had an increase in PETCO2, suggesting that, once arterial hypoxemia has been prevented, maximal exercise capacity may be limited by ventilatory function. This will require further study and cannot be concluded from our data because increases in end-exercise PETCO2 have been observed in normal subjects exercising with added VD (44).

Limitations of experimental methods. Measuring ventilation and expired gas concentrations under hyperoxic conditions may lead to measurement errors when V̇O2 max is determined (38, 46). If this is so, we would expect progressive differences in V̇O2 at increasing submaximal workloads between control and hyperoxic condition. We examined V̇O2 during submaximal exercise in a patient that desaturated to <92% and found that V̇O2 max at maximal workloads was identical, suggesting that measurement error due to increased inspired O2 fraction was unlikely to have been the cause for the differences in V̇O2 max observed with supplemental O2 (data not shown). There are also concerns about whether factors limiting maximal exercise were the same in the two study populations. Although this would not change the overall conclusions, Table 1 shows that baseline characteristics were very similar between the two study groups. Absolute V̇O2 max was higher at end exercise in the control arm of study 2 compared with study 1, although this was not statistically significant. Also, when

| Table 4. Study 2: comparison of breathing pattern during control and added Vd/O2 studies at matched ventilation |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Control         | Added Vd/O2     | P Value         |
|                                | 75% Peak V̇E    |                 |                 |
| V̇E, l/min                     | 41 ± 4          | 41 ± 4          | NS              |
| f                              | 36 ± 4          | 31 ± 2          | <0.01           |
| VT, liters                     | 1.2 ± 0.1       | 1.3 ± 0.1       | <0.01           |
|                                |                 |                 |                 |
|                                | 85% Peak V̇E    |                 |                 |
| V̇E, l/min                     | 47 ± 5          | 47 ± 4          | NS              |
| f                              | 39 ± 2          | 35 ± 2          | <0.05           |
| VT, liters                     | 1.3 ± 0.1       | 1.4 ± 0.1       | NS              |
| Values are means ± SE.         |                 |                 |                 |

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converted to percent predicted, the difference is only 4%, indicating that the differences in VO2 max between the two patient groups are a result of differences in height, age, and gender. These factors would not be expected to result in different mechanisms of exercise limitation between the two groups.

**Arterial hypoxemia and exercise limitation in CF.** It is unclear why arterial hypoxemia limits exercise in CF patients. Arterial O2 desaturation occurs frequently during maximal exercise in patients with CF (6, 10, 19) and is likely to be due to combinations of elevated venous admixture, ventilation/perfusion mismatch, intrapulmonary shunting, and alveolar hypoventilation. Patients with CF have been shown to have an increased venous admixture at rest that persists throughout exercise (12, 16). In a study of a small number of CF patients using the multiple inert gas elimination technique, Dantzker et al. (12) demonstrated that venous admixture reduces slightly during exercise, largely as a result of improved ventilation/perfusion matching, and in the majority of cases this improvement in venous admixture is sufficient to maintain arterial Po2. This study also demonstrated that there was no evidence of diffusion impairment contributing to arterial desaturation. It has also been shown that, in some patients with CF (6, 10), arterial desaturation is associated with increases in PETCO2, suggesting that alveolar hypoventilation may play a role in arterial hypoxemia at end exercise. In a study looking at O2 saturation during exercise, Henke and Orenstein (19) found considerable variation in gas exchange during exercise in CF patients. The majority of their patients maintained their O2 saturations throughout exercise. Some patients desaturated with a fall in PETCO2, suggesting ventilation/perfusion mismatch with alveolar hyperventilation, whereas a significant number increased their PETCO2, suggesting alveolar hypoventilation. It is clear that the gas-exchange abnormalities observed during exercise in CF patients are complicated and require further study. This is important because, based on our findings, therapeutic interventions that improve gas exchange during exercise could improve maximal exercise capacity.

The mechanism of improved exercise capacity with supplemental O2 may include increased O2 availability to exercising muscles or reduced sensation of dyspnea associated with preventing arterial hypoxemia. Because significant arterial hypoxemia is most marked at end exercise, it is possible that supplemental O2 improved end-exercise O2 delivery to exercising muscles, which improved exercise performance.

Another possible mechanism is that supplemental O2 reduced the sensation of dyspnea at end exercise. In both studies, added VD caused an increase in VT at a given level of ventilation (Table 4). We found that, in study 1, added VD alone was associated with a mild increase in dyspnea sensation at end exercise that has also been observed in patients with idiopathic pulmonary fibrosis (26). This was not seen in study 2 when supplemental O2 was used with added VD, despite patients reaching a significantly higher Ve and PETCO2. It is possible that preventing hypoxemia improved exercise capacity by decreasing perception of dyspnea intensity normally caused by a combination of high Ve and arterial hypoxemia (37, 43), although whether arterial hypoxemia contributes to dyspnea independent of the effect on ventilatory muscle activity is not fully known (7, 24, 36, 41).

In conclusion, we found that adult patients with CF, with moderate to severe lung disease and desaturation during maximal exercise, are limited by respiratory function and that arterial hypoxemia is a significant limiting factor.

**GRANTS**

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\[ V_{\text{O}_2}\text{max} \] 