Effect of respiratory rate on airway deadspace ventilation during exercise in cystic fibrosis

A.G. Thin\textsuperscript{a,b}, J.D. Dodd\textsuperscript{b}, C.G. Gallagher\textsuperscript{c}, M.X. Fitzgerald\textsuperscript{b}, P. Mcloughlin\textsuperscript{a,b,*}

\textsuperscript{a}Department of Human Anatomy and Physiology, Conway Institute of Biomolecular and Biomedical Research and the Dublin Molecular Medicine Centre, University College, Earlsfort Terrace, Dublin, Ireland
\textsuperscript{b}Department of Medicine and Therapeutics, St. Vincent’s University Hospital, Elm Park, Dublin, Ireland
\textsuperscript{c}National Referral Centre for Adult Cystic Fibrosis at St. Vincent’s University Hospital, Elm Park, Dublin, Ireland

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Summary Gas exchange during exercise in patients with cystic fibrosis (CF) is characterised by an elevated physiological deadspace to tidal volume ratio. While this has been attributed to alveolar ventilation-perfusion mismatch, there are other potential causes of the high proportion of wasted ventilation, including factors relating to the volume and the ventilation of the airway deadspace. CF (n = 6, F = 1, FEV$_1$ 26–63\% pred) and control (n = 6, F = 2) subjects completed steady-state exercise on a cycle ergometer. Gas exchange was measured breath-by-breath and the volume of the airway deadspace (V$_{Daw}$) determined using the equal areas method. Exercise data were interpolated to a CO$_2$ output of 0.7 l/min. V$_{Daw}$ was similar in the two groups both at rest and during exercise. However, the airway deadspace ventilation (V'$_{Daw}$) (median (inter-quartile range)), patients, 6.8 (5.1–7.1) l/min; controls, 4.9 (3.5–5.6) l/min, P < 0.05) was significantly greater in the CF group due to a greater respiratory frequency. These results indicate that in CF patients, abnormally increased V'$_{Daw}$ is an important contributor to the total (physiological) deadspace ventilation. Exercise performance in CF might be enhanced by efforts directed at facilitating an increase in exercise tidal volume and therefore the adoption of a more efficient pattern of breathing.

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Introduction

There is an increasing body of evidence regarding the benefits of regular exercise to patients with cystic fibrosis (CF).\textsuperscript{1,2} Higher initial levels of aerobic fitness have also been shown to be associated with an enhanced rate of survival.\textsuperscript{3} Furthermore, regular aerobic exercise can halt the progressive decline in lung function that is a feature of CF.\textsuperscript{4} These findings therefore give impetus to efforts directed at finding ways to enhance both the intensity and the duration of aerobic exercise that patients with CF can undertake on a regular basis.

During exercise in patients with CF, a large proportion of their ventilation is wasted, as indicated by an elevated physiological deadspace...
to tidal volume ratio ($V_{D_{phys}}/V_T$), even in cases of relatively mild lung disease. Elevated ventilatory equivalents for oxygen ($V_E/V_D$) and carbon dioxide ($V_E/V_{CO_2}$) are also seen and have been attributed to alveolar ventilation-perfusion ($V_A/O_2$) mismatch. While there is some evidence of altered $V_A/O_2$ distributions in CF patients during exercise, the causes of the characteristic elevation of $V_{D_{phys}}/V_T$ in CF have not been fully investigated.

$V_{D_{phys}}$ can be partitioned into alveolar ($V_{D_{aw}}$) and airway deadspaces ($V_{D_{aw}}$). In functional terms $V_{D_{aw}}$ is related to the position of the interface between airway and alveolar gas, where gas moves by convection in the former and diffusion in the latter. Given that there are estimated to be in excess of 100,000 interfaces distributed throughout the bronchial tree, $V_{D_{aw}}$ represents the volume of gas exhaled before the mean of this distribution arrives at the mouth. The size of $V_{D_{aw}}$ is determined by the interaction of a number of factors including airway cross-sectional area and geometry, inspiratory and early expiratory flow patterns and diffusion coefficient of the gas. A good example of this interaction is a post-inspiratory pause, which favours a proximal (mouthward) advancement of the interface due to an increase in the time available for diffusion. Conversely, an increase in respiratory rate, by way of both reducing the time available for diffusion and increased flow rates, would be expected to shift the interface more distally, thereby increasing the size of $V_{D_{aw}}$.

There are a number of features of CF-related lung disease that could therefore potentially impact on the size of $V_{D_{aw}}$. Bronchiectasis is a significant feature in the progression of CF-related lung disease and might be expected to increase the volume of the conducting airways and therefore be manifest as an increase in $V_{D_{aw}}$. In addition, dynamic hyperinflation is a feature of the ventilatory response during exercise. The resultant increase in the calibre of the airways could also potentially contribute to an increase in $V_{D_{aw}}$. Furthermore, in normal subjects, increases in ventilation ($V_E$) during exercise are brought about by increasing both tidal volume ($V_T$) and respiratory frequency ($f_R$). In contrast, if the ability to increase $V_T$ is limited and as a consequence, increases in $V_E$ are brought about primarily by increasing $f_R$, then the increased flow rates may also increase the size of $V_{D_{aw}}$.

There are no previous studies that measure $V_{D_{aw}}$ during exercise in patients with CF and compare these directly to normal, healthy subjects. It is therefore of value to determine if $V_{D_{aw}}$ is abnormally elevated and/or how much of a problem is a high $f_R$, low $V_T$ breathing pattern during exercise in patients with CF. This study was therefore undertaken to compare the size of $V_{D_{aw}}$ in CF patients during steady-state exercise with those of control subjects, at a similar $CO_2$ output ($V_{CO_2}$).

### Methods

#### Subjects

Six patients with CF, diagnosed on the basis of clinical history and abnormal sweat electrolyte measurements (chloride > 60 mmol/l), were recruited from the National Referral Centre for Adult Cystic Fibrosis at St. Vincent’s University Hospital. All patients were free of acute pulmonary exacerbation for at least 2 months. Six control subjects were recruited from amongst university students. The study was approved by the Ethics Committee of St. Vincent’s University Hospital. All subjects gave written informed consent.

#### Measurements

Anthropometric measurements were undertaken and spirometry performed using the spirometry module of the Vmax229 (Sensor Medics, Yorba Linda, California, USA) and results expressed as a percentage of the predicted values. Previous experience indicated that CF patients with more severe lung disease could perform at most 40 W before the onset of an exercise-induced metabolic acidosis. The exercise protocol comprised of four stages and was designed so that data would be available over a comparable range of submaximal steady-state ventilations. The first stage was at rest and the second at 10 W. The third stage was at 40 W and the final stage selected with regard to the subject’s ventilatory response at 40 W (maximum 100 and 80 W for control and CF subjects, respectively) unless a subject’s ventilatory response at 10 W indicated that they were unlikely to be able to sustain a work rate greater than 40 W. In this case for their third and fourth stages comprised 20 and 40 W, respectively. All subjects were instructed to pedal at a rate of 50 rev/min. Across all subjects, the respiratory quotient did not exceed unity, except at the final work rate in a single CF patient, where it rose to 1.03.

Bipolar electrocardiogram (SensorMedics, Yorba Linda, CA, USA) and ear lobe pulse oximetry (SatTrak, SensorMedics, Yorba Linda, CA, USA) were monitored and recorded throughout the test. Subjects wore a nose clip and a mouthpiece connected to a hot-wire anemometer (Sensor
Medics, Yorba Linda, CA, USA) for measurement of flow which was digitally integrated to obtain tidal volume. Oxygen and carbon dioxide were measured continuously using fast response paramagnetic O₂ and non-dispersive infrared CO₂ analysers (Vmax 229, Sensor Medics, Yorba Linda, CA, USA). Calibration was carried out before each test using a calibration syringe and precision oxygen and carbon dioxide mixtures (SensorMedics, Yorba Linda, CA, USA). The flow and gas concentration signals were time aligned in order to compensate for the delay due to the transit and response times of the analysers. This was achieved by rapidly switching between calibration gases using a solenoid valve and timing the transit and response times of each analyser. Data for each breath were stored on hard disk for later analysis.

At the end of each stage, two sets of tidal loops were captured and placed within the resting forced flow-volume loop by instructing subjects to inspire maximally to total lung capacity. Since two sets of tidal loops were captured at each stage, the inspiratory and expiratory reserve volumes (IRV and ERV, respectively), were taken as the mean of the two values.

Data analysis

Determination of $V_{Daw}$ requires the time-aligned expiratory flow and CO₂ fractional concentration signals. From the analogue output module of the Vmax229, the time-aligned signals of flow, O₂ and CO₂ fractional concentrations were captured using a data acquisition unit (MP100 workstation, Biopac Systems, Santa Barbara, CA, USA) connected to an Apple Macintosh computer. Since the digital to analogue conversion rate of the Vmax229 was 125 Hz, the signals were sampled at 250 Hz per channel. Software control was provided by AcqKnowledge 3.2 (Biopac Systems, Santa Barbara, CA, USA) with data stored to hard disk for subsequent off-line analysis. Ten breaths were selected for computation of $V_{Daw}$ from data at the end of each stage. The breaths were selected consecutively unless an unusually short or prolonged breath occurred, in which case it was ignored and the next breath selected.

$V_{Daw}$ was estimated using an algorithm based on Fowler’s equal areas method. The raw data points were imported into a spreadsheet program (Excel 97, Microsoft, Redmond, WA, USA) and the data reduced by taking the mean of groups of four consecutive data points, giving a resolution of 62.5 Hz. The first 80 ml of the data were discarded as this represents the external deadspace between the end of the mouthpiece and the gas sampling port.

Data from the control and CF groups were linearly interpolated in order to compare the ventilatory and gas exchange responses at the same CO₂ load ($V_{CO2} = 0.7$ l/min), which was close to 40 W.

Statistical analysis

All data are presented as median and inter-quartile range. Data from the two groups were compared using the non-parametric Mann–Whitney U test on SPSS (ver. 10.0 for Windows, SPSS Inc., Chicago, IL, USA). A $P$ value of <0.05 was accepted as being statistically significant.

Results

The age and height of the control subjects and the CF patients were similar (Table 1). The body weight tended to be lower in the CF group and the difference approached statistical significance. All spirometric indices were significantly reduced in the CF group (Table 2). There were no significant post-exercise falls in FEV₁ in any of the subjects. At rest, the median (inter-quartile range) $V_{Daw}$ (patients, 0.14(0.10–0.20) l; controls, 0.15(0.11–0.18) l) was similar in the two groups ($P = 0.749$).

Figure 1 shows a plot of the individual $V_{Daw}$ versus $V_T$ data and indicates that the former increased with increases in $V_T$ in a similar manner in the two
groups. At the same CO₂ output (\( V_{CO_2} = 0.7 \text{ l/min} \)), the size of \( V_t \) was similar in the two groups (Fig. 2), but \( f_R \) and hence \( V_t \) were increased in the CF group. The volume of the airway deadspace (\( V_{Daw} \)) was also similar in the two groups, but because of the increased \( f_R \) in the CF group, the airway deadspace ventilation (\( V_{Daw} \)) was significantly higher in the patient group (Fig. 2).

Analysis of the captured tidal loops placed within the resting forced expiratory flow-volume loops, indicated that at rest, ERV was significantly reduced in the CF group (Table 3). During exercise, ERV was increased in the CF group, suggesting that dynamic hyperinflation had occurred. This change was significantly different from the reduction in ERV observed in the control group. Furthermore, the reduction in IRV in the CF group was significantly greater than that observed in the controls. Examination of the individual tidal loops from the CF patients, indicated that at 40 W, the expiratory phase either met (\( n=1 \)) or exceeded (\( n=5 \)) the resting forced expiratory flow loop (Fig. 3). There was no evidence of flow limitation in the control subjects (data not shown).

**Table 2** Spirometric indices for control and CF groups.

<table>
<thead>
<tr>
<th></th>
<th>CF</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (%pred)</td>
<td>62 (52–93)</td>
<td>113 (94–124)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV₁ (%pred)</td>
<td>47 (25–59)</td>
<td>107 (96–120)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>57 (41–67)</td>
<td>88 (77–95)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FEF₂₅–₇₅% (%pred)</td>
<td>19 (7–27)</td>
<td>90 (77–123)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PEF (%pred)</td>
<td>63 (43–85)</td>
<td>99 (92–115)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Abbreviations: FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; FEF₂₅–₇₅%: mean expiratory flow over 25-75% FVC; PEF: peak expiratory flow; %pred: percentage of predicted value.

**Figure 1** Plot of individual airway deadspace volume (\( V_{Daw} \)) data both at rest and during exercise versus tidal volume (\( V_t \)). Open circles joined with solid lines indicate individual control subjects; filled circles joined with dashed lines indicate individual CF subjects.

**Discussion**

At rest, there was no evidence of an increased airway deadspace volume (\( V_{Daw} \)) in the CF group. Surprisingly, during exercise at the same CO₂ output (0.7 l/min), the size of \( V_t \) was similar in the two groups (Fig. 2), but \( f_R \) and hence \( V_t \) were increased in the CF group. The volume of the airway deadspace (\( V_{Daw} \)) was also similar in the two groups, but because of the increased \( f_R \) in the CF group, the airway deadspace ventilation (\( V_{Daw} \)) was significantly higher in the patient group (Fig. 2).

Analysis of the captured tidal loops placed within the resting forced expiratory flow-volume loops, indicated that at rest, ERV was significantly reduced in the CF group (Table 3). During exercise, ERV was increased in the CF group, suggesting that dynamic hyperinflation had occurred. This change was significantly different from the reduction in ERV observed in the control group. Furthermore, the reduction in IRV in the CF group was significantly greater than that observed in the controls. Examination of the individual tidal loops from the CF patients, indicated that at 40 W, the expiratory phase either met (\( n=1 \)) or exceeded (\( n=5 \)) the resting forced expiratory flow loop (Fig. 3). There was no evidence of flow limitation in the control subjects (data not shown).
Figure 2 Comparison of ventilatory changes with exercise in control and CF groups. Open circles indicate individual control subjects; filled circles indicate individual CF subjects; solid horizontal bars indicate group mean data at rest (R) and during exercise (E) at a $\dot{V}_{\text{CO}_2}$ of 0.7 l/min. Abbreviations: $V_T$: tidal volume; $V_{Daw}$: volume of airway deadspace; $f_R$: respiratory frequency; $V_{E}$: minute ventilation; $V_{Daw}$: ventilation of airway deadspace; $V_A$: alveolar ventilation.

Table 3 Changes in tidal volume and inspiratory and expiratory reserve volumes between rest and 40 W.

<table>
<thead>
<tr>
<th></th>
<th>Rest Median (inter-quartile range)</th>
<th>P-value</th>
<th>Change Median (inter quartile range)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CF</td>
<td>Control</td>
<td></td>
<td>CF</td>
</tr>
<tr>
<td>$V_T$ (I)</td>
<td>0.64 (0.49-0.94)</td>
<td>0.70 (0.64-0.91)</td>
<td>0.361</td>
<td>+0.39 (+0.26-+0.45)</td>
</tr>
<tr>
<td>IRV (I)</td>
<td>1.44 (1.00-1.99)</td>
<td>2.04 (1.75-3.04)</td>
<td>0.068</td>
<td>-0.51 (-0.78--0.28)</td>
</tr>
<tr>
<td>ERV(I)</td>
<td>0.73 (0.47-1.37)</td>
<td>2.05 (1.56-2.16)</td>
<td>&lt;0.05</td>
<td>+0.10 (-0.04++0.39)</td>
</tr>
</tbody>
</table>

Abbreviations: $V_T$: tidal volume; IRV: inspiratory reserve volume; ERV: expiratory reserve volume.
Note: In error, resting tidal loops for a single control subject were not stored for analysis. Thus in this table the data for the control group are for only n = 5, F = 2.
output, despite some evidence of dynamic hyper-inflation in the CF group, the volume of this deadspace in the patient group was not elevated above that of the control group. However, the higher $f_R$ in the CF group at the same CO$_2$ output resulted in a disproportionate increase in airway deadspace ventilation ($V_{Daw}$) compared to the control group.

Given the various factors that can affect the location of the interface between airway and alveolar gas, it should not be surprising that the size of $V_{Daw}$ increased with exercise (Fig. 1). Indeed, even if only anatomical factors were considered, $V_{Daw}$ would be expected to increase with the degree of lung inflation. However, during exercise, superimposed on top of this factor are changes in inspiratory and expiratory flow patterns and rates. At this point it is also worth considering two as yet unmentioned aspects of ventilation, namely laminar versus turbulent flow and the distribution of the time constants of the gas exchange units in the lungs. Increased inhomogeneity of time constants will result in a greater spread in the distribution of interfaces arriving at the mouth. Conversely, turbulent gas flow will tend to speed up airway washout, thereby reducing the spread of the distribution of interfaces, and thus the size of phase II. The effect of inhomogeneity of time constants will become more marked at higher flow rates. There is some evidence from elevated phase III slopes during a single breath nitrogen washout test in patients with CF that this may be a problem. If there were a population of gas exchange units with particularly long time constants, then the interfaces from these units would be subsumed with alveolar gas from the rest of the lung. In this case, since there is insufficient information contained in the CO$_2$ concentration versus flow trace measured at the mouth to delineate these late arriving interfaces, the determined value of $V_{Daw}$ should be considered a minimum estimate. It is therefore possible, that in the present study there was a degree of underestimation in the size of $V_{Daw}$ in the CF patients.

While not previously reported during exercise, Wood et al. determined $V_{Daw}$ at rest in pediatric CF patients and found values similar to those in healthy children. We have extended their finding, by demonstrating that the size of $V_{Daw}$ is not elevated in adult CF patients compared to control subjects during exercise. It might have been expected that $V_{Daw}$ would be elevated in the CF patients, since bronchiectasis is a major feature of the disease process. However, a potential explanation for the lack of a demonstrable increase in $V_{Daw}$ in the CF patients is the presence of airway plugging, a feature observed in radiographs and post-mortem studies. Such blockages would result in functional loss of part of the bronchial tree and as a consequence the measured volume of gas in the conducting airways would not be increased, despite the presence of bronchiectatic lung disease.

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**Figure 3** Panels (A)-(F) show individual tidal loops captured 40W and placed inside resting forced flow-volume loops for the six CF patients. (—) indicates resting forced flow-volume loop; (....) indicates resting tidal breathing; (- - -) indicates tidal loop captured at 40W. Note difference in scale in panel F.
Dynamic hyperinflation is apparent during exercise in patients with CF, an adaptation also observed in the present study (Table 3). In normal subjects at rest, the size of $V_{Daw}$ has been shown to increase with increasing end-inspiratory lung volume. In the absence of measurements of residual volume and total lung capacity it is not possible to make direct comparisons between the two groups. However, the size of the reduction in IRV in the CF group shown in Table 3 in going from rest to 40 W indicates a relative increase in lung volume of approximately 440 ml compared to the control group. Results from the above studies indicate that while varying end-inspiratory lung volume at rest in normal subjects, the size of $V_{Daw}$ increased at the rate of about 3 ml per 100 ml increase in lung volume. On this basis, going from rest to 40 W, dynamic hyperinflation would have contributed an increase in the region of 13 ml to the size of $V_{Daw}$. Therefore, much larger degrees of dynamic hyperinflation than seen in the present study would be required before this would become a physiologically significant effect.

The increased $f_R$ and therefore flow rates seen in the CF patients at the same $V_{O_2}$ as the control subjects did not appear to result in an increase in the size of $V_{Daw}$. However, the increased flow in the CF group may have resulted in a degree of underestimation in the size of $V_{Daw}$ due to an exacerbation of the effect of inhomogeneity of time constants between gas exchange units, as discussed above.

In contrast to the above, we observed an abnormal increase in the ventilation of the airway deadspace ($V_{Daw}$) in the CF group, arising as a consequence of the breathing strategy adopted by the CF patients. While the disproportionate increase in $f_R$ did not impair gas exchange by increasing the size of $V_{Daw}$, the lack of a compensatory increase in $V_T$ resulted in a reduction in ventilatory efficiency, resulting in a higher proportion of wasted ventilation. The clinical implications of this finding for patients with CF are important. Breathing at higher lung volumes is a recognised adaptation to prevent dynamic airway collapse and therefore minimise flow limitation in obstructive lung diseases. However, it means operating on a less compliant region of the pressure–volume curve of the lungs and so in order to prevent diaphragmatic fatigue, the size of any increase in $V_T$ is constrained. At a $V_{O_2}$ of 0.71 l/min, $V_{Daw}$ was on average 36% greater in the CF group than in the control group. At higher intensities of exercise, ever greater dependence on $f_R$ rather than $V_T$ to bring about the necessary increase in ventilation, will result in this difference becoming even more significant.

Several studies of different inspiratory muscle training protocols (i.e., various combinations of loading and duration) have been undertaken in patients with CF. The study by Sawyer et al. had the longest training period (10 weeks) and was the only one to demonstrate an increase in maximal exercise capacity. However, since no gas exchange measurements were made, it is not possible to comment on the reason(s) for the increase. Furthermore, none of these studies had the primary aim of bringing about increases in exercise $V_T$. Increases in $V_T$ in normal, healthy subjects have been produced by means of servo-assisted positive pressure ventilation. The results of the present study indicate that were it possible to facilitate such an increase in $V_T$ in patients with CF, it would be likely to be of significant benefit to their exercise performance. However, use of servo-assisted positive pressure ventilation in patients with CF will necessitate the development of a protocol that permits the application of a training stimulus sufficient to bring about increases in $V_T$ while at the same time avoiding exhausting the diaphragm.

In conclusion, the major findings of this study were that, in contrast to our initial expectations, the airway deadspace volume is not elevated during exercise in patients with CF. However, because in these patients the size of the increase in $V_T$ was limited, the increased $V_E$ required to maintain gas exchange was therefore brought about primarily by increasing $f_R$. As a result their airway deadspace ventilation was significantly elevated and contributes significantly to the high proportion of wasted ventilation observed in these patients.

Acknowledgements

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References