An open-circuit method for determining lung diffusing capacity during exercise: comparison to rebreathe

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Snyder, Eric M., Bruce D. Johnson, and Kenneth C. Beck. An open-circuit method for determining lung diffusing capacity during exercise: comparison to rebreathe. J Appl Physiol 99: 1985–1991, 2005. First published July 14, 2005; doi:10.1152/japplphysiol.00348.2005.—To avoid limitations associated with the use of single-breath and rebreath methods for assessing the lung diffusing capacity for carbon monoxide (DLCO) during exercise, we developed an open-circuit technique. This method does not require rebreathing or alterations in breathing pattern and can be performed with little cognition on the part of the patient. To determine how this technique compared with the traditional rebreath (DLCO, RB) method, we performed both the open-circuit (DLCO, OC) and the DLCO, RB methods at rest and during exercise (25, 50, and 75% of peak work) in 11 healthy subjects [mean age = 34 yr (SD 11)]. Both DLCO, OC and DLCO, RB increased linearly with cardiac output and external work. There was a good correlation between DLCO, OC and DLCO, RB for rest and exercise (mean of individual $r^2 = 0.88$, overall $r^2 = 0.69$, slope = 0.97). DLCO, OC and DLCO, RB were similar at rest and during exercise [e.g., rest = 27.2 (SD 5.8) vs. 29.3 (SD 5.2), and 75% peak work = 44.0 (SD 7.0) vs. 41.2 ml·min⁻¹·mmHg⁻¹ (SD 6.7) for DLCO, OC vs. DLCO, RB]. The coefficient of variation for repeat measurements of DLCO, OC was 7.9% at rest and averaged 3.9% during exercise. These data suggest that the DLCO, OC method is a reproducible, well-tolerated alternative for determining DLCO, particularly during exercise. The method is linearly associated with cardiac output, suggesting increased alveolar-capillary recruitment, and values were similar to the traditional rebreath method.

The diffusing capacity of the lungs for carbon monoxide (DLCO) is reduced in a number of disease states (e.g., emphysema, heart failure, interstitial lung disease), and a low value measured at rest may be predictive of exercise intolerance and ventilatory inefficiency (increased minute ventilation/CO2 production) (1, 17). In addition, the rise in DLCO with exercise [typically paralleling the rise in cardiac output (Q) in health] may be reduced in these same patient groups, suggesting a limited expansion of the alveolar-capillary bed (15, 17, 27).

There are a number of techniques that have been used to assess DLCO. These include the single-breath (DLCO, SB), the rebreath (DLCO, RB), and the steady-state methods (DLCO, SS) (16, 23, 25). The single-breath method is clinically the most widely used, largely because of standardization efforts from a number of organizations (2). In contrast, the other two techniques have been used primarily in research settings, with the rebreath technique gaining the most prominence (15). Each method of assessing DLCO has its advantages and disadvantages, with the single-breath and rebreath methods having particular shortcomings for use during heavy exercise. For example, the DLCO, SB method requires a breath hold at a full inflation volume, whereas the DLCO, RB technique is accompanied by a rise in carbon dioxide, leading to dyspnea and an unpredictable change in the rebreath volume due to a changing CO2 production/O2 uptake relationship (5, 20). Thus, during heavy exercise or in patient populations in which dyspnea is a contributor to exercise intolerance, the DLCO, RB method may further contribute to exercise limitations. The DLCO, SS allows a natural breathing pattern on the part of the subject without a buildup of carbon dioxide. However, the DLCO, SS takes more time to perform, appears to be more affected by changes in alveolar dead space (compared with the other methods), and has classically required an arterial blood sample (4, 18, 26).

Given the usefulness of assessing DLCO with exercise, it would be optimal to have a technique that allowed a natural breathing pattern, did not cause a buildup of CO2, and did not require a lengthy measurement time or a blood draw. Our laboratory has recently developed an eight-breath, open-circuit gas washin technique to measure Q during exercise (19). This technique takes advantage of the solubility of acetylene (C2H2) in the blood as it passes through the pulmonary circulation. The maneuver and algorithms for assessing Q can be adapted to measure the disappearance of carbon monoxide (CO) in the lungs [open-circuit DLCO (DLCO, OC)]. Using this technique, the subject can breathe at a normal rate and tidal volume over 8–10 breaths. We have found that this method is much more easily tolerated for use during heavy exercise. We hypothesized that the DLCO, OC technique would yield similar values as the classic DLCO, RB technique at rest and throughout exercise.

METHODS

The protocol was reviewed and approved by the Mayo Clinic Institutional Review Board, and all participants signed informed consent before study. Eleven subjects were screened, agreed to participate in the study, and had no exclusion criteria (history of cardiac or pulmonary-related abnormalities, use of prescription medications, pregnancy, or an inability to exercise).

Protocol. Subjects performed an initial maximal exercise test on a stationary cycle ergometer to determine workloads for the test day. On a subsequent visit, subjects performed incremental cycle ergometry at work levels that approximated 25, 50, and 75% of their maximal work intensity for 10 min per exercise stage. At each work intensity, subjects performed DLCO, OC, DLCO, RB, and a repeat DLCO, OC, each separated by 1–2 min to allow test gas to be cleared from the lungs. The DLCO measures were started after 3 min following a change in breathing pattern, did not cause a buildup of CO2, and did not require a lengthy measurement time or a blood draw. Our laboratory has recently developed an eight-breath, open-circuit gas washin technique to measure Q during exercise (19). This technique takes advantage of the solubility of acetylene (C2H2) in the blood as it passes through the pulmonary circulation. The maneuver and algorithms for assessing Q can be adapted to measure the disappearance of carbon monoxide (CO) in the lungs [open-circuit DLCO (DLCO, OC)]. Using this technique, the subject can breathe at a normal rate and tidal volume over 8–10 breaths. We have found that this method is much more easily tolerated for use during heavy exercise. We hypothesized that the DLCO, OC technique would yield similar values as the classic DLCO, RB technique at rest and throughout exercise.
conditions. Following completion of each series of measurements at a given workload, the workload was increased, so that the testing was completed with no pause between stages.

**DLCO,RB.**

For the DLCO,RB, subjects breathed into a two-way switching valve (Hans Rudolph, Kansas City, MO), which was connected to a pneumotachometer (Hans Rudolph) and a mass spectrometer (Perkin-Elmer, 1100). Custom software was used to acquire data and perform the analyses. The inspiratory port of the switching valve was set to either room air or a 5-liter anesthesia bag (Hans Rudolph), which was filled with 1.0–3.0 liters of test gas (35% O₂, 0.6% C₂H₂, 0.3% C¹⁸O, 9% He, and balance N₂), depending on the tidal volume of the subject and the exercise intensity. Consistent bag volumes were ensured by using one of the following methods: 1) the use of a timed switching circuit, which, given a consistent flow rate from the tank, resulted in the desired volume; or 2) filling of a 3-liter syringe with the test gas to the appropriate bag volume and subsequently injecting this into the evacuated rebreathe bag. Target volumes for the bag were estimated, starting with 1.2 liters at rest and increasing to 2.5–3.0 liters during exercise, depending on subject size and measurement of tidal volumes obtained from the initial incremental exercise test. C¹⁸O was used instead of the more common C¹⁴O as the test gas, because the mass spectrometer cannot distinguish C¹⁴O from N₂. At the end of a normal expiration [end-expiratory lung volume (EELV)], the subjects were switched into the rebreathing bag. The subjects were then instructed to nearly empty the bag with each breath for 10 consecutive breaths. The respiratory rate was controlled at 20 breaths/min with a metronome at rest. During exercise, the subjects were allowed to breathe at a normal respiratory rate. Following each DLCO,RB maneuver, the anesthesia bag was emptied with a suction device and refilled for the next maneuver. Gas concentrations were continuously sampled with the mass spectrometer by using custom data-acquisition software sampling at 120 s⁻¹. From these data streams, DLCO was obtained by the Roughton-Forster method (24). Briefly, end-inspiratory and end-tidal gas concentrations for each breath were identified from the volume tracing and after shifting the

**DLCO,OC.**

The open-circuit method has been described previously for the assessment of Q (19). In brief, during the DLCO,OC test, subjects breathed into a non-rebreathing valve (Hans Rudolph) with the inspiratory port connected to a pneumatic switching valve with low dead space and low resistance (Hans Rudolph). A pneumotachometer (Hans Rudolph) and mass spectrometer sampling line were connected to the common port of the non-rebreathing valve. Custom data acquisition and analysis software were used to acquire data at 120 Hz and perform the analysis to determine DLCO,OC (see Fig. 2 and appendix). The inspiratory ports of the switching valve were connected to room air and a large reservoir that was filled with 10–30 liters of a test gas mixture (35% O₂, 0.6% C₂H₂, 0.3% C¹⁸O, 9% He, and balance N₂). To make a measurement, an operator switched the two-way valve during a normal expiration, allowing the next inspiration to be from the gas reservoir. Subjects breathed the gas mixture for up to 10 breaths and were subsequently switched back to room air. During the maneuver, the subject’s breathing pattern could be visualized by the operator on the computer screen. At rest, the respiratory rate was controlled at 20 breaths/min, while, during exercise, subjects were allowed to breathe at their usual respiratory rate and tidal volume. The data were analyzed after shifting the gas concentration channels by 0.25–0.29 s to align them with the flow signal. DLCO,OC was calculated by an iterative solution of alveolar gas exchange equations (see Fig. 3, appendix, and Ref. 19).

The final DLCO,OC value was then corrected to account for the difference in alveolar PO₂ (PAO₂), as measured by average end-tidal PO₂ during the maneuvers, using the correction recommended by the American Thoracic Society (11). This correction is necessary because...
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>BMI, kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>M</td>
<td>182</td>
<td>82</td>
<td>25</td>
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<tr>
<td>2</td>
<td>30</td>
<td>F</td>
<td>183</td>
<td>75</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>M</td>
<td>183</td>
<td>80</td>
<td>24</td>
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<td>38</td>
<td>M</td>
<td>194</td>
<td>89</td>
<td>24</td>
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<td>M</td>
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<td>74</td>
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<td>26</td>
<td>M</td>
<td>176</td>
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<td>32</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>F</td>
<td>163</td>
<td>77</td>
<td>29</td>
</tr>
<tr>
<td>8</td>
<td>34</td>
<td>M</td>
<td>193</td>
<td>106</td>
<td>28</td>
</tr>
<tr>
<td>9</td>
<td>24</td>
<td>M</td>
<td>178</td>
<td>69</td>
<td>22</td>
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<tr>
<td>10</td>
<td>22</td>
<td>M</td>
<td>180</td>
<td>82</td>
<td>25</td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>M</td>
<td>168</td>
<td>58</td>
<td>21</td>
</tr>
<tr>
<td>Mean</td>
<td>34</td>
<td></td>
<td>180.2</td>
<td>81.0</td>
<td>25</td>
</tr>
<tr>
<td>SD</td>
<td>11</td>
<td></td>
<td>9.2</td>
<td>13.4</td>
<td>4</td>
</tr>
</tbody>
</table>

M, male; F, female; BMI, body mass index.

The Pao₂ decreases during the DLCO, RB maneuver but stays constant during the DLCO, OC maneuver. The end-tidal fractional O₂ concentration (O₂) fell to ~16% during the DLCO, RB tests but remained at nearly 21% during the DLCO, OC maneuvers, despite both techniques using gas with 35% O₂ (see Table 3). Because of these O₂ differences, there is likely less competition between O₂ and CO during the DLCO, OC maneuver. The end-tidal fractional O₂ concentration (O₂) was slightly lower than DLCO, RB at rest and slightly higher during exercise, although these differences reached statistical significance only at level 2 of exercise, where DLCO, OC was 40.6 ml/min/mmHg⁻¹ and DLCO, RB was 37.6 ml/min/mmHg⁻¹.

Comparison of DLCO, OC to DLCO, RB. The end-tidal P0₂ was lower during DLCO, RB maneuver compared with DLCO, OC, with the difference becoming greater with exercise (Table 3). The mean correction for this difference increased the DLCO, OC by 0.8 (SD 0.7) vs. 0.0 (SD 0.0) and with exercise, with the differences being accentuated with the higher exercise intensities [exercise 1 = 0.2 (SD 0.4), exercise 2 = 3.0 (SD 0.6), and exercise 3 = 3.7 (SD 0.5) vs. 2.3 (SD 0.6), P < 0.001].

Discussions

We have shown that DLCO obtained using an open-circuit method I) increases linearly with Q, 2) is reproducible at rest...
and during exercise, 3) is similar to established rebreathe method, and 4) can be performed during exercise with little or no alteration in the subject’s breathing pattern.

Measurement of the DL\(\text{CO,OC}\) for assessing physiological parameters of the lung has been used since the early 20th century (7). There are several techniques that allow for assessment of DL\(\text{CO,OC}\) at rest and during exercise, including the DL\(\text{CO,OC,RB}\), DL\(\text{CO,OC,SB}\), and DL\(\text{CO,OC,SS}\) techniques (3, 21). The major limitation of the DL\(\text{CO,OC,SB}\) method is the requirement of a full inspiration and a breath hold, which are difficult for most subjects to perform during exercise. Limitations of the DL\(\text{CO,OC,SS}\) method include the requirement of an arterial blood sample to estimate alveolar CO\(\text{2}\), the nearly 2 min required to perform the maneuver (for allowance of steady-state breathing by the subject), and the large amount of CO that the subject absorbs, limiting the number of trials per session.

All methods for measuring DL\(\text{CO}\) can be affected by inhomogeneities of alveolar ventilation (\(\dot{V}_{\text{A}}\)), \(\dot{Q}\), and \(\dot{V}_{\text{A}}/\dot{Q}\). The issue of how closely any laboratory estimate of DL\(\text{CO}\) matches “true” DL\(\text{CO}\) is a matter of considerable debate. For instance, it has been shown that DL\(\text{CO,OC,SB}\) is affected by subtle differences in calculation techniques that can lead to overestimation or underestimation of DL\(\text{CO}\) in the presence of lung disease (3a, 9). Modeling analysis suggests any measurement of DL\(\text{CO}\) will be affected by lung inhomogeneities (13), although a detailed modeling comparison of DL\(\text{CO,OC,SS}\) to DL\(\text{CO,OC,RB}\) has not been performed. Because both DL\(\text{CO,OC,OC}\) and DL\(\text{CO,OC,SS}\) involve tidal breathing (as opposed to breath hold), gas exchange in each breath will be likely equally inefficient for both techniques, so it is our expectation that DL\(\text{CO,OC}\) and DL\(\text{CO,OC,RB}\) will be nearly equally affected by \(\dot{V}_{\text{A}}/\dot{Q}\) mismatch.

Advantages of DL\(\text{CO,OC}\) over traditional methods. The advantages of the DL\(\text{CO,OC}\) technique include 1) minimal coaching of the subjects in breathing technique (no need to match bag volume to tidal volume or to match the timing of the switch to the rebreathe bag exactly at EELV), 2) subjects do not experience increased shortness of breath due to CO\(\text{2}\) buildup, 3) O\(\text{2}\) uptake remains normal and PAO\(\text{2}\) is more stable during the maneuver compared with single-breath and rebreathing methods, and 4) subjects can breathe normally (no breath hold, which makes the maneuver easy during exercise). The maneuver is also brief, only requiring the gas washin for 8–10 breaths, allowing for multiple runs within an exercise test.

Limitations to the DL\(\text{CO,OC}\) method. The DL\(\text{CO,OC}\) method requires a higher volume of test gas compared with either the single-breath methods or rebreathing methods, potentially add-

Table 3. Breathing pattern using the DL\(\text{CO,OC}\) and DL\(\text{CO,OC,RB}\) techniques

<table>
<thead>
<tr>
<th>Level</th>
<th>Tidal Volume, liters</th>
<th>End-Expiratory Lung Volume, liters</th>
<th>Breathing Frequency, breaths/min</th>
<th>PAO(\text{2}), Torr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DL(\text{CO,OC})</td>
<td>DL(\text{CO,OC,RB})</td>
<td>(P)</td>
<td>DL(\text{CO,OC})</td>
</tr>
<tr>
<td>Rest</td>
<td>0.89 (0.13)</td>
<td>1.09 (0.20)</td>
<td>0.013</td>
<td>3.75 (0.93)</td>
</tr>
<tr>
<td>1</td>
<td>1.76 (0.36)</td>
<td>1.83 (0.45)</td>
<td>0.656</td>
<td>3.82 (1.00)</td>
</tr>
<tr>
<td>2</td>
<td>2.14 (0.29)</td>
<td>2.44 (0.54)</td>
<td>0.031</td>
<td>3.93 (0.95)</td>
</tr>
<tr>
<td>3</td>
<td>2.67 (0.56)</td>
<td>2.89 (0.42)</td>
<td>0.011</td>
<td>4.17 (0.95)</td>
</tr>
</tbody>
</table>

Values are means (SD). PAO\(\text{2}\), alveolar PO\(\text{2}\).
ing to the cost of measurements and exposure of subjects to the noxious gas CO. The costs can be greatly reduced by using a fast-response CO analyzer rather than using the mass spectrometer that requires the more expensive isotope of CO. The increased exposure of the subjects to CO could cause an increase in carboxyhemoglobin with repeat maneuvers. However, we did not see substantial increases in end-tidal C18O during the course of this study, in which we performed more maneuvers than a typical study would require. However, we did not measure blood carboxyhemoglobin levels.

The DLCO,OC method analyzes the kinetics of gas washin and thus is computationally more complex than either the single-breath or rebreathing methods, although the computational method is very similar to that used by the “three-equation” solution of the DLCO,SB (8, 9). The technique and algorithms applied in this study result in DLCO values that are similar to those obtained by the rebreathe method.

Differences between DLCO,OC and DLCO,RB: The DLCO,RB method is a well-accepted method that uses a 5- to 7-liter bag that is typically filled with 1–3 liters of test gas mixture. The subject is asked to breathe in and out of the bag for 10–12 breaths, and calculations usually involve the end-expiratory points fitted to a logarithmic decay. This technique requires the subject to nearly empty the rebreath bag without a complete inspiratory collapse of the bag. To prevent forceful collapse of the bag (which could alter breathing pattern or pressurize the gas sample line, influencing the measured gas concentration values), the rebreath bag is filled to a volume that is at least as big as the tidal breath, although some laboratories use volumes as large as the subject’s inspiratory capacity (31). A recent innovation for precisely matching bag volume to the subject is to use a double-switching valve, allowing the subject to freely draw from an inspired bag on the first breath and subsequently turning into the rebreath bag (31). Although, in theory, this method should allow more appropriate matching of bag volume, even this method could result in an uncomfortable mismatch between bag and tidal volume, if the first breath were not representative of the subject’s average breathing pattern. In addition, the rise in end-tidal and alveolar PCO2 (PACO2) during rebreathing stimulates subjects to increase tidal volume toward the end of the maneuver, often causing them to reach the bag volume limits. The DLCO,OC does not require precise matching of the subject’s lung volume and does not substantially alter PAO2 and PACO2, and breathing pattern does not need to change during the maneuver. In our experience, a regular breathing pattern during the maneuver produces more reliable data, however.

We anticipated that the DLCO,OC and DLCO,RB methods would yield generally similar results, particularly if breathing patterns were similar between the techniques and they were performed at similar EELVs and similar PAO2. As shown in Table 3, our subjects tended to breathe with larger tidal volumes and at higher EELVs during the DLCO,RB method, which would expose a slightly larger alveolar surface area with the DLCO,RB (12, 29, 30). The larger tidal volume was largely due to coaching of the subjects to collapse the rebreathe bag with each breath, an increasing tidal volume during the maneuver secondary to increasing PACO2, and due to our attempts to make the initial rebreathe bag volume slightly higher than the subjects’ actual tidal volume. The apparently lower EELV found using DLCO,OC may, in part, be an underestimate due to the effects of inhomogeneities on the calculation of lung volumes in early breaths of the open-circuit method (which uses simple single-compartment model gas dilution equations), similar to what was described in the studies of Horsfield and Cumming (6, 14). This difference in EELV had little impact on the final DLCO,OC; substituting higher EELV values into the analysis program during calculations yielded lower DLCO,OC by <0.2 ml·min⁻¹·mmHg⁻¹·L⁻¹ change in EELV.

When using the same test gas for both maneuvers, the average PAO2 is lower during the DLCO,RB maneuver due to continual oxygen uptake and depletion of O2 in the closed lung-bag system (Table 3). For this study, we corrected for this difference using standard correction methods (11), although it would be appropriate to use lower [O2] in the test gas mixture for the DLCO,OC test. It should be noted that the PAO2 is more consistent during the DLCO,OC maneuver, since inspired [O2] remains constant, compared with either the DLCO,SB or DLCO,RB, where inspired [O2] is continually falling, potentially making the DLCO,OC more appropriate for studying the effects of altered PAO2 on DLCO in future studies.

In conclusion, the present study showed that the DLCO,OC compared favorably with the DLCO,SB at rest and during exercise. We also found the DLCO,OC to be reproducible, linearly associated with Q with a Q vs. DLCO,OC slope that was similar to the Q vs. DLCO,SB slope, and it was better tolerated compared with DLCO,SB, DLCO,OC is, therefore, a suitable method for measuring DLCO. The technique used for assessing DLCO in clinical or research studies should reflect a balance of subject comfort, equipment availability, implementation expertise, cost, and possibly other considerations related to specific protocols.

APPENDIX: CALCULATION METHOD FOR DETERMINING DLCO,OC

The DLCO,OC technique requires a subject to breathe a mixture of gases containing trace amounts of C18O, acetylene (C2H2), ~10% helium and balance O2 and N2 (Fig. 3). During the maneuver, concentrations of C18O, C2H2, helium, and gas flow, all measured at the mouth, are obtained at a 120-Hz sampling rate using custom data-acquisition software running on a personal computer with a 16-bit resolution analog-to-digital board. The DLCO is obtained by iteratively adjusting the DLCO value to minimize the sum square error between measured end-tidal gas concentrations and end-tidal values obtained from a mathematical model of gas exchange for every breath recorded.

The lung is modeled as an alveolar compartment separated from the inspired gas by a non-gas-exchanging conductive dead space. Exchange of C18O occurs in the alveolar compartment following simple laws of diffusion (see below). The volume of the dead space (Vd) for each run is determined from mass balance of helium in the first few breaths of washin, as detailed in our laboratory’s previous study (19):

\[
V_d = \frac{F_{He,ex} - F_{He,es}}{F_{He,es} - F_{He,in}} \cdot V_T
\]

where \(F_{He,in}\), \(F_{He,es}\), and \(F_{He,ex}\) are mixed-expired, end-expired, and inspired helium concentrations, respectively; and \(V_T\) is the tidal volume. \(F_{He,in}\) is obtained from the ratio of volume of helium expired (obtained by simple integration of flow and helium signals) to \(V_T\) for each breath. Equation 1 is evaluated and averaged only over the first three breaths to avoid aberrant values when \(F_{He,in}\) approaches \(F_{He,es}\) near the end of washin. To simulate “plug” flow of gas through the dead space, the computer program divides the \(V_d\) into 1-ml units. At the
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beginning of a calculation for a washin run, gas values in all of the Vo units are set to end-expiratory values found for the breath immediately before the start of washin.

The solution for DLCO begins with setting DLCO to a nominal value, typically 20 ml·min⁻¹·mmHg⁻¹. Mixed-venous partial pressure of C¹⁸O (PV_c18o) (see Eq. 2 below) is obtained from the end-expiratory value for C¹⁸O in the breath immediately preceding the start of washin. The PV_c18o values could be a few percentages of the tank value, if adequate time for purging of gas from the previous maneuver has not elapsed. Gas exchange in the lung is then modeled for every 8.33-ms time point in the raw data stream as follows (19), starting with inspiration. First, the flow, volume increment, and gas concentrations for the time point are read from the data stream. The dead space elements are then advanced by the number of milliliters in the volume increment, filling the mouth-end elements with gas concentrations equal to the values in the data stream. For instance, if the volume increment is 3 ml, the gas values in the first three elements of dead space are set to gas concentrations from the data stream. At the alveolar end of the dead space, the last three dead space elements are read, and volumes of helium and C₂H₂ are added to the alveolar compartment using simple gas dilution equations, and the total volume of the alveolar compartment is increased by the volume increment.

To model uptake of C¹⁸O, a simple gas diffusion process is assumed:

\[ V_c18o = DL_{CO} \cdot (PA_{C18O} - PV_{C18O}) \]  

where \( PA_{C18O} \) is partial pressures of C¹⁸O in alveolar gas; \( DL_{CO} \) is the rate constant for diffusion for C¹⁸O in units of ml·min⁻¹·mmHg⁻¹, and \( V_c18o \) is the transfer rate of C¹⁸O across the alveolar membrane in ml/min.

The following equation dictates gas uptake in the alveolar region:

\[ \frac{d[V_A \cdot FAC18O(t)]}{dt} = -DL_{CO} \cdot [FA_{C18O}(t) - FV_{C18O}] + \left[ \frac{FDS'_{C18O}}{VA} \right] \]  

where \( V_A \) is the alveolar volume, \( FA_{C18O} \) is alveolar concentration of C¹⁸O, \( FV_{C18O} \) is mixed-venous concentration of C¹⁸O, \( FDS'_{C18O} \) is the concentration of C¹⁸O at the alveolar end of the dead space element during inspiration, and \( t \) is time. Because of the plug flow through the dead space element, \( FDS'_{C18O} \) equals expiratory values from the end of the previous breath early in inspiration and becomes equal to concentration of C¹⁸O of the inspired bag for inspired volumes greater than \( V_0 \). The term on the left is the change in volume of C¹⁸O in the alveolus per unit time, the first term on the right is the diffusion of gas into the alveolar blood, and the second term is the contribution of changing gas volume from the dead space, either during inspiration (top term) or during expiration (bottom term). The change in \( VA \) per time interval, \( dVA/dt \) has a positive value for inspiration and negative value for expiration. This equation can be solved for \( dFA_{C18O}/dt \):

\[ \frac{dFA_{C18O}}{dt} = -DL_{CO} \cdot (FA_{C18O} - FV_{C18O}) - \frac{dVA}{dt} \]  

Using this equation, the \( FA_{C18O} \) is updated for each time increment in the data stream. At end expiration, the value at the mouth end of the dead space is saved. At the end of each run through the complete data stream, the mean square error between model-estimated values and actual end-tidal values is calculated for C¹⁸O, excluding the values for the first two breaths. Because the first two breaths are likely affected by dead space more than subsequent breaths, we found the DLCOLOC value was more reasonable and reproducible, if we excluded those breaths from the mean square error (note the first two breaths were included in the gas uptake calculations, however). The Powell iterative search method is used to change the DLCO value to minimize the mean square error term (22). Briefly, this method uses results from pairs of iterations to find the rate of change in mean square error per unit change in DLCO and uses this slope to find the point at which mean square error is at a minimum.

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