Dead Space Loading and Exercise Limitation in Patients With Interstitial Lung Disease*

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Study design: We tested the hypothesis that maximal exercise performance in subjects with interstitial lung disease (ILD) is limited by respiratory factors. Assuming this is so, ventilatory stimulation by added dead space (Vd) should impair exercise capacity. Methods: Six subjects with ILD each underwent three maximal incremental exercise studies on a bicycle ergometer; control 1, added Vd, and control 2. During the Vd study, external Vd (500 ml) was added to the circuit, and results obtained were compared with the mean results from the control studies. Results: Exercise duration (Tlim) was significantly less in the Vd study when compared to the control study (360±50 vs 439±55, p < 0.05), as was work rate (102±13 vs 125±14 W, p < 0.05) and peak oxygen uptake per minute (V02p) (1.08±0.09 vs 1.43±0.14 L/min, p < 0.05). At end-exercise, the Borg scale was higher in the Vd study compared to the control study (6±1 vs 5±1, p < 0.05), while no significant difference in minute ventilation (Vt) or oxygen desaturation was noted. When compared to the control study at matched times during exercise, the addition of Vd resulted in a significant increase in Vt, while no significant change was noted in V02p, carbon dioxide output (VCO2), or heart rate (HR). Conclusion: The decrease observed in Tlim, work rate, and peak V02p with added Vd, associated with a lack of change in Vt or oxygen desaturation at end-exercise, suggests that exercise limitation in ILD is primarily due to respiratory factors.

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Methods

All subjects underwent three maximal incremental exercise tests on a bicycle ergometer; control 1, added Vd, and control 2. The added Vd test was bracketed by two control tests to prevent the results from being affected by any possible training effect.

Patient Population

Subjects with clinical, radiographic and pulmonary function testing evidence of ILD, but no evidence of pulmonary restriction secondary to chest wall disease, pleural disease, or respiratory muscle weakness were recruited for the study from the outpatient clinics of the Division of Respiratory Medicine. All subjects were

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clinically stable for at least 2 months prior to entering the protocol and had no rheumatologic, neuromuscular, cardiac, peripheral vascular, or any disease apart from ILD that might impair exercise tolerance. All subjects gave informed consent to the procedures, but none was aware of the specific purpose of the study. The study was approved by the Medical Ethics Committee of the University of Saskatchewan.

**Protocol**

Prior to the start of the study, pulmonary function was measured in each subject. The FEV1, forced vital capacity (FVC) were measured using recommended techniques; lung volumes were obtained using helium dilution and the carbon monoxide diffusing capacity was measured by the single breath technique. Normal values of Morris et al were used for spirometry, while those of Goldman and Becklake were used for lung volumes and those of Burrows et al for diffusing capacity.

All testing was performed at the same time of the day for each subject’s three tests. Subjects had not consumed food or caffeinated drinks in the preceding 2 hours, nor had they undergone strenuous activity on the day of testing. For each subject, the study was conducted during a 25-day period, with each exercise test separated by at least 7 days.

Exercise testing was performed on an electrically braked cycle ergometer (Godart) while the subject breathed room air. Electrocardiographic leads attached to the chest monitored heart rate (HR) and ECG. The SaO2 was monitored continuously by pulse oximetry (Nellcor 200). The FEV1 and FVC were measured by a pneumotachograph system prior to each exercise test to ensure stability between the three exercise days. At least three well-coordinated maximal efforts were obtained, and the highest value for each variable obtained was recorded.

Each subject rested quietly for 2 min before starting to pedal. The initial exercise work load was 15 W for all subjects; this was increased by 15 W every minute of exercise until exhaustion. Each subject chose his own pedaling rate with speedometer feedback within the range of 50 to 70 revolutions per minute. All subjects were instructed in an identical manner by the same person for all exercise studies, and they were told that they should continue to exercise until they could exercise no more. No encouragement was offered to the subjects while they exercised.

During control studies, subjects breathed through a mouthpiece attached to a Hans Rudolph valve. An added V0 of 500 ml measured by water displacement, was inserted between the mouthpiece and the Hans Rudolph valve for the V0 exercise study. The resistance of both the inspired and expired limbs of the breathing circuit was 0.9 cm H2O/L/s at flow rates up to 4 L/s, and was matched for both control and added V0 studies. This was achieved by adding a piece of tubing, of length and internal radius identical to the V0 tube, to both the inspired and expired limbs for the control studies only, as previously described by Ward and Whipp.

Inspiratory flow and volume were measured by an inspirational pneumotachogaph-transducer-demodulator-integrator system. Mean expired O2 and CO2 were analyzed with a mass spectrometer (Airspec 2200). Equipment calibration was performed before and after each exercise study. All signals were displayed continuously in real time on an eight-channel recorder (Gould) and on a computer for later analysis.

**Data Analysis**

By the use of standard formulas, 
\[ V_i, V_r, f, HR, \text{ oxygen uptake per minute (VOJ), and carbon dioxide output (VCOJ) were measured for each minute of exercise. To facilitate analysis of the group response, data corresponding to each 10 percent increment of exercise in the control study was calculated by interpolation from the measured data for each subject. Data from the added V0 study was then calculated by interpolation at matched times in order to facilitate comparison. VOJ and VCOJ were expressed at standard temperature, pressure, dry, while VI and VR were expressed at body temperature, pressure, saturated. Predicted peak VOJ during exercise was calculated as follows:}^{16}
\[ \text{Peak VOJ } = 0.83 \text{ height}^{1.6} \times (1 - 0.007 \text{ age}) \times (1 - 0.25s) \]
where height is in meters and S is a factor taking account of gender: 
- S = 0 for males and 1 for females.

**Peak HR** was calculated as follows:^{16}
\[ \text{Peak HR } = 210 - 0.65 \text{ age (years)} \]

Each subject’s breathing pattern was examined with the plot of Hey et al with VI on the ordinate and VR on the abscissa. Data points, describing the mean response at various time intervals, were connected by straight lines.

The modified Borg scale was used to assess the sense of dyspnea at the end of exercise. Subjects were familiarized with the scale prior to exercise. At the end of each exercise test, subjects were asked, “How difficult is your breathing?” Then they were instructed to point with a finger to a number on the scale.

**Statistical Analysis**

Results collected at end-exercise from the VOJ exercise study were compared with the mean results from both control exercise studies by paired t testing. All other variables were compared by the use of analysis of variance with repeated measures. The p < 0.05 value was taken to be statistically significant. All results are reported as mean ± SEM.

The Borg scale was analyzed using Wilcoxon’s signed rank test because it is a category scale, not characterized by a normal distribution.

**Results**

Subject characteristics and maximal exercise performance of the study population are outlined in Table 1. Interstitial lung disease was due to idiopathic pulmonary fibrosis in three patients, to sarcoidosis in two patients, and to scleroderma in one patient; the conditions in three patients were confirmed by lung biopsy. Subjects completed every exercise test without any complications, and no exercise test was terminated by the physician. No subjects were excluded, and all data collected for the study were used in the analysis. No significant differences were found between the first and second control exercise study results.

Group mean values collected at rest for both control and VOJ studies (not shown) revealed no significant differences in spirometry, SaO2, or HR values. The FEV1 for all subjects measured at rest was 2.36 ± 0.21

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Subject Characteristics and Maximal Exercise Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44 ± 6</td>
</tr>
<tr>
<td>Sex</td>
<td>5 male, 1 female</td>
</tr>
<tr>
<td>Total lung capacity, L</td>
<td>4.67 ± 0.41 (68% predicted)</td>
</tr>
<tr>
<td>Vital capacity, L</td>
<td>2.83 ± 0.22 (57% predicted)</td>
</tr>
<tr>
<td>Single-breath diffusing capacity, for CO2 %</td>
<td>57 ± 9</td>
</tr>
<tr>
<td>FEV1/FVC ratio, %</td>
<td>83 ± 2</td>
</tr>
<tr>
<td>Peak VOJ, % predicted</td>
<td>55 ± 4 (range, 44 to 65)</td>
</tr>
<tr>
<td>Peak HR, % predicted</td>
<td>80 ± 3 (range, 72 to 90)</td>
</tr>
</tbody>
</table>

*Mean values ± SEM.
L (64 percent predicted). During the control studies, the mean ratio of peak \( \dot{V}_E \) at end-exercise to FEV\(_1\) measured at rest, was 28 ± 2 for the group (range, 17 to 34).

Table 2 shows mean control and Vd values collected at end-exercise. There were no significant differences in any of the variables except for \( \dot{V}_O_2 \) and \( \dot{V}_CO_2 \), which were less in the Vd study. There was also no significant difference in the degree of oxygen desaturation at end-exercise between control and Vd studies (12 ± 2 percent vs 12 ± 2 percent).

Individual and group mean results for maximal work load achieved and Borg scale at end-exercise, as well as exercise duration in both control and Vd studies are shown in Figure 1. Subjects achieved a lower work load in the Vd study when compared to the control study (102 ± 13 W vs 125 ± 14 W, \( p < 0.05 \)). In addition, subjects, during the Vd study, experienced significantly more dyspnea (Borg scale, 61 vs 51, \( p < 0.05 \)) and exercised for a significantly shorter duration of time (369 ± 50 s vs 439 ± 55 s, \( p < 0.05 \)) than they did in the control study experiments.

Figure 2 displays individual results obtained for \( \dot{V}_E \) and oxygen desaturation versus exercise duration (in minutes) for subject 3; it is representative of results obtained for all subjects. Exercise duration was less in the Vd study and was associated with a higher \( \dot{V}_E \) throughout exercise. There was no significant difference in maximal \( \dot{V}_E \) at end-exercise in both control and Vd studies (85.7 vs 85.3 L/min). Figure 2 also demonstrates a trend toward greater \( O_2 \) desaturation for a given work rate in the Vd study.

Figure 3 plots mean group results for \( \dot{V}_E \), \( f \), and \( \dot{V}_T \) versus exercise duration, for both control and Vd studies, expressed as a percentage of exercise duration in the control study. Mean end-exercise results from the control study represent 100 percent, while values collected at rest represent 0 percent. Mean exercise duration of the Vd studies was 83 percent of the control studies, and therefore Vd test results are plotted at matched times up to 83 percent of control study duration. While there were no significant differences in end-exercise results (Table 2), when compared at matched times, subjects during the Vd study had a significantly increased \( \dot{V}_E \) throughout exercise. Except for early exercise, \( f \) was significantly higher in the Vd study. The \( \dot{V}_T \) was also significantly higher in early exercise in the Vd study, although this difference became less apparent as exercise progressed.

Group mean results for \( \dot{V}_O_2 \), \( SaO_2 \), and HR are plotted versus exercise duration at matched times for both control and Vd studies in Figure 4. As noted in
Exercise Duration

\[ \text{TABLE 2—Mean Values Obtained at End-Exercise}^{*} \]

<table>
<thead>
<tr>
<th>Study</th>
<th>Values</th>
<th>Control</th>
<th>VD</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI, L</td>
<td>63.8±6.0</td>
<td>63.0±5.3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>f, breaths per minute</td>
<td>38±4</td>
<td>38±4</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>VT, L</td>
<td>1.66±0.06</td>
<td>1.67±0.06</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>VO2, L/min</td>
<td>1.43±0.14</td>
<td>1.08±0.09</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>VCO2, L/min</td>
<td>1.75±0.17</td>
<td>1.17±0.14</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>SaO2, %</td>
<td>83±2</td>
<td>81±3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>HR, beats per minute</td>
<td>149±3</td>
<td>143±5</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*Mean values ± SEM.
†NS = p>0.05.

Exercise Limitation in Interstitial Lung Disease (Marciniuk, Watts, Gallagher)
the V-slope method.22,23 There was no significant difference in \( \text{VO}_2 \) at the anaerobic threshold between control and \( \text{VO}_2 \) studies (0.89 ± 0.10 vs 0.86 ± 0.09 L/ min).

**DISCUSSION**

It is well known that patients with ILD have impaired exercise tolerance,7 as demonstrated by reduced peak \( \text{VO}_2 \) and reduced endurance time when compared with age- and sex-matched normal subjects.2,11 While various abnormalities during exercise in patients with ILD have been described, the contribution of each of these abnormalities to exercise limitation in ILD is not yet fully known. It is possible that the impaired exercise tolerance in these patients may be due to respiratory factors. Patients with ILD usually have an elevated \( \dot{V}l \) for a given work rate during exercise; this is due to increased \( \text{VO}_2 \) ventilation and in some to alveolar hyperventilation.5,5 Because of their impaired pulmonary mechanics, their maximum ventilatory capacity is significantly reduced compared to normal subjects. Therefore, the ventilatory demands of exercise in these patients represent a much greater fraction of maximum ventilatory capacity than in normal humans. Accordingly, it is possible that they stop exercise when they are breathing at or near their maximum ventilatory capacity. Ventilatory factors might also contribute to exercise limitation by causing severe respiratory discomfort;24,25 patients might stop exercising because of severe breathlessness before ventilatory factors become limiting from a physiologic point of view.

Also it is possible that exercise limitation in these patients is due to the marked arterial oxygen desaturation which they usually develop during exercise. Arterial hypoxemia can impair exercise tolerance because of inadequate oxygen delivery to working muscles.

Exercise limitation in ILD also might be due to cardiac dysfunction. The well documented increase in HR and reduction in stroke volume,26,27 as well as abnormal central hemodynamics28 demonstrated during exercise, may contribute to limiting the exercise performance in these patients. Furthermore, some patients with ILD have been shown to demonstrate resting abnormalities in left ventricular ejection fraction,27 and these resting abnormalities may be accentuated during exercise.

While there are many potential causes which may impair exercise tolerance in patients with ILD, the question of which factor truly limits exercise performance in these subjects is not yet resolved. In order to directly examine this question, we used the technique of \( \text{VO}_2 \) loading to selectively stress the respiratory system during exercise.

While the effect of \( \text{VO}_2 \) loading on maximal incre-
hence, the achieved work load was significantly less.

Maximal ventilatory capacity has frequently been estimated as FEV$_1 \times 35$. The VI at end-exercise in our subjects was significantly less than the predicted maximal ventilatory capacity; the ratio of peak VI to FEV$_1$ was 28 ± 2. This suggests that these subjects were breathing below their maximal ventilatory capacity at end-exercise. However, this must be interpreted with caution because FEV$_1 \times 35$ is not an accurate measure of maximal ventilatory capacity at end-exercise.$^{11}$

The effect of VD$_L$ loading on breathlessness in patients with ILD has not previously been examined during exercise. Our study results show that VD$_L$ loading in subjects with ILD significantly increases the sense of dyspnea at end-exercise to a level beyond that experienced at the end of the control study exercise. This increased dyspnea was not accounted for by any increase in VI or decrease in SaO$_2$. While the reason for the increase in dyspnea with added VD$_L$ is unclear, it is also evident that it is not due to changes in $f$ or VR. It may be related to the increase in PCO$_2$, which is likely seen during the added VD$_L$ study, which has been shown to increase dyspnea at equivalent levels of ventilation.$^{33}$ While we cannot exclude a possible significant contributing role, our results suggest that dyspnea does not appear to be solely responsible for exercise limitation in these subjects.

Previous studies of normal humans and patients with chronic airflow limitation have shown that arterial/mean alveolar PCO$_2$ during exercise is increased with added VD$_L$.$^{12,17,31}$ While VD$_L$ increases, alveolar ventilation is less than in the absence of added VD$_L$. While PaCO$_2$ was not measured in this study, it is likely that it was slightly greater with added VD$_L$ than with control study exercise. Such a decrease in alveolar ventilation (compared with control study exercise) is the most likely reason for the trend toward a lower SaO$_2$, albeit nonsignificant, at a given work rate with added VD$_L$ (Fig 4). We also found that in addition to the similar levels of maximum ventilation reached by our subjects in control and VD$_L$ studies, they also discontinued exercise in both control and added VD$_L$ studies after a similar degree of arterial O$_2$ desaturation. It is therefore possible that the fall in peak VO$_2$ with added VD$_L$ was related to O$_2$ desaturation. Our protocol does not allow us to distinguish which of these two factors may be of more importance in limiting exercise, but our results confirm that respiratory dysfunction (ventilatory or oxygenation abnormalities or both) is primarily responsible for exercise limitation in these patients.

In summary, we have shown that VD$_L$ loading in patients with ILD impairs exercise performance, as evidenced by reduced work load, exercise duration, and peak VO$_2$. This reduction in exercise performance was associated with similar levels of peak VI in both control and added VD$_L$ study tests. Our results suggest that exercise limitation, in subjects with ILD, is primarily due to respiratory abnormalities.

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References