On-Line Data Supplement

Exercise Ventilatory Efficiency in COPD:
Advanced Mathematical and Physiological Considerations

As outlined in the main text, ventilation (\(\dot{V}_E\)) required to washout a given rate of CO\(_2\) production (\(\dot{V}_{CO_2}\)) is higher the lower the arterial partial pressure for CO\(_2\) (PaCO\(_2\)) (as more \(\dot{V}_E\) is needed to keep PaCO\(_2\) at a low compared to a high value) and the larger the ventilation “wasted” in the dead space (\(V_D\)), i.e.,[1][2][3][4]

\[
\frac{\dot{V}_E}{\dot{V}_{CO_2}} = \frac{1}{PaCO_2} \times (1 - V_D/V_T)
\]

Eq.(1)

where \(\dot{V}_E/\dot{V}_{CO_2}\) ratio is the ventilatory equivalent for CO\(_2\) and \(V_D/V_T\) is the physiological (anatomic plus alveolar) dead space fraction of tidal volume.

However, \(\dot{V}_E\) is known to change as a linear function of \(\dot{V}_{CO_2}\) during mild to moderate exercise, i.e.,

\[
\dot{V}_E = (m \times \dot{V}_{CO_2}) + c
\]

Eq.(2)

where \(m\) is the slope of the \(\dot{V}_E-\dot{V}_{CO_2}\) relationship (the rate at which \(\dot{V}_E\) increases as \(\dot{V}_{CO_2}\) increases) and \(c\) is the intercept (i.e., \(\dot{V}_E\) when \(\dot{V}_{CO_2}=0\)) (Figure S1A). Thus, the \(\dot{V}_E/\dot{V}_{CO_2}\) response contour is intrinsically linked to how \(\dot{V}_E\) dynamically changes in relation to \(\dot{V}_{CO_2}\) (\(m\)) taking into consideration its starting point (\(c\)) divided by \(\dot{V}_{CO_2}\) (Figure S1B), i.e.

\[
\dot{V}_E/\dot{V}_{CO_2} = m + (c/\dot{V}_{CO_2})
\]

In other words, the ventilatory equivalent for CO\(_2\) exceeds \(m\) (by the variable factor \(c/\dot{V}_{CO_2}\)) but it approaches it at high levels of \(\dot{V}_{CO_2}\). [1][2][3][4] In practice, it means that the \(\dot{V}_E/\dot{V}_{CO_2}\) nadir equates to \(\dot{V}_E-\dot{V}_{CO_2}\) slope provided \(c\) is a small number relative to \(\dot{V}_{CO_2}\) at the nadir - as it is often the case in healthy, young subjects (Figure S1).[1]
Figure S1.

Fig. 2. Schematic representation (panel A) of the responses of ventilation ($\dot{V}_E$) and the ventilatory equivalent for CO$_2$ ($\dot{V}_E/\dot{V}_{CO_2}$) to the increased CO$_2$ output ($\dot{V}_{CO_2}$) during the course of a bout of moderate constant-load exercise, and the actual responses (panel B) of these functions during the transition from unloaded cycling to 250 watts in a fit subject (i.e. below the anaerobic threshold). Points (i), (ii) and (iii) on the $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship in panel A represent predicted $\dot{V}_E$, $\dot{V}_{CO_2}$ responses at three arbitrary times during the course of the work; and the slopes of the dashed lines joining these points to the origin define the corresponding $\dot{V}_E/\dot{V}_{CO_2}$ responses (c.f. lower panel). Note that the actual $\dot{V}_E/\dot{V}_{CO_2}$ response fits well the predicted hyperbolic decrease through the transition. See text for further details.

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A different scenario, however, may emerge in patients in whom \(c\) is relatively a large number compared to \(\dot{V}\)CO\(_2\) - as in patients with COPD. Table S1 shows actual average values (rounded to the first decimal) obtained in a large group of age-matched controls and patients with COPD spirometric stages 1 to 4: [5]

<table>
<thead>
<tr>
<th>Table S1.</th>
<th>(\dot{V})E-(\dot{V})CO(_2) slope (m)</th>
<th>(\dot{V})E-(\dot{V})CO(_2) intercept (c)</th>
<th>(\dot{V})CO(_2) at the nadir</th>
<th>(c)/(\dot{V})CO(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls (N= 69)</td>
<td>27.3</td>
<td>2.6</td>
<td>1.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Stage 1 COPD (N= 81)</td>
<td>33.9</td>
<td>4.1</td>
<td>1.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Stage 2 COPD (N= 112)</td>
<td>30.8</td>
<td>5.9</td>
<td>1.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Stage 3 COPD (N= 84)</td>
<td>28.0</td>
<td>6.5</td>
<td>1.0</td>
<td>6.5</td>
</tr>
<tr>
<td>Stage 4 COPD (N= 39)</td>
<td>25.1</td>
<td>8.3</td>
<td>0.8</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Table S2 compares observed (ref. [5] and manuscript’s Figure 2) \(\dot{V}\)E/\(\dot{V}\)CO\(_2\) nadir and calculated (based on Eq [2] and table S1) \(\dot{V}\)E/\(\dot{V}\)CO\(_2\) nadir in controls and patients

<table>
<thead>
<tr>
<th>Table S2.</th>
<th>Observed (\dot{V})E/(\dot{V})CO(_2) nadir[5]</th>
<th>Estimated (\dot{V})E/(\dot{V})CO(_2) nadir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls (N= 69)</td>
<td>29.2</td>
<td>28.7</td>
</tr>
<tr>
<td>Stage 1 COPD (N= 81)</td>
<td>35.1</td>
<td>36.7</td>
</tr>
<tr>
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<td>35.2</td>
</tr>
</tbody>
</table>

Figure S2 depicts the fractional contribution of \((c/\dot{V}\)CO\(_2\)) to the observed \(\dot{V}\)E/\(\dot{V}\)CO\(_2\) nadir in patients and controls. This analysis demonstrates that due to progressively lower \(\dot{V}\)E-\(\dot{V}\)CO\(_2\) slope, higher \(\dot{V}\)E intercept and lower \(\dot{V}\)CO\(_2\) at the nadir as disease progressed from GOLD stages 1 to 4 (table S1), the \(\dot{V}\)E intercept contributed to a greater extent to \(\dot{V}\)E/\(\dot{V}\)CO\(_2\) nadir values in patients than controls. Thus, compared to healthy controls, the \(\dot{V}\)E intercept’s relative contribution to \(\dot{V}\)E/\(\dot{V}\)CO\(_2\) nadir increased three- and six-fold in moderate to severe and very-severe COPD, respectively.
Figure S2. The fractional contribution of ventilation ($\dot{V}_E$) intercept/carbon dioxide output ($\dot{V}_{CO_2}$) ratio to $\dot{V}_E/\dot{V}_{CO_2}$ nadir in COPD patients GOLD spirometric stages 1-4 and healthy controls. Values based on data showed in Tables 1 and 2.
Figure S3. Influence of progressive airway obstruction on ventilatory efficiency parameters in patients with mild (a,b), moderate (c,d), severe (e,f) and very severe (g,h) COPD. Left panels show the linear ventilation (\( \dot{V}_E \)) / carbon dioxide output (\( \dot{V}C_{O_2} \)) relationship which determines the \( \dot{V}_E/\dot{V}C_{O_2} \) behavior on the right. The nadir is the lowest \( \dot{V}_E/\dot{V}C_{O_2} \) and \( \Delta \) is the difference between the \( \dot{V}_E/\dot{V}C_{O_2} \) nadir and the \( \dot{V}_E-\dot{V}C_{O_2} \) slope. See text for further elaboration. Reproduced, with permission, from ref. [5]
Figure S4. The impact of mild COPD on ventilatory and gas exchange responses to incremental CPET. Increased ventilation ($\dot{V}_E$) (A) was associated with an upward displacement of the $\dot{V}_E$/carbon dioxide output ($\dot{V}CO_2$) ratio, i.e. poor ventilatory efficiency (B). These abnormalities were secondary to increased dead space ($V_D$)/tidal volume ($VT$) ratio (C) due to a high $V_D$ (D). Thus, greater $V_D/VT$ explain the wider dissociation between $\dot{V}_E$ and alveolar ventilation ($\dot{V}_A$) in patients compared to controls. Reproduced, with permission, from ref. [6].

Footnotes: *$P < 0.05$, patients with mild COPD versus healthy control subjects at rest, at standardized work rates, or at peak exercise; †$P < 0.05$, difference between $\dot{V}_E$ and $\dot{V}_A$ in patients with COPD versus healthy control subjects at rest, at a standardized work rate, or at peak exercise.
Figure S5. Receiver operating characteristic curves of ventilatory efficiency parameters (ventilation ($\dot{V}E$)-carbon dioxide output ($\dot{V}CO_2$) intercept and slope and $\dot{V}$ $E/\dot{V}CO_2$ peak) and peak end-tidal PCO$_2$ (PETCO$_2$) to discriminate COPD-heart failure overlap from COPD. Circles depict the optimal thresholds according to individual variables. Reproduced, with permission, from ref. [7]

Footnote: *$P < 0.05$. †$P < 0.05$ versus peak PETCO$_2$
Figure S6. Physiological and perceptual responses to incremental exercise in a patient with heart failure-COPD presenting with exercise oscillatory ventilation (EOV) ((a), (b) and (c)). Note the progressive increases in operating lung volumes up to a point at which critical inspiratory constraints ((d)) precluded further oscillations. The descending trajectory of arterialized PCO$_2$ was then interrupted (c) and dyspnea scores rose fast (data not shown). Reproduced, with permission, from ref. [8]

**Abbreviations:** MVV = maximal voluntary ventilation; TLC = total lung capacity; IRV = inspiratory reserve volume; VT = tidal volume; IC = inspiratory capacity.
References


