Evaluation of estimates of alveolar gas exchange by using a tidally ventilated nonhomogenous lung model

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Busso, Thierry, and Peter A. Robbins. Evaluation of estimates of alveolar gas exchange by using a tidally ventilated nonhomogenous lung model. J. Appl. Physiol. 82(6): 1963–1971, 1997.—The purpose of this study was to evaluate algorithms for estimating \( \text{O}_2 \) and \( \text{CO}_2 \) transfer at the pulmonary capillaries by use of a nine-compartment tidally ventilated lung model that incorporated inhomogeneities in ventilation-to-volume and ventilation-to-perfusion ratios. Breath-to-breath \( \text{O}_2 \) and \( \text{CO}_2 \) exchange at the capillary level and at the mouth were simulated by using realistic cyclical breathing patterns to drive the model, derived from 40-min recordings in six resting subjects. The SD of the breath-by-breath gas exchange at the mouth around the value at the pulmonary capillaries was 59.7 ± 25.5% for \( \text{O}_2 \) and 22.3 ± 10.4% for \( \text{CO}_2 \). Algorithms including corrections for changes in alveolar volume and for changes in alveolar gas composition improved the estimates of pulmonary exchange, reducing the SD to 20.8 ± 10.4% for \( \text{O}_2 \) and 15.2 ± 5.8% for \( \text{CO}_2 \). The remaining imprecision of the estimates arose almost entirely from using end-tidal measurements to estimate the breath-to-breath changes in end-expiratory alveolar gas concentration. The results led us to suggest an alternative method that does not use changes in end-tidal partial pressures as explicit estimates of the changes in alveolar gas concentration. The proposed method yielded significant improvements in estimation for the model data of this study.

VARIous METHODS have been proposed to estimate breath-to-breath gas transfer at the pulmonary capillaries from measurements made at the mouth combined with compensation for changes in pulmonary gas stores (2, 3, 7, 11, 13). Estimation of the change in pulmonary gas stores includes allowing for both changes in alveolar gas concentrations and for changes in alveolar volume. A single-compartment model of the lung represented by a nominal volume at the end of each expiration is used in this process. Whereas end-tidal measurements are used to estimate the composition of alveolar gas, the methods proposed to estimate alveolar gas exchange (2, 3, 7, 11, 13) differ in the assessment of the end-expiratory nominal lung volume used in the computations.

Because no direct measurement of gas transfer at the pulmonary capillaries is available, the different estimates cannot be compared with a standard reference. The various proposed methods yield estimates of alveolar gas exchange with differences in breath-to-breath variability (5). The technique proposed by Swanson (11) yields a relatively smooth estimate of breath-to-breath alveolar gas exchange (5, 10). Nevertheless, it is difficult to assess whether the interbreath variability in alveolar gas exchange arises from artifacts in the computation methods or is a physiological phenomenon (5).

The purpose of this study was to evaluate the methods for estimating alveolar gas exchange proposed by Auchincloss et al. (2), Wessel et al. (13), and Swanson (11) by using a mathematical model of a tidally ventilated and steadily perfused lung that includes within its structure unevenness in ventilation-to-volume and ventilation-to-perfusion ratios. Alveolar gas transfer has been simulated with the model by using realistic breathing patterns derived from experimental data. The simulated gas exchange at the pulmonary capillaries has been compared with the estimates obtained with the use of alternative algorithms applied to the simulated gas exchange and end-tidal values at the mouth. The following questions have been addressed: 1) How much variability is there in gas exchange at the level of the pulmonary capillaries that is induced by the normal variability in breathing pattern? 2) How do the three different algorithms compare in estimating the gas exchange at the level of pulmonary capillaries? 3) How much error occurs through using the estimates of lung volume or change in lung volume obtained via the algorithm compared with using true (model) values for lung volume? 4) How much error occurs through using the end-tidal values as estimates of alveolar gas composition compared with using true (model) values for alveolar gas composition? The findings led us to develop a new method for estimating breath-to-breath alveolar gas transfer not using explicit estimation of the change in alveolar composition between two subsequent breaths. Finally, the variability in the estimates of alveolar gas exchange from the different algorithms has been compared by using the real experimental data associated with the breathing patterns that were used to drive the model.

METHODS

Glossary

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( F_{\text{Igas}} )</td>
<td>Alveolar end-expiratory gas fraction</td>
</tr>
<tr>
<td>( F_{\text{Agas}} )</td>
<td>Alveolar end-expiratory gas fraction from previous breath</td>
</tr>
<tr>
<td>( F_{\text{ETgas}} )</td>
<td>Mixed-expired gas fraction</td>
</tr>
<tr>
<td>( F_{\text{ETgas}} )</td>
<td>End-tidal gas fraction</td>
</tr>
<tr>
<td>( F_{\text{ETgas}} )</td>
<td>End-tidal gas fraction from previous breath</td>
</tr>
<tr>
<td>( F_{\text{IGas}} )</td>
<td>Mixed-inspired gas fraction</td>
</tr>
<tr>
<td>( V_I )</td>
<td>Inspired volume</td>
</tr>
<tr>
<td>( V_E )</td>
<td>Expired volume</td>
</tr>
<tr>
<td>( V_L )</td>
<td>End-expiratory nominal lung volume</td>
</tr>
</tbody>
</table>

1 Here and elsewhere, the term "true" is used in the statistical sense to distinguish correct values from their estimates obtained via the various algorithms.
values for the sum of all nine compartments were set to 2,500 for each unit were taken from the data of West (14). The end-expiratory alveolar volume, ventilation, and perfusion perfused by a set of capillaries. The relative values for each compartment was modeled as a single alveolar space ventilated through a constant-volume dead space and steadily perfused by a set of capillaries. The relative values for end-expiratory alveolar volume, ventilation, and perfusion for each unit were taken from the data of West (14). The values for the sum of all nine compartments were set to 2,500 ml for functional residual capacity (FRC), 5.1 l/min BTPS for alveolar ventilation, and 6 l/min for pulmonary blood flow. Each alveolar unit was connected to a portion of the anatomical dead space. The total anatomical dead space was given a value of 150 ml, and the fraction associated with each lung unit was set to be the same as the fractional ventilation. All nine portions of anatomical dead space were joined onto a single apparatus dead space set to 100 ml.

The variables of the model were first initialized by using the mass balance equations for a steadily ventilated homogeneous (i.e., ideal) lung. Initial gas pressures within the alveoli were set to the same in all compartments and were estimated from the alveolar gas equations by using a constant alveolar ventilation of 5.1 l/min BTPS, O₂ uptake (V₀₂) set to 300 ml/min STPD and CO₂ uptake (V₀₂) to 240 ml/min STPD. End-capillary PO₂ (P₀₂) and PCO₂ (P₀₂), respectively, were taken to be 4 Torr lower and 1 Torr higher than the alveolar values, respectively, based on the data of West (14). End-capillary contents of O₂ and CO₂ were calculated from P₀₂ and P₀₂. The O₂ dissociation curve was taken from Lødbell (9), and the CO₂ content was calculated from the equation of Douglas et al. (6). Mixed venous contents of O₂ and CO₂ were then calculated to give the predetermined V₀₂ (300 ml/min) and V₀₂ (240 ml/min) by using the Fick principle. This gave values for the mixed venous contents of 14.6 and 52.6 ml/100 ml, for O₂ and CO₂, respectively. These mixed venous compositions were used throughout the model simulations for all the nine lung compartments.

Once the venous contents for O₂ and CO₂ have been set, the model can be set in motion by using some cyclical breathing pattern. The ventilation of each lung unit is calculated every 20 ms from the breathing pattern and the relevant fraction of total ventilation ascribed to each lung unit. The model equations were applied for all of the nine lung units through the respiratory cycle, with an incremental time of 20 ms. The capillary gas exchange for each unit for the 20-ms period is calculated (assuming no diffusion limitation) from the alveolar PO₂ and PCO₂ (P₀₂ and P₀₂, respectively), the mixed venous PO₂ and PCO₂, and the fractional blood flow ascribed to the unit. From the ventilation and gas exchange over the 20-ms period, the PO₂ and PCO₂ for the alveolar space and dead space of each unit may be updated. This cycle is repeated every 20 ms. No gradient for diffusive and convective mixing was assumed in the computations.

The second stage of the initialization process is to determine appropriate values for PO₂ and PCO₂ in each of the nine compartments of the model. This was achieved by using a typical breathing pattern, as illustrated in Fig. 1. The ventilatory profile used for this initialization procedure was adapted for each experimental data set to match the inspiratory and expiratory durations to the mean values for the data set. The alveolar ventilation was maintained at 5.1 l/min. In each lung unit, there will be small changes in volume in the model occurring over each respiratory cycle because CO₂ output from the pulmonary capillaries will not in general equal O₂ uptake by the capillaries. To prevent this from causing progressive decreases or increases in alveolar volume over time, an adjustment was made to expiratory flow for each lung unit in the current breath based on the difference between O₂ and CO₂ capillary gas exchange that had occurred in the preceding breath. The respiratory cycle was repeated for successive breaths, until PAO₂ and PACO₂ at end expiration did not differ between two subsequent breaths by >0.01 Torr in any lung compartment (this took between 40 and 57 breaths). Figure 2 gives an example of intrabreath variation in PAO₂ and PACO₂ and gas fluxes for a tidal volume (V₁) of 590 ml, an inspiratory time of 1,500 ms, and an expiratory time of 2,500 ms.

Once the model had been fully initialized, it could be used to simulate breath-to-breath gas exchange in real breathing sequences. Data were collected over 40 min from six seated subjects during air breathing at rest. The volumes and flows were measured by a turbine volume-measuring device and pneumotachograph connected in series (8). PO₂ and PCO₂ at the mouth were measured continuously by using a mass spectrometer. Table 1 gives the characteristics of the respiratory data collected. The flow data from the pneumotachograph were calibrated every half cycle by using the values for inspired and expired tidal volume recorded by the turbine volume-measuring device. The flows were then corrected to BTPS and integrated to yield a continuous record of volume. The volume sequence was then smoothed to remove any long-term trends in FRC and scaled so that the mean alveolar ventilation was equal to the value designated in the model.

The respiratory volume sequences were then used to drive the model to simulate breath-to-breath variations in pulmonary gas stores and pulmonary gas exchange. The breath-to-

![Fig. 1. Profile of total respiratory flow (in l/s) used to initialize model simulations for a tidal volume of 590 ml, inspiratory time of 1,500 ms, and expiratory time of 2,500 ms.](http://jap.physiology.org/ Downloaded from)
breath values for alveolar gas exchange were summed across all lung compartments through the respiratory cycle to provide true (model) values for breath-to-breath gas exchange at the pulmonary capillaries. The profiles of the gas tensions at the frontier between anatomic and apparatus dead spaces were used to compute the breath-to-breath gas exchange at the mouth and the end-tidal composition. These variables were used to calculate the estimates of breath-to-breath alveolar gas exchange by using the algorithms described below.

Algorithms for computing breath-to-breath gas exchange at pulmonary capillaries. Auchincloss et al. (2) proposed the basic algorithm for estimating breath-to-breath gas exchange at the pulmonary capillaries with the use of a correction for changes in pulmonary gas stores ($\Delta S_{\text{gas}}$).

$$V_{A_{\text{gas}}} = F_{I_{\text{gas}}} V_l - F_{E_{\text{gas}}} V_e - \Delta S_{\text{gas}} = V_{M_{\text{gas}}} - \Delta S_{\text{gas}} \quad (1)$$

Note that for CO₂ elimination, the signs in Eq. 1 should be inverted. The $\Delta S_{\text{gas}}$ is computed as follows

$$\Delta S_{\text{gas}} = F_{A_{\text{gas}}} V_l - F_{A_{\text{gas}}} V_l' = F_{A_{\text{gas}}} \Delta V_l + \Delta F_{A_{\text{gas}}} V_l' \quad (2)$$

$\Delta V_l$ is estimated by assuming that the net transfer of N₂ at the alveolar level is equal to zero

$$\Delta V_l = (V_{M_{N2}} - \Delta F_{A_{N2}} V_l')/F_{A_{N2}} \quad (3)$$

Auchincloss et al. (2) and other groups (3, 7) assumed that the $V_l'$ term could be treated as a constant and equal to the measurement at the mouth minus the change in pulmonary gas stores ($\Delta S_{\text{gas}}$).

**Table 1.** Means and coefficients of variation of respiratory variables

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>No. of Breaths</th>
<th>$V_{T1}$, liters</th>
<th>$V_{TE}$, liters</th>
<th>$T_i$, s</th>
<th>$T_e$, s</th>
<th>$V_e$, l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>952</td>
<td>630</td>
<td>0.62</td>
<td>0.60</td>
<td>1.46</td>
<td>2.32</td>
<td>9.7</td>
</tr>
<tr>
<td>971</td>
<td>367</td>
<td>0.69</td>
<td>0.68</td>
<td>1.57</td>
<td>1.78</td>
<td>9.5</td>
</tr>
<tr>
<td>973</td>
<td>664</td>
<td>0.63</td>
<td>0.68</td>
<td>1.46</td>
<td>2.32</td>
<td>9.7</td>
</tr>
<tr>
<td>997</td>
<td>504</td>
<td>0.51</td>
<td>0.52</td>
<td>1.93</td>
<td>2.80</td>
<td>12.6</td>
</tr>
<tr>
<td>998</td>
<td>534</td>
<td>0.69</td>
<td>0.71</td>
<td>1.98</td>
<td>2.76</td>
<td>9.0</td>
</tr>
<tr>
<td>999</td>
<td>418</td>
<td>0.79</td>
<td>0.79</td>
<td>2.18</td>
<td>3.60</td>
<td>8.4</td>
</tr>
</tbody>
</table>

$V_{T1}$, inspiratory tidal volume; $V_{TE}$, expiratory tidal volume; $T_i$, inspiration time; $T_e$, expiration time; $V_e$, expired ventilation; CV, coefficient of variation.
subject's FRC measured at rest with other techniques. If $F_{AGas}$ and $\Delta F_{AGas}$ are approximated by $F_{ETgas}$ and $\Delta F_{ETgas}$ and $V_{L}'$ is set to equal FRC, Eqs. 1, 2, and 3 describe the method proposed by Auchincloss et al. (2).

Wessel et al. (13) proposed to omit in Eq. 1 the term containing $V_{L}'$ (thus assumed to be 0) because the differences in alveolar fractions between two successive breaths could be considered small. With $\Delta F_{AGas}$ or $V_{L}'$ set equal to 0, Eqs. 1, 2, and 3 yield

$$V_{0gas} = V_{Mgas} - F_{AGas} V_{N2}/F_{N2}$$

which, when the alveolar fractions are approximated by using end-tidal fractions, is the estimate of alveolar gas exchange proposed by Wessel et al. (13).

Swanson (11) adopted a different approach to assign a value to $V_{L}'$. Instead of setting $V_{L}'$ either to 0 or to FRC, he computed an effective lung volume (ELV) that was taking part in gas exchange by determining the value of $V_{L}'$ that minimized breath-to-breath variations in gas exchange at the pulmonary capillaries.

All three algorithms were applied to the model data for end-tidal values together with values for gas exchange at the mouth. The gas exchange at the pulmonary capillary calculated by using each algorithm could then be compared with the actual gas exchange at the pulmonary capillaries. Additionally, to evaluate the error caused by the various assumptions relating to $V_{L}$, in these three algorithms, alveolar gas exchange was estimated by using Eqs. 1, 2, and 3 with the true breath-to-breath alveolar volumes of the model. Moreover, to evaluate the error caused by using end-tidal values as estimates of alveolar fractions in the algorithms, the computations were repeated by using the true $F_{AGas}$, averaged according to the volume of gas within each compartment of the lung.

Finally, the algorithms were applied to the real (nonmodel) breath-to-breath gas exchange and end-tidal values associated with the respiratory data used for driving the ventilation of the model lung. This enables a comparison between the variations in gas exchange calculated by using real data with those computed from the model for the three algorithms by using a similar breathing pattern. FRC for the original data set was estimated from anthropometric data (4).

RESULTS AND DISCUSSION

Precision of the estimates at the pulmonary capillaries. Figure 3 illustrates successive values for gas exchange over 50 breaths for one of the model simulations. First, it can be seen that, under conditions of breathing air at rest, there is little variation in true $O_2$ exchange at the pulmonary capillaries. In contrast, variations in breathing pattern induce considerable variability into true $CO_2$ exchange at the pulmonary capillaries. It can also be seen that all three algorithms reduce considerably the breath-by-breath variations in gas exchange when compared with gas exchange values at the mouth. There is the suggestion that the algorithms may differ in the accuracy with which they estimate the exchange at the pulmonary capillaries, and this is explored further in Table 2.

Table 2 shows the standard deviation (SD) for the breath-by-breath estimates of gas exchange around their true values, expressed as a percentage of the mean level of gas exchange. Results are shown for each breathing pattern and for each algorithm. The algorithm of Swanson (11) gave better estimates at the pulmonary capillaries when compared with the other two algorithms. Generally, assuming $V_{L}' = 0$ [algorithm of Wessel et al. (13)] gave better results than assuming $V_{L}' = FRC$ [algorithm of Auchincloss et al. (2)], although this was not always the case. The ELV values were $1,310 \pm 550$ ml BTPS for $O_2$ and $1,180 \pm 820$ ml BTPS for $CO_2$ (mean $\pm$ SD for the 6 data sets). Higher values for $V_{L}'$ like FRC induced a degradation in the estimates of alveolar gas exchange.
The effect of replacing the constant values for VL (i.e., 0, FRC, or ELV) with the real time varying values is also shown in Table 2. This generally degraded the estimates of the gas transfer at the capillary level, in particular when compared with the estimates from Swanson’s algorithm (11). This finding clearly suggests that improving the volume estimates in these algorithms is unlikely to improve the breath-to-breath estimate of pulmonary gas exchange. The effect of replacing the estimates of FAgas and \( \Delta F_{Agas} \) (i.e., the end-tidal values) with the true alveolar composition is shown in Table 2. This yielded a much more precise estimation of the gas transfer at the capillary level, even though a single constant value (FRC) was used for VL’. Finally, the effect of replacing only the estimates of \( \Delta F_{Agas} \) with the true changes in alveolar composition and using \( F_{ET_{gas}} \) to estimate \( F_{Agas} \) is also shown in Table 2. This did not degrade the estimation of gas transfer at the capillary level when compared with the estimates using the true values for both \( F_{Agas} \) and \( \Delta F_{Agas} \). A comparison of the effects of using end-tidal vs. true alveolar values in the algorithms is shown for O2 in Fig. 4 and for CO2 in Fig. 5. In these figures, the precision of the estimates for \( V_{O2} \) and \( V_{CO2} \) at the pulmonary capillaries is plotted as a function of VL’. The errors associated with the use of end-tidal fractions were close to those for alveolar fractions at low values of VL’. They diverged as the value of VL’ increased. The precision of

Table 2. Standard deviations for breath-to-breath differences between estimates of gas exchange and true (model) values, expressed as % of mean level of gas exchange

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Mouth</th>
<th>( V_{L}^{'0} )</th>
<th>( V_{L}^{\text{FRC}} )</th>
<th>( V_{L}^{\text{ELV}} )</th>
<th>( V_{L}^{\text{Va}} )</th>
<th>( V_{L}^{\text{FRC}} )</th>
<th>( V_{L}^{\text{ELV}} )</th>
<th>( V_{L}^{\text{FRC}} )</th>
<th>( \Delta F )</th>
<th>( \Delta F )</th>
<th>( \Delta F )</th>
<th>( \Delta F )</th>
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<tbody>
<tr>
<td>952</td>
<td>45.7</td>
<td>19.9</td>
<td>16.1</td>
<td>13.1</td>
<td>14.2</td>
<td>2.9</td>
<td>3.0</td>
<td>8.6</td>
<td>11.5</td>
<td>14.2</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>971</td>
<td>104.9</td>
<td>35.8</td>
<td>53.5</td>
<td>32.1</td>
<td>55.3</td>
<td>5.9</td>
<td>8.0</td>
<td>18.8</td>
<td>21.7</td>
<td>25.5</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>973</td>
<td>60.7</td>
<td>35.0</td>
<td>41.9</td>
<td>30.1</td>
<td>42.0</td>
<td>4.0</td>
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<td>19.9</td>
<td>22.7</td>
<td>26.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>997</td>
<td>36.4</td>
<td>17.2</td>
<td>12.1</td>
<td>11.4</td>
<td>13.3</td>
<td>1.7</td>
<td>1.6</td>
<td>9.9</td>
<td>12.7</td>
<td>16.5</td>
<td>1.5</td>
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<td>998</td>
<td>70.2</td>
<td>27.8</td>
<td>34.3</td>
<td>22.9</td>
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<td>4.7</td>
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<td>21.5</td>
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<td>999</td>
<td>40.5</td>
<td>18.7</td>
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<td>9.9</td>
<td>12.7</td>
<td>16.5</td>
<td>1.5</td>
<td>1.5</td>
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</table>

Mean ± SD 59.7 ± 25.5 25.7 ± 8.3 29.2 ± 16.7 20.8 ± 8.9 28.2 ± 17.6 3.7 ± 1.5 4.1 ± 2.2 13.6 ± 4.9

\( V_{O2} \), O2 consumption; \( V_{CO2} \), CO2 output; \( V_{L}^{'0} \), end-expiratory nominal lung volume from previous breath; \( V_{A} \), alveolar volume from previous breath; \( F_{RC} \), functional residual capacity; \( ELV \), effective lung capacity; \( F_{ET} \), end-tidal gas fraction; \( F_{A} \), alveolar end-expiratory gas fraction.

![Fig. 4](https://example.com/fig4.png)  
Fig. 4. SD of breath-by-breath differences between estimated and true (model) \( V_{O2} \) at capillary level, using end-tidal \( (F_{ET_{O2}}) \) and true (model) alveolar fractions \( (F_{A_{O2}}) \) for subject 952.

![Fig. 5](https://example.com/fig5.png)  
Fig. 5. SD of the breath-by-breath differences between estimated and true (model) \( V_{CO2} \) at capillary level, using \( F_{ET_{CO2}} \) and true (model) \( F_{A_{CO2}} \) for subject 952.
the estimates using the true alveolar composition reached a minimum for a $V_l$ close to FRC.

The results above show clearly that the limitations of the algorithms in compensating for $D_{FS}$ arise more from the inadequacy of using breath-to-breath differences in the end-tidal measurements as an assessment of breath-to-breath differences in alveolar composition than from the assessment of $V_l$. Furthermore, the results show that the changes in end-tidal composition generally overestimate the real changes in alveolar composition. This can be seen from 1) the fact that when end-tidal values are used the effective $V_l$ appears systematically less than FRC; 2) the SD for the breath-to-breath differences in end-tidal values are 2.10 ± 1.16 Torr (mean ± SD for the 6 data sets) for $O_2$ and 1.33 ± 0.65 Torr for $CO_2$ compared with the SD for the breath-to-breath differences in true mean alveolar values (1.87 ± 0.75 Torr for $O_2$ and 1.04 ± 0.31 Torr for $CO_2$); and 3) the tendency for variations in alveolar composition to be greatest where the ventilation-to-volume ratio is greatest, and these will have a greater influence on end-tidal values that are flow-weighted means than on alveolar values that are volume-weighted means.

Development of an alternative algorithm. The above results lead us to suggest an alternative algorithm that does not use the end-tidal values to calculate the change in alveolar composition directly. We use FRC as $V_l'$, $F_{\text{ET}}$ as $F_{A_{\text{gas}}}$, and assume that the true $D_{A_{\text{gas}}}$ lies between 0 and $D_{F_{\text{ET}}}$ from this, it follows that true $F_{\text{gas}}$ lies between $F_{\text{gas}}$ [algorithm of Wessel et al. (13)] and $F_{\text{FC}}$ [algorithm of Auchincloss et al. (2)]. $V_{AO_2}$ and $V_{ACO_2}$ are then estimated by minimizing their respective breath-to-breath variation, subject to the constraints that for each breath:

$$\text{Min} \left( V_{AO_2}^i, V_{FCO_2}^i \right) \leq V_{A_{O_2}}^i \leq \text{Max} \left( V_{AO_2}^i, V_{FCO_2}^i \right) \quad (5)$$

$$\text{Min} \left( V_{ACO_2}^i, V_{FCO_2}^i \right) \leq V_{A_{CO_2}}^i \leq \text{Max} \left( V_{ACO_2}^i, V_{FCO_2}^i \right) \quad (6)$$

where Min is a function that returns the minimum value in the list and Max is a function that returns the maximum value in the list.

The minimization functions may be written as

$$J_{O_2} = \sum_{i=0}^{n} (V_{A_{O_2}}^i - V_{A_{O_2}}^{i-1})^2$$

$$J_{CO_2} = \sum_{i=0}^{n} (V_{A_{CO_2}}^i - V_{A_{CO_2}}^{i-1})^2$$

and solved as an iterative process. The iterative solution was undertaken as follows. First, the starting values for the $V_{AO_2}$ and $V_{ACO_2}$ of each breath were set midway between the estimates from the Wessel and Auchincloss algorithms (Refs. 13 and 2, respectively)

$$V_{I_{gas}}^i = \frac{V_{I_{gas}}^0 + V_{I_{gas}}^{FRC}}{2}$$

where the superscript 0 indicates that they are the starting values for the procedure. The iterative solution was undertaken as follows. First, the starting values for the $V_{AO_2}$ and $V_{ACO_2}$ were calculated sequentially.
tially, starting at \( i = 1 \), so as to minimize the breath-by-breath variation in the gas-exchange estimates, subject to the bounds of Eqs. 5 and 6. The procedure is as follows. First, for \( i = 1 \)

\[
\dot{V}_{g}^{1:j} = \frac{\text{Min}(\dot{V}_{g}^{j}, \dot{V}_{FRC}^{j})}{\text{Max}(\dot{V}_{g}^{j}, \dot{V}_{FRC}^{j})}
\]

Then, for \( i = 2 \) through \( n - 1 \) (in increasing value for \( i \), so that \( \dot{V}_{g}^{i-1:j} \) is available before \( \dot{V}_{g}^{i:j} \) is calculated)

\[
y = \frac{\dot{V}_{g}^{i-1:j} + \dot{V}_{g}^{i+1:j-1}}{2}
\]

Finally, for \( i = n \)

\[
\dot{V}_{g}^{n:j} = \frac{\text{Min}(\dot{V}_{g}^{n:j-1}, \dot{V}_{FRC}^{n:j})}{\text{Max}(\dot{V}_{g}^{n:j-1}, \dot{V}_{FRC}^{n:j})}
\]

This procedure was repeated (next increment in \( j \)) until the mean change in gas exchange from one iteration (\( j \)) to the next (\( j + 1 \)) was \( < 0.1 \) ml/min

\[
\frac{1}{n} \sum_{i=1}^{n} (|\dot{V}_{g}^{i:j} - \dot{V}_{g}^{i:j+1}|) < 0.1 \text{ ml/min}
\]

This was achieved for our data sets at between 6 and 13 iterations. An example of the solution with the bounds provided by the Wessel and Auchincloss algorithms (Refs. 13 and 2) is shown in Fig. 6.

To check that the starting point for the iterations has no effect on the final solution, the iterative process was also begun with different starting points. Both \( \dot{V}_{FRC}^{1} = \dot{V}_{FRC}^{0} \) and \( \dot{V}_{g}^{1} = \dot{V}_{g}^{0} \) were tried, and in all data analyzed, the final solutions were the same.

A sample of the results obtained with this algorithm is shown in Fig. 3, and this suggests some reduction in the error around the simulated gas exchange at the pulmonary capillaries compared with the other algorithms. The reduction in the error is confirmed by the results in Table 2, which show in every case, for both \( CO_{2} \) and \( O_{2} \), an improvement in the estimate over the estimates obtained via the other algorithms.

The assumed values of \( \Delta F_{A} \) and \( \Delta F_{ACO_{2}} \) are not explicitly calculated in the above algorithm. However, some idea of their likely values can be obtained from the ratio

\[
R_{gas} = \frac{\dot{V}_{g}^{1:j} - \dot{V}_{g}^{i:j}}{\dot{V}_{FRC}^{1:j} - \dot{V}_{g}^{i:j}}
\]

Because of the constraints imposed on \( \dot{V}_{A} \) and \( \dot{V}_{ACO_{2}} \), the ratios for \( O_{2} (R_{O_{2}}) \) and for \( CO_{2} (R_{CO_{2}}) \) lie between 0 and 1. A value close to 0 for \( R_{gas} \) implies \( \dot{V}_{g} \) corresponds closely to the estimate from Wessel’s algorithm where \( \Delta F_{gas} = 0 \), and a value close to 1 corresponds closely to the estimate from Auchincloss’s algorithm where \( \Delta F_{gas} = \Delta F_{ET}^{CO_{2}} \). The mean breath-to-breath value of \( R_{O_{2}} \) was 0.55 ± 0.44 (mean ± SD averaged across the subjects), which was similar to \( R_{CO_{2}} \) at 0.57 ± 0.46 (mean ± SD averaged across the subjects).

By assuming \( R_{CO_{2}} \) is equal to \( R_{O_{2}} \), it is possible to calculate the breath-to-breath \( \dot{V}_{ACO_{2}} \) from the minimization of breath-to-breath \( \dot{V}_{A} \) or vice versa. If breath-to-breath \( \dot{V}_{ACO_{2}} \) is calculated from the minimization of \( J_{CO_{2}} \), then the overall SD of estimate around the true value is 10.1 ± 3.1% of the mean \( V_{CO_{2}} \), very close to the value of 10.3 ± 3.7% for the minimization of \( J_{O_{2}} \). For the estimates of breath-to-breath \( \dot{V}_{A} \), based on the minimization of \( J_{O_{2}} \), the overall SD of the estimate around the true value is 15.9 ± 6.2%, slightly higher than the value of 13.6 ± 4.9% based on the minimization of \( J_{CO_{2}} \), but still substantially below the values obtained with the other algorithms. These findings suggest that the relationships between the breath-to-breath changes in mean alveolar compositions and end-tidal compositions are affected by the breathing pattern in a broadly similar way for \( O_{2} \) as for \( CO_{2} \).

Variability in gas exchange in both simulated data and real data. As a final study, the various algorithms were applied to the original experimental data (gas exchange at the mouth and end-tidal values) from which the breathing patterns driving the model were obtained. The segment which matches that in Fig. 3 is shown for the real data in Fig. 7. Similar trends can be observed for the variability in breath-to-breath gas exchange in the real data and in the model data. Furthermore, the differences in breath-to-breath variability for the different algorithms observed in the model data appear to be reflected in the results for the real data. A more detailed examination of this can be made from Table 3, which gives the coefficient of variation for each algorithm for both the model data and the real data. For each algorithm, the variations are similar for the model and the real data, except in the case of the algorithm of Auchincloss et al. (2), where using FRC as an estimate of \( V_{L} \) caused the estimates substantially to be more variable for the real data compared with the model data. The method developed in the present study for estimating gas exchange at the pulmonary capillaries yielded less variability in alveo-
lar gas exchange compared with the other algorithms when applied to the real (nonmodel) data. The model of the lung used in this study included 1) inhomogeneities in the ventilation-to-volume ratio, 2) inhomogeneities in ventilation-to-perfusion ratio, and 3) unevenness in the cyclical nature of the ventilation. In the present study, the variability in the true O₂ transfer at the alveolar level was six- to tenfold lower than for CO₂. The physiological reason for this is the difference in shape of the blood O₂ and CO₂ dissociation curves. The model used did not consider certain other possible sources of inhomogeneity. These include incomplete gas mixing in alveoli and airways, cyclical variations in the perfusion of the lung of both cardiac and respiratory origin, and intra- and interbreath variations in ventilation-perfusion distribution. Interbreath variations could also arise from fluctuations in the pulmonary blood flow and the mixed venous composition. Despite the much greater complexity of the real lung when compared with the model, it is noteworthy that the variability in V˙O₂ and V˙CO₂, both measured at the mouth and estimated at the alveolar level for the simulated data, were comparable with the variability for the original experimental data (Table 3). The degree of variability is also similar to earlier observations made at rest (5, 7). Moreover, the patterns of V˙O₂ and V˙CO₂ showed some remarkable similarities between model and experimental data (Figs. 3 and 7). These findings indicate that variations in the cyclical nature of the ventilation and the ventilation-volume-perfusion inequalities underlie a major part of the variability in gas exchange.

For the algorithm of Swanson, the ELV values for the experimental data were 125 ± 98 ml BTPS for alveolar exchange of O₂ and 42 ± 94 ml BTPS for CO₂, which were lower than the values obtained with the simulated data from the model (Table 4). For the algorithm developed in the present study (Eq. 7), the mean value for R₀₂ was 0.38 ± 0.43 (mean ± SD averaged across the subjects), and the mean value for R₂CO₂ was 0.47 ± 0.46 (mean ± SD averaged across the subjects). The ratios for both O₂ and CO₂ were systematically lower for the experimental data than for the simulated data. These findings suggest that the overestimation of the breath-to-breath changes in mean alveolar fractions by using end-tidal measurement is greater for the actual data than for the simulated data from the lung model. This could arise from the dependence of the end-tidal values in life on other factors that were not included in the model and also from the possibility that the data used to generate the model did not account for the full degree of inhomogeneity within the lung. Additionally, R₂CO₂ was systematically greater than R₀₂ for the experimental data. This difference did not appear with the data simulated by using the model. The explanation for this is not entirely clear.

### Table 3. Coefficients of variation for gas exchange at mouth and of estimates at capillary level for both model and actual data

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Capillary</th>
<th>Mouth</th>
<th>ELV</th>
<th>FRC</th>
<th>ELV with Vl&lt;sup&gt;−&lt;/sup&gt;</th>
<th>Capillary</th>
<th>Mouth</th>
<th>ELV</th>
<th>FRC</th>
<th>ELV with Vl&lt;sup&gt;−&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>952</td>
<td>1.5</td>
<td>45.4</td>
<td>20.2</td>
<td>16.1</td>
<td>13.3</td>
<td>50.5</td>
<td>19.6</td>
<td>19.2</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>971</td>
<td>4.8</td>
<td>102.1</td>
<td>35.5</td>
<td>53.3</td>
<td>31.6</td>
<td>129.9</td>
<td>40.4</td>
<td>66.5</td>
<td>40.2</td>
<td></td>
</tr>
<tr>
<td>973</td>
<td>3.6</td>
<td>61.2</td>
<td>36.0</td>
<td>42.7</td>
<td>32.5</td>
<td>64.7</td>
<td>27.6</td>
<td>126.1</td>
<td>27.6</td>
<td></td>
</tr>
<tr>
<td>997</td>
<td>1.3</td>
<td>35.7</td>
<td>17.2</td>
<td>12.1</td>
<td>12.0</td>
<td>34.8</td>
<td>19.0</td>
<td>39.7</td>
<td>18.9</td>
<td></td>
</tr>
<tr>
<td>998</td>
<td>3.2</td>
<td>71.0</td>
<td>28.9</td>
<td>35.1</td>
<td>23.9</td>
<td>64.9</td>
<td>28.4</td>
<td>82.4</td>
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<tr>
<td>999</td>
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<td>40.1</td>
<td>19.0</td>
<td>17.2</td>
<td>15.1</td>
<td>38.3</td>
<td>19.6</td>
<td>114.5</td>
<td>19.6</td>
<td></td>
</tr>
</tbody>
</table>

**Mean ± SD** 2.7 ± 1.4 59.3 ± 24.9 26.1 ± 8.5 26.1 ± 8.5 14.2 ± 5.2 63.9 ± 34.8 25.8 ± 8.3 28.2 ± 32.7 25.6 ± 8.3 19.4 ± 7.4

### Table 4. ELV and FRC values for data simulated by using model and for actual experimental data

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>ELV for V₀₂, ml</th>
<th>FRC, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>952</td>
<td>1,478</td>
<td>68</td>
</tr>
<tr>
<td>971</td>
<td>1,570</td>
<td>206</td>
</tr>
<tr>
<td>973</td>
<td>1,399</td>
<td>102</td>
</tr>
<tr>
<td>997</td>
<td>1,343</td>
<td>-63</td>
</tr>
</tbody>
</table>

*Predicted for individual subjects by using anthropometric data (Ref. 4).
In conclusion, it appears from the above results that many of the features of breath-by-breath gas exchange can be simulated by using an irregularly ventilated inhomogenous model of the lung. The new method proposed in the present study for the estimation of the breath-to-breath gas exchange at the pulmonary capillaries appears promising, although the usefulness of the algorithm would clearly have to be evaluated further under conditions of hypoxia and during transients in pulmonary blood flow and/or in inspiratory gas composition.

The authors thank Dr. J. Sato for helpful collaboration. The Laboratoire de Physiologie and Groupement d’Intérêt Public Exercice, Saint-Etienne (France) provided financial support for T. Busso. Present address of T. Busso: Laboratoire de Physiologie, CHU de Saint-Etienne, Hôpital de Saint-Jean-Bonnefonds, Pavillon 12, 42055 Saint-Etienne cedex 2, France. Address for reprint requests: P. A. Robbins, Univ. Laboratory of Physiology, Parks Rd., Oxford OX1 3PT, UK (E-mail: peter.robbins@physiol.ox.ac.uk).

Received 11 April 1996; accepted in final form 17 December 1996.

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