Variance of ventilation during exercise

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Beck, Kenneth C., and Theodore A. Wilson. Variance of ventilation during exercise. J Appl Physiol 90: 2151–2156, 2001.—Expired gas concentrations were measured during a multibreath washin maneuver of He in one female and seven male subjects at rest (seated) and during cycle exercise at work rates of 70–210 W. In a computational model, the ventilation distribution was represented as a log-normal distribution with standard deviation (σV); values of σV were obtained by fitting the output of the model to the data. At rest, σV was 0.89 ± 0.18; during exercise, σV was 0.60 ± 0.13, independent of the level of exercise. These values for the width of the functional ventilation distribution at the scale of the acinus are approximately two times larger than those obtained from anatomic measurements in animals at a scale of 1 cm³. The values for σV, together with data from the literature on the width of the functional ventilation-perfusion distribution, show that ventilation and perfusion are highly correlated at rest, in agreement with anatomic data. The structural sources of nonuniform ventilation and perfusion and of the correlation between them are unknown.

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METHODS

Experiment design. Eight subjects were studied, one was female. All eight were hospital employees or physicians in training. All read, understood, and signed an informed consent form that was approved by the Mayo Institutional Review Board. Morphometric characteristics of the subjects are listed in Table 1.

Each subject was studied in the exercise laboratory a day before the He washin study. In the preliminary study, the subject was familiarized with the stationary exercise cycle, and the subject’s maximal exercise capacity was measured.

Gas washin measurements were made using an apparatus that has been described previously (11). Briefly, a Hans-Rudolph non-rebreathing Y valve was connected directly to a low-dead-space switching valve that allowed rapid switching of inspired gas from room air to a gas mixture. A Hans-Rudolph pneumotachograph was connected to the mouth end of the non-rebreathing valve. The subject wore a nose clip and breathed into the pneumotachograph through a flanged rubber mouthpiece. The pneumotachograph was connected to a differential pressure transducer to measure flow. The pneumotachograph was linearized using the method of Yeh and colleagues (28) and calibrated daily using a 3-liter syringe to pump test gas through the entire valve assembly. Data for flow and gas concentration were acquired every 8 ms and stored in computer files for later analysis.

To perform the gas washin, the subject breathed normally (resting or exercise ventilation), and the switching valve was thrown during an expiration so that, on the next inspiration, the subject inhaled test gas from a 60-liter bag containing 0.7% acetylene (C₂H₂), 9% He, 21% O₂, and balance N₂. During gas washin, a computer sampled data for flow at the mouth and fractional concentrations of O₂, CO₂, N₂, He, and C₂H₂ (mass spectrometer, Perkin-Elmer, Norwalk, CT). The subject was encouraged to maintain a steady breathing pattern during the washin; otherwise, no constraints on breathing were imposed. After 12–15 breaths, the subject was asked to perform a maximal inspiration to total lung capacity (TLC), and the inspired gas was then switched back to room air. The flow signal was integrated digitally to obtain a continuous volume signal. These data were submitted to computerized routines to find end-tidal gas concentrations,
Vt for each breath, and end-inspiratory volume and to fit the data to a computational model (see below). Gas washin studies were performed in duplicate at rest and at each exercise intensity. Intensities chosen for this study were 70, 140, and 210 W.

Within a week of the exercise session, functional residual capacity (FRC) and TLC were measured using a constant volume body plethysmograph (Medical Graphics, St. Paul, MN, model 1085 Dx). The subject was seated comfortably in the plethysmograph for 2–3 min to allow thermal equilibrium to be established. The subject breathed normally into the mouthpiece attached to a shutter valve for four to five breaths to establish a consistent breathing pattern. The shutter was closed at end expiration and kept closed for 2–4 s while the subject continued to make breathing efforts against the shutter. Thoracic gas volume was determined from airway and plethysmograph pressure changes during these efforts using standard procedures. The shutter was opened, and the subject immediately inhaled fully. The flow signal was integrated, and TLC was determined as thoracic gas volume plus the inspired volume. At least two maneuvers were obtained for which the mouth pressure vs. box pressure loops were closed, and values for TLC for these maneuvers were averaged.

**Data analysis.** From the raw data streams, the average Vt, inspiratory and end-expiratory gas concentrations, and dead space volume (Vd) were determined. Vd was obtained by mass balance

\[ V_d = \frac{F_{He} - F_{H2}}{F_{H2} - F_{He}} \times V_t \]

where \( F_{He} \) is mixed expired He concentration and \( F_{H2} \) and \( F_{He} \) represent end-expiratory and end-inspiratory He concentrations, respectively. \( F_{H2} \) was determined for each breath by taking the sum of the instantaneous expired He fraction times the expired volume increment for each 8-ms sampling interval during expiration and then dividing this sum by expired Vt. In each run, Vd was averaged for all breaths in which \( F_{He} \) was <90% of \( F_{H2} \). This exclusion was applied to avoid problems with reduced signal-to-noise ratio as expiratory concentration approached inspiratory concentration near the end of the maneuver.

The data were submitted to the computational model (see below) using volumes and gas fractions expressed in STPD conditions. The model output was a set of values for \( \sigma_V \) and FRC. To validate the estimate of FRC from the model, “true” alveolar FRC was obtained by subtracting the inspired volume obtained at the end of the maneuver and Vd from the plethysmographic TLC value for each subject. That is, we assumed that the TLC obtained in the body plethysmograph is accurate and that TLC does not change with exercise. To document the significance of the changes in FRC and change in \( \sigma_V \) with exercise, data for both variables were first submitted to one-way ANOVA followed by paired \( t \)-tests to determine significance of changes during exercise compared with preexercise.

**Table 1. Subjects’ morphometric characteristics**

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>TLC, liters</th>
<th>TLC, %pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>180</td>
<td>80</td>
<td>7.5</td>
<td>111</td>
</tr>
</tbody>
</table>

Means values are shown, with ranges in parentheses; \( n = 8 \) subjects. TLC, total lung capacity.

**Computational model.** Alveolar volume at end expiration (VARE) is imagined to be subdivided into a large number of compartments with equal gas volumes at end expiration. During each breath, each compartment expands from an initial volume \( (V_0) \) to a final volume \( (V_0 + dV) \), where \( V_0 \) is the same for all compartments but \( dV \) differs among compartments. The fractional volume expansion of each compartment \( (dV/V_0) \) is denoted \( v \). The distribution of volume change among compartments, \( f(v) \), is assumed to be a log-normal distribution with a peak at \( \ln(v) = \mu \) and width \( \sigma_V \)

\[ f(v) = \frac{1}{\sqrt{2 \pi \sigma_V}} \exp \left( -\frac{[\ln(v) - \mu]^2}{2 \sigma_V^2} \right) \]  

Vt equals the sum of the volume changes of all lung compartments

\[ V_t/V_{ARE} = \int v \cdot f(v) \cdot d \ln(v) \]  

Because of this equality, the parameter \( \mu \) is related to other variables by the following equation

\[ \mu = \ln\left( \frac{V_A}{V_{ARE}} - \frac{\sigma_V^2}{2} \right) \]  

It is assumed that each compartment receives gas from the dead space in proportion to its volume expansion. Therefore, during the first inspiration of the test gas with He concentration \( C_0 \), the concentration of He in the dead space is zero and the amount of He delivered to a compartment is \( C_0 (1 - V_d/V_t) dV \). The compartment is assumed to be well mixed, and the concentration of He in the compartment at the end of the first inhalation, denoted \( C(v,1) \), is computed from a mass balance for He. The mass balance yields the following equation, where \( C(v,1) = C(v,1)/C_0 \)

\[ C(v,1) = \frac{1}{1 + 2v} \times \left( 1 - \frac{V_d}{V_t} \right) \]  

During the next expiration, expired gas from all compartments is assumed to be well mixed in the common Vd. Thus the concentration of He in the alveolar gas expired in the first breath, denoted \( C_{exp} \), is given by Eq. 5, where \( c_{exp}(1) = C_{exp}(1)/C_0 \)

\[ c_{exp}(1) = \frac{V_{ARE}}{V_t} \times \int c(v,1) \times v \times f(v) \times d \ln(v) \]  

In subsequent breaths, for instance breath number \( i \), the concentration in each compartment is \( c(v,i - 1) \) at the beginning of inspiration, and gas from the dead space reenters each compartment at the beginning of inspiration. It is assumed that the concentration of He in the dead space gas equals the mixed alveolar concentration in the previous breath, \( c_{exp}(i - 1) \). Thus, for the \( i \)th breath, Eq. 4 is modified to the following

\[ c(v,i) = \frac{c(v,i - 1) + v \times \left[ \left( 1 - \frac{V_d}{V_t} \right) + \frac{V_d}{V_t} \times c_{exp}(i - 1) \right]}{(1 + v)} \]  

The concentration of expired gas in subsequent breaths \( c_{exp}(i) \) is calculated from Eq. 5, with \( c(v,1) \) replaced by \( c(v,i) \).

The model contains four parameters: \( V_{ARE}, V_t, V_d, \) and \( \sigma_V \). Three of these, \( V_{ARE}, V_t, \) and \( V_d \), were experimentally determined, independently of the values of \( c_{exp}(i) \). Thus only one remains to be determined from the fit of the values of
c_{exp}(i), calculated from Eq. 5, to the measured values of \(c_{exp}(i)\). However, to test the accuracy of the modeling, we purposely used values for only two of the independently determined parameters, \(V_T\) and \(V_D\), and varied two parameters, \(V_{AEE}\) and \(\sigma_V\), to obtain the best fit of the predicted values of \(c_{exp}(i)\) to the data.

The right side of Eq. 5 was evaluated numerically, and the Powell iterative search method (17) was used to find the values of \(V_{AEE}\) and \(\sigma_V\) for which the sum of the squared differences between the predicted and measured values of \(c_{exp}(i)\) was minimum. An example of the measured and best-fit values of \(c_{exp}(i)\) is shown in Fig. 1. The fit to the model was excellent in all cases (lowest \(r^2 = 0.99\) among all subjects).

RESULTS

Values of \(V_{AEE}\) obtained from the fit of the model to the washin data are shown in Fig. 2, plotted vs. values obtained from the independent measurements of TLC. The mean difference between the values is 0.14 ± 0.43 liter (mean plethysmographic value greater than mean washin value), which was not significantly different from 0 (\(P > 0.05\)).

Values of \(\sigma_V\) are plotted vs. work rate in Fig. 3. In one subject, the \(\sigma_V\) values were near zero at rest and at lower levels of exercise. Including data from this subject reduced the mean slightly; therefore, we opted to report means excluding data from this subject. The mean and SD of the resting value of \(\sigma_V\) for the remaining seven subjects was 0.89 ± 0.18. Mean values of \(\sigma_V\) during exercise at different levels of exercise are significantly different from resting values, but mean \(\sigma_V\) at different levels of exercise are not significantly different. The average of \(\sigma_V\) for all levels of exercise are 0.60 ± 0.13.

Values of \(\sigma_V\) are plotted vs. \(V_T\) in Fig. 4. In general, \(\sigma_V\) decreased with increasing \(V_T\).

DISCUSSION

In this study, we measured expired gas concentrations at end-expiration during a multibreath washin of He at rest and with increasing levels of exercise in eight normal subjects (one woman). We interpreted these data to obtain values for \(\sigma_V\) at different levels of exercise, and we found that \(\sigma_V\) decreased with increasing ventilation of exercise.

The interpretation of washin and washout data by compartmental models has a long history. Fowler and colleagues (4) used two- and three-compartment models to interpret data on nitrogen washout, and, since then, others have used models of varying complexity (7, 12). Our model is similar to these. We assume that terminal alveolar units are connected to the mouth via a common dead space. Transport by diffusion is not explicitly described, but the dead space and alveolar compartments are assumed to be well-mixed. The re-inspiration of gas from the dead space is included in the model. We assume that \(V_D\) is redistributed to the alveolar compartments in the same proportion as \(V_T\). Asynchronies of filling and emptying are not included,
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Fig. 4. Values of $\sigma_V$ for the 8 subjects vs. tidal volume as a fraction of end-expiratory volume.

Fig. 5. Values of the coefficient of correlation between ventilation ($V_A$) and perfusion ($Q$) plotted against values of the width of the perfusion distribution ($\sigma_Q$).

and the model cannot account for the slope of phase III of expiratory gas concentration. We describe the distribution of regional ventilation by log-normal distribution with one adjustable parameter, the $\sigma_V$. With this model, the fits to the data were very good ($r = 0.998 \pm 0.002$). We also tried a more complicated model, namely, a two-parameter logarithmic distribution with skew. However, the fits of that model to the data were only marginally improved, and the inferred values of the $\sigma_V$ were not substantially different. Thus, although the log-normal distribution might be too limited to describe the ventilation distribution in patients with respiratory disease, it seems to describe the ventilation distribution in normal subjects adequately.

Although we had an independent experimental measurement of $V_{AEE}$, we purposely included $V_{AEE}$ as a parameter that was determined by fitting the model to the washin data because a comparison of the value of $V_{AEE}$ inferred from the washin data with the plethysmographically measured value of $V_{AEE}$ (TLC - IC - Vd), where IC is inspiratory capacity, provides a test of the model. The agreement between the two, shown in Fig. 2, is quite good. As a result, we have some confidence in the validity of the model.

Our values of $\sigma_V$ can be compared with those reported by others. Although the distribution function used by Gomez and colleagues (7) is somewhat different from ours, the relative half-width of their distribution ($0.78 \pm 0.28$) is comparable to our $\sigma_V$ value ($0.89 \pm 0.18$). Lewis and colleagues (12) used a 50-compartment model to fit their $N_2$ washout data and obtained SD of log(V) values of $0.56 \pm 0.13$ in young subjects and $0.86 \pm 0.19$ in older subjects. Recently, Prisk and colleagues (18) applied the Lewis model to data obtained from subjects who flew on the space shuttle. They obtained preflight control values of $0.73 \pm 0.05$, $0.64 \pm 0.02$, and $0.73 \pm 0.03$ from data on washout of $N_2$ and washin of He and SF$_6$, respectively. $V_T$ for the Gomez study varied considerably but averaged >1 liter. The $V_T$ values in the Lewis and Prisk studies were 500 and 700 ml, respectively. Our value of $\sigma_V$ for resting subjects is slightly higher than the values reported by others. $V_T$ values for our resting subjects were larger than the average of Lewis and colleagues but in the range of values found by Gomez and associates. Our values of $\sigma_V$ at $V_T$ of 700–1,400 ml are much the same as theirs.

The first studies of the anatomic distributions of regional ventilation measured washin or washout of radioactive gases detected by rather coarse-grained external counters. The results of these studies are summarized in the review article by Milic-Emili (14). This technique revealed a vertical gradient of ventilation, but, as Piiper and Scheid (16) pointed out, the variance of ventilation implied from these data (25) is considerably smaller than the value obtained from gas mixing studies; this implies the existence of nonuniformities in addition to the gravitational gradient.

The first direct observation of a nongravitational component of nonuniform ventilation was reported by Hubmayr and colleagues (10). They used parenchymal markers and biplane video fluoroscopy to measure regional expansion at a scale of ~1 cm$^3$. Since then, Treppo and colleagues (24) measured regional ventilation and perfusion simultaneously using positron emission tomography, and others (1, 13, 20) have measured regional ventilation by fluorescent aerosol deposition. The resolution of these techniques is about the same as that of the parenchymal marker technique, but these methods provide data that sample the lung more uniformly and thoroughly. These methods are restricted to use in animals. More recently, another method, computed tomographic measurements of regional washin of a radiodense gas, has been developed (23); this method is potentially applicable to humans.

Wilson and colleagues (21, 27) noted that the variance of regional volume measured by the parenchymal marker technique depended on the size of the region sampled, with variance increasing as sample size decreased. They argued that the observed variance was the residue of a larger variance at a smaller scale. This
question has continued to vex the field: To what extent do anatomic measurements at a scale of 1 cm³ underestimate the functional variance of ventilation at the scale of the acinus? The question can be addressed by comparing the functional and anatomic values of \( \sigma_V \). The results of Hubmayr and colleagues (10) are described in somewhat different terms from ours, and their data must be reinterpreted before they can be compared with ours. Hubmayr and associates measured regional volume as a fraction of volume at TLC during deflation from TLC. Plots of fractional regional volume vs. lung volume were linear, and they report the variance of the slopes of these plots. Thus the volume excursions in these experiments were large, and regional volume change was normalized by regional volume at TLC, not by volume at end expiration. They report a distribution of slopes with a standard deviation of \( \sim 0.12 \). To account for the fact that these data are normalized by TLC rather than by FRC, they should be multiplied by \( \sim 2.5 \). Thus we obtain an estimate for \( \sigma_V \) at FRC of \( \sim 0.3 \) for their data. The data of Treppo and associates (24) describe specific regional ventilation, and their value of \( \sigma_V \) can be compared directly with ours. Their value for \( \sigma_V \) is \( \sim 0.25 \), in reasonable agreement with the value inferred from the data of Hubmayr and colleagues. Measurements of regional ventilation by the aerosol deposition technique in goats (13) and pigs (20) give larger values of \( \sigma_V \), namely, \( \sim 0.40 \). Perhaps these slightly higher values are caused by a species dependence of \( \sigma_V \), or perhaps they are the result of the fact that the mechanics of aerosol deposition and gas transport are different. Thus the comparison between the functional value of \( \sigma_V \) in humans and the value obtained from anatomic measurements in animals indicates that the value measured at a scale of 1–2 cm³ is approximately two times smaller than the value at the scale of the acinus. Gas mixing studies in excised dog lobes (27) also showed that a standard deviation of regional volume of approximately two times that measured at the scale of 1 cm³ would be required to explain the mixing efficiency, and computer tomographic measurements of regional volume confirmed this estimate of small-scale variability (21). Thus comparison of gas mixing studies with studies of anatomic heterogeneity of regional ventilation lead us to conclude that the functional unit of gas exchange is smaller than the 1–2 cm³ of most anatomic studies.

The value of \( \sigma_V \) has implications for gas exchange. The effectiveness of transport between inspired gases and the blood depends primarily on the distribution of \( V_a/Q \). The width of the \( V_a/Q \) distribution (\( \sigma_{V/Q} \)) depends on the widths of the ventilation and perfusion distributions, \( \sigma_V \) and \( \sigma_Q \), and on the correlation between ventilation and perfusion, \( \rho \). The relation between the widths of the three distributions, each described as a log-normal distribution, and \( \rho \) is given in Eq. 2 (26)

\[
\sigma_{V/Q}^2 = \sigma_V^2 + \sigma_Q^2 - 2\rho \times \sigma_V \times \sigma_Q
\]

(7)

Our data provide values of \( \sigma_V \), and values of \( \sigma_{V/Q} \) are available in the literature. Reported values for \( \sigma_{V/Q} \) at rest are 0.4–0.5 in resting subjects and 0.4–0.6 during exercise (5, 6, 8, 9, 19, 22). Thus \( \sigma_{V/Q} \) is smaller than \( \sigma_V \), and, from Eq. 7, it follows that \( \sigma_Q \) must be of the same magnitude as \( \sigma_V \) and that \( \rho \) must be high. The relations between \( \rho \) and \( \sigma_Q \) that are obtained by substituting the values of \( \sigma_V \) and \( \sigma_{V/Q} \) for resting \( (\sigma_V = 0.89, \sigma_{V/Q} = 0.45) \) and exercise \( (\sigma_V = 0.60, \sigma_{V/Q} = 0.5) \) into Eq. 7 are shown in Fig. 5. For resting conditions, the range of possible values for \( \sigma_Q \) is fairly wide, but the value of \( \rho \) is more restricted: \( \rho > 0.85 \). Simultaneous anatomic measurements of ventilation and perfusion in animals allow a direct evaluation of the correlation between ventilation and perfusion. Values obtained by positron emission tomography and microsphere techniques are 0.7–0.8 (1, 13, 15, 20, 24). The possible values of \( \sigma_Q \) and \( \rho \) during exercise cover a broader range (Fig. 5). It is clear that \( \sigma_Q \), like \( \sigma_V \), might decrease during exercise and that \( \sigma_{V/Q} \) rises slightly because the correlation between ventilation and perfusion decreases.

The value of \( \sigma_V \) that we measure at rest is large. The decrease with increasing \( V_T \) is caused, at least in part, by the decrease in the vertical gradient of ventilation with increasing \( V_T \) (2). Our value of \( \sigma_V \) at higher \( V_T \) agrees with the value obtained by Prisk and colleagues (18) in microgravity. At higher \( V_T \), the remaining non-uniformity appears to be caused by lung expansion that is nonuniform at the scale of the acinus. Presumably, this nonuniform expansion is the result of nonuniform parenchymal compliance at that scale. The range of \( v \) from one SD above the mean to one SD below the mean covers a factor of six at rest and three during exercise. The identity of the structural component that is the source of this nonuniformity, as well as the source of the equally large and highly correlated non-uniformity of perfusion, is unknown.

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