Tidal volume dependency of gas exchange in bronchoconstricted pig lungs

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Kleinsasser A, Olftert IM, Loeckinger A, Prisk GK, Hopkins SR, Wagner PD. Tidal volume dependency of gas exchange in bronchoconstricted pig lungs. J Appl Physiol 103: 148–155, 2007. First published March 29, 2007; doi:10.1152/japplphysiol.00451.2006.—Independent of airway pressure, pulmonary resistance is known to fall with increasing tidal volumes, traditionally thought to result from radial traction on the airways. R. C. Anafi and T. A. Wilson (J Appl Physiol 91: 1185–1192, 2001) recently presented a model of a single terminal airway that explains the tidal volume-associated fall in resistance with an additional mechanism pertinent to narrow airways: a stable, nearly closed airway that is challenged with an increase in tidal volume “pops open” to become a stable, well-opened airway, and thus resistance drops suddenly. To test this model in vivo, the effects of high (24 ml/kg) and low (9 ml/kg) tidal volume in bronchoconstricted lungs were assessed using 1) the multiple inert gas elimination technique (MIGET) and 2) a 15-breath multiple breath inert gas washout (MBW) technique in anesthetized pigs. With high tidal volume, ventilation/perfusion (VA/Q) mismatch was reduced (log SD Q from 1.30 ± 0.11 to 1.09 ± 0.12, P < 0.05), and blood flow to lung units with VA/Q ratios < 0.1 was significantly reduced (37 ± 4% of cardiac output to 7 ± 4%, P < 0.05). Dynamic compliance was twice as high during high-tidal-volume ventilation (P = 0.002). MBW analysis revealed that, while heterogeneity of ventilation during bronchoconstriction was not significantly different between either low or high tidal volume (log SD Vmaw = 1.39 ± 0.09 and 1.34 ± 0.02, respectively), preinspiratory lung volume (PILV) decreased by 42% with low-tidal-volume ventilation (P < 0.05), whereas it did not change with high-tidal-volume ventilation. The higher PILV during high tidal volume is also consistent with Anafi and Wilson’s model. In summary, the outcomes from MIGET, and to some extent the MBW, in our anesthetized and mechanically ventilated pigs are consistent with a bistable terminal airway model as proposed by Anafi and Wilson. However, our data do not allow exclusion of other mechanisms that may lead to improved ventilatory distribution when tidal volume is increased.

bistable airways; multiple breath washout; multiple inert gas elimination technique; ventilation/perfusion inequality

IN THE HEALTHY LUNG, the longitudinal profile of airway resistance to gas flow is well defined. Combined resistance is greatest in the intermediate-size bronchi (segmental bronchi) and decreases as peripheral airways become much more numerous and the all-over cross-sectional area increases. However, on the basis of insoluble gas washout studies, a tidal volume-dependent decrease in inhomogeneities of gas concentrations in the lung periphery has been shown (9), indicating that tidal volume modulates small airway diameter.

In bronchoconstricted lungs, airway resistance is heterogeneously distributed. Evidence for this has been found using high-resolution computed tomography (1, 6) and by examining the fit of models to experimental data on lung impedance (5, 18, 20). In such constricted lungs, tidal volume and airway resistance are inversely related (13, 16, 22). Canine airways show a decreased responsiveness to methacholine (MCh)-induced bronchoconstriction at high tidal volume, regardless of mean airway pressure (16, 22), and a similar relation between tidal volume and airway resistance has been shown in rabbits (22).

In a recent theoretical study, Anafi and Wilson (3) argued that terminal airways in a bronchoconstricted lung existed either in a stable, well-open or a nearly closed condition; when tidal volume amplitude was increased in their model, a nearly closed airway passed through an unstable condition to finally “pop open” and turn into a well-ventilated airway. The total number of airways in each state is determined by the particular tidal volume and end-expiratory pressure applied (3). Bronchoconstriction is accordingly heterogeneous at a given tidal volume, with airways distributed between effectively open and nearly closed states (3). This is remarkably predictive of the original observations on ventilation/perfusion (VA/Q) inequality in asthmatic patients where strikingly bimodal patterns with regions of normal or very low VA/Q ratio, but not of intermediate VA/Q ratios, are commonly observed (21).

If Anafi and Wilson’s bistable theory (3) is correct, increases in tidal volume should lead to less VA/Q mismatch. Indeed, uneven airway constriction with MCh must change the distribution of ventilation in the lung and consequently alter the VA/Q relationship. If the number of open airways increases with higher tidal volume, greater evenness of the distribution of ventilation, and therefore a better VA/Q ratio distribution, could be expected.

Distributions of ventilation and perfusion in experimentally constricted or occluded lungs are well described (4, 11, 15, 22) and comparable with those seen in human asthma. A characteristic finding is the bimodal shape of the distribution of perfusion with blood flow to lung units with either normal or low VA/Q ratio. If the above described bimodality is, even in part, based on the behavior predicted by Anafi and Wilson (3), ventilation with high tidal volume should convert some poorly ventilated units to well-ventilated units and improve overall VA/Q inequality, even when total ventilation is unaltered. On the other hand, if raised tidal volumes had no such effect, VA/Q inequality would not be diminished or might even become more pronounced as less bronchoconstricted regions absorbed more of the ventilation.
The aim of this study was to assess whether different tidal volumes alter the distribution of ventilation and perfusion in a MCh-constricted lung. We used the multiple inert gas elimination technique (MIGET) to test the hypothesis that MCh-induced \( V_{A}/Q_{A} \) mismatch would be reduced and low \( V_{A}/Q_{A} \) regions converted to more normally ventilated regions with the application of high compared with low tidal volume. Moreover, if terminal airways in constricted lungs exist in a bistable state, application of a higher tidal volume should convert “nearly closed” airways into “well-opened” airways and result in a more homogeneous distribution of ventilation, in conjunction with the expected improvement in \( V_{A}/Q_{A} \) matching. Therefore, we independently measured the distribution of ventilation using the multiple breath inert gas washout (MBW) technique, in tandem with MIGET analyses, to test this hypothesis.

**METHODS**

**Animal Preparation**

After approval of the Animal Subjects Committee of the University of California, San Diego, this study was performed in seven healthy domestic pigs weighing 20–25 kg. Animals were fasted overnight but had free access to water. Anesthesia was intramuscularly induced with ketamine (6 mg/kg) followed by intravenous propofol (2–4 mg/kg). After tracheal intubation, the lungs were ventilated in a volume-controlled, time-cycled mode (Harvard 613; Harvard Apparatus, South Natick, MA) at a tidal volume of 9 ml/kg. Respiratory rate was then adjusted to achieve an arterial partial pressure of carbon dioxide (\( Pa_{CO_{2}} \)) of ~40 Torr. Femoral arterial and pulmonary arterial catheters were placed, after which animals were positioned prone as this is a physiological position for a pig. Ringer solution (10 ml-kg\(^{-1}\)-h\(^{-1}\)) was continuously administered intravenously throughout the study period. Body temperature was maintained between 38°C and 39°C using heating pads.

**Experimental Protocol**

Baseline measurements of all observed variables were taken either at a tidal volume of 24 or 9 ml/kg. The starting tidal volume was based on an alternating design, so that three pigs started on high tidal volume and four pigs on low tidal volume to allow assessment of any ordering effect of tidal volume administration. Figure 1 graphically displays the study protocol.

The rationale behind the tidal volume settings was to use a physiological value (9 ml/kg) and the largest possible tidal volume (24 ml/kg) with corresponding respiratory frequencies (32 and 10 breaths/min, respectively) such that each resulted in a \( Pa_{CO_{2}} \) close to 40 Torr before administration of MCh. These settings were determined in two pilot animals. The inspiratory fraction of oxygen was 0.21 throughout the experiment, and positive end-expiratory pressure was set to 3 cmH\(_2\)O and maintained at this level throughout the entire experiment.

After completing baseline measurements at the two tidal volume levels, MCh (30 mg/ml in saline) was intermittently aerosolized using an ultrasonic nebulizer (Mistogen ENIYS, Mistogen Equipment, Oakland, CA) to maintain a constant doubling of baseline mean airway pressure for each pig throughout the study (16). Duplicate measurements were made at each tidal volume in an alternating fashion (Fig. 1) so that four time points during MCh application could be observed in each animal (i.e., 2 at each tidal volume). Pigs were equilibrated for 15 min at each tidal volume level before measurements were made. The purpose of alternating between tidal volumes of 9 and 24 ml/kg was to verify the reproducibility of the effects of tidal volume differences on gas exchange.

![Graphical display of study protocol. After two baseline measurements starting at a tidal volume (V\textsubscript{T}) of either 9 ml/kg (top) or 24 ml/kg (bottom), where the initial V\textsubscript{T} was chosen by alternating between low and high V\textsubscript{T}, two measurements at a V\textsubscript{T} of 9 or 24 ml/kg were carried out during continuous nebulization of methacholine.](image)

**Hemodynamic Measurements**

A 5-F catheter was advanced into the aorta for withdrawal of arterial blood and measurement of mean arterial blood pressure. A 7-F pulmonary artery catheter was advanced into the pulmonary artery to monitor mean pulmonary artery pressure and to withdraw mixed venous blood. All catheters were saline filled and connected to standard pressure transducers that had been zeroed to ambient pressure at the level of the right atrium before each experimental time point.

**Blood Gas and Inert Gas Measurements**

Arterial and mixed venous blood gas variables were determined at 37°C using a blood gas analyzer (Instrumentation Laboratory, Lexington, MA) and then corrected and reported for actual body temperature measured. \( V_{A}/Q_{A} \) ratio distributions were determined using MIGET (22, 23). Briefly, a mixture of six inert gases including sulfur hexafluoride, ethane, cyclopropane, enflurane, ether, and acetone dissolved in saline was infused via an auricular vein (rate in ml/min = 0.25 \times \) respiratory minute ventilation in l/min). This infusion was started 30 min before the first set of measurements. Six-milliliter arterial blood samples were collected in duplicate into heparinized matched-barrel glass syringes. Mixed expired gas samples were collected from a heated mixing chamber into gas-tight glass syringes. Blood gas partition coefficients, retentions (equal to the ratio of arterial to mixed venous partial pressure), and excretions (equal to the ratio of mixed expired to mixed venous partial pressure) for the inert gases were determined using gas chromatography (HP-5890, Series II; Hewlett-Packard, Wilmington, DE). \( V_{A}/Q_{A} \) distributions were obtained from the inert gas data and assessed by determining the following.

1) *Modality of the distributions of \( V_{A} \) and \( Q_{A} \).* The modality (unimodality or bimodality) of the distributions of \( V_{A} \) and \( Q_{A} \) was determined.
2) Mean of $Q$. The mean of $Q$ was defined as the first moment of the distribution on a log scale over all $i$ units in the distribution except the two extreme units ($\frac{V_{\text{A}}}{Q_{\text{i}}} = 0$ and infinity):

$$\text{mean} (\frac{V_{\text{A}}}{Q_{\text{i}}}) = \frac{\sum [Q_{\text{i}} \times \log (\frac{V_{\text{A}}}{Q_{\text{i}}})]}{\sum Q_{\text{i}}}$$

$$\text{log mean} (\frac{V_{\text{A}}}{Q_{\text{i}}}) = \frac{\sum [\log(\frac{V_{\text{A}}}{Q_{\text{i}}})]}{\sum Q_{\text{i}}}$$

3) Log SD $Q$. The log SD $Q$ was defined as the second moment about the above mean on a log scale, again over all units except $\frac{V_{\text{A}}}{Q_{\text{i}}} = 0$ and infinity:

$$\text{log SD } Q = \left( \frac{\sum [Q_{\text{i}} \times [\log(\frac{V_{\text{A}}}{Q_{\text{i}}})]^2]}{\sum Q_{\text{i}}} - \text{log mean} (\frac{V_{\text{A}}}{Q_{\text{i}}})^2 \right)$$

4) Mean of $V$. The mean of $V$ was defined as the first moment of the distribution on a log scale over all units except $\frac{V_{\text{A}}}{Q_{\text{i}}} = 0$ and infinity:

$$\text{mean} (\frac{V_{\text{A}}}{Q_{\text{i}}}) = \frac{\sum [V_{\text{A}} \times \log (\frac{V_{\text{A}}}{Q_{\text{i}}})]}{\sum V_{\text{A}}_{\text{i}}}$$

$$\text{log mean} (\frac{V_{\text{A}}}{Q_{\text{i}}}) = \frac{\sum [\log(\frac{V_{\text{A}}}{Q_{\text{i}}})]}{\sum V_{\text{A}}_{\text{i}}}$$

5) Log SD $V$. The log SD $V$ was defined as the second moment about the above mean on a log scale, again over all units except $\frac{V_{\text{A}}}{Q_{\text{i}}} = 0$ and infinity:

$$\text{log SD } V = \left( \frac{\sum [V_{\text{A}} \times [\log(\frac{V_{\text{A}}}{Q_{\text{i}}})]^2]}{\sum V_{\text{A}}_{\text{i}}} - \log mean (\frac{V_{\text{A}}}{Q_{\text{i}}})^2 \right)$$

6) Low-$\frac{V_{\text{A}}}{Q}$ regions. Low-$\frac{V_{\text{A}}}{Q}$ regions were defined as blood flow in regions of $0.005 < \frac{V_{\text{A}}}{Q_{\text{i}}} < 0.1$.

7) Shunt. The shunt was defined as blood flow to essentially unventilated regions (i.e., $\frac{V_{\text{A}}}{Q_{\text{i}}} < 0.005$).

8) High-$\frac{V_{\text{A}}}{Q}$ regions. High-$\frac{V_{\text{A}}}{Q}$ regions were defined as ventilation to regions with $\frac{V_{\text{A}}}{Q}$ ratios greater than 10 and less than 100 (i.e., $10 < \frac{V_{\text{A}}}{Q_{\text{i}}} < 100$).

9) Dead space. Dead space was defined as ventilation of essentially unperfused lung units (i.e., $\frac{V_{\text{A}}}{Q_{\text{i}}} > 100$).

The residual sum of squares (RSS) was used as an indicator of the adequacy of fit of the model to the data and data quality.

Ventilatory Measurements

Ventilatory measurements and calculations included expiratory tidal volume, ventilatory minute volume ($V_{\text{E}}$) using a calibrated Wright Respirometer (Ferraris, New York), peak and mean airway pressures, respiratory system dynamic compliance at the frequency used for ventilation (dynamic compliance = tidal volume (ml)/(peak inspiratory pressure − end-expiratory pressure)), and alveolar tidal volume ($V_{\text{TA}}$) = tidal volume $\times [1 - \text{Vd}/\text{VT}]$, where $\text{Vd}/\text{VT}$ (i.e., the dead space volume as a percentage of tidal volume) was obtained from MIGET.

MBW Analysis

To make a MBW measurement, the inspiratory gas mixture was rapidly changed from air to gas mixture containing 5% Ar, 5% He, 21% $O_2$, balanced with $N_2$. Expired fractions of Ar and He were sampled at the Y-piece on the respirator circuit and analyzed using a respiratory mass spectrometer (MGA-1100, Perkin Elmer, Pomona, CA). Expired gas volume was simultaneously obtained using a Fleisch no. 2 pneumotachometer (Fleisch, Lausanne, Switzerland). Gas concentrations and expired volume during a 15-breath washin and washout maneuver were collected and logged at a rate of 60 Hz using a 12-bit analog-to-digital converter in a computer recording system. Before each experiment, the pneumotachometer was calibrated using a 3-liter-volume syringe. Additionally, gas concentration signals were aligned with the volume signal based on mass spectrometer transit time (~400 ms), which was determined by measuring the time required for a sharp puff of gas containing $CO_2$ to be detected by the mass spectrometer. The transit time was defined as the instance flow is detected to when the midpoint in the rise of $CO_2$ is measured by the mass spectrometer and thus includes the lag time and dynamic response time of system components.

The distributions of ventilation and lung volume ($V_{\text{L}}$) as a function of their ratio were obtained using enforced smoothing in a 50-compartment model describing the best fit of the 15-breath MBW concentrations (i.e., similar method to that used in the MIGET analysis) (12, 14). This assessment was performed, independently for both Ar and He, from which the first two moments of the distribution (mean and log SD) for ventilation and volume were determined using the mixed-expired Ar and He concentrations, respectively.

The descriptions of ventilation/volume distributions and indexes of ventilatory inhomogeneity we derived from the inert gas washout data were as follows.

1) Modality of the distributions of ventilation and volume. The modality (unimodality or bimodality) of the distributions of ventilation and volume was determined.

2) Mean of $V_{\text{MBW}}$. The mean of $V_{\text{MBW}}$ was defined as the first moment of the distribution on a log scale over all units except the two extreme units ($\frac{V_{\text{A}}}{V_{\text{L}}}$ = 0 and infinity):

$$\text{mean} (\frac{V_{\text{A}}}{V_{\text{L}}}) = \frac{\sum [V_{\text{A}} \times \log (\frac{V_{\text{A}}}{V_{\text{L}}})]}{\sum V_{\text{A}}_{\text{i}}}$$

$$\text{log mean} (\frac{V_{\text{A}}}{V_{\text{L}}}) = \frac{\sum [\log(\frac{V_{\text{A}}}{V_{\text{L}}})]}{\sum V_{\text{A}}_{\text{i}}}$$

3) Log SD $V_{\text{MBW}}$. The log SD $V_{\text{MBW}}$ was defined as the second moment about the above mean on a log scale, again over all units except $\frac{V_{\text{A}}}{V_{\text{L}}}$ = 0 and infinity:

$$\text{log SD } V_{\text{MBW}} = \left( \frac{\sum [V_{\text{A}} \times [\log(\frac{V_{\text{A}}}{V_{\text{L}}})]^2]}{\sum V_{\text{A}}_{\text{i}}} - \text{log mean} (\frac{V_{\text{A}}}{V_{\text{L}}})^2 \right)$$

4) Mean of $V_{L}$. The mean of $V_{L}$ was defined as the first moment of the distribution on a log scale over all units except $\frac{V_{\text{A}}}{V_{\text{L}}}$ = 0 and infinity:

$$\text{mean} (\frac{V_{\text{A}}}{V_{\text{L}}}) = \frac{\sum [V_{\text{A}} \times \log (\frac{V_{\text{A}}}{V_{\text{L}}})]}{\sum V_{\text{A}}_{\text{i}}}$$

$$\text{log mean} (\frac{V_{\text{A}}}{V_{\text{L}}}) = \frac{\sum [\log(\frac{V_{\text{A}}}{V_{\text{L}}})]}{\sum V_{\text{A}}_{\text{i}}}$$

5) Log SD $V_{L}$. The log SD $V_{L}$ was defined as the second moment about the above mean on a log scale, again over all units except $\frac{V_{\text{A}}}{V_{\text{L}}}$ = 0 and infinity:

$$\text{log SD } V_{L} = \left( \frac{\sum [V_{\text{A}} \times [\log(\frac{V_{\text{A}}}{V_{\text{L}}})]^2]}{\sum V_{\text{A}}_{\text{i}}} - \log mean (\frac{V_{\text{A}}}{V_{\text{L}}})^2 \right)$$

6) High $V_{\text{MBW}}/V_{L}$ ratio. A high $V_{\text{MBW}}/V_{L}$ ratio was defined as ventilation to areas of high resolution/volume ratio (i.e., $V_{\text{MBW}}/V_{L} > 100$).

Last, preinspiratory lung volume (PILV) was calculated as the cumulative ventilation ($\sum V_{E}$) from breaths 1 to 15 divided by the fraction of inert gas at the start of MBW maneuver ($FG_{\text{breath}}$).
subtracted from fraction of inert gas at the final MBW breath \((\text{FGas}^{\text{breath 15}})\); therefore

\[
P_{\text{ILV}} = \sum_{\text{breaths 1-15}} \left( \text{FGas}^{\text{breath 0}} - \text{FGas}^{\text{breath 15}} \right)
\]

Statistical Analysis

Criteria to compare effects of tidal volume change included differences in modality of the distribution of perfusion, blood flow to units with a low \(V_{A}/Q_{A}\) ratio, log SD \(Q_{A}\), and MBW parameters of dispersion. Values obtained with different tidal volumes were compared using an ANOVA for repeated measures. In addition, all variables obtained during the two runs at each tidal volume during MCh administration were compared. Because no significant differences between first and second measurements at the same tidal volume were observed, the arithmetic mean of each variable was used for comparison to baseline values. Significant differences were examined post hoc using the Newman-Keuls test. The probability threshold was set to \(P < 0.05\).

RESULTS

Data shown in Figs. 2 and 3 depict the \(V_{A}/Q_{A}\) and \(V_{A}/V_{L}\) distributions from MIGET and MBW analyses, respectively, obtained from a representative pig at high and low \(V_{T}\) during MCh-induced bronchoconstriction.

Inert Gas Variables

Irrespective of order of tidal volume administration, increasing the tidal volume shifted the distribution to an overall higher \(V_{A}/Q_{A}\) range (i.e., greater mean of \(Q_{A}\), Table 1), decreased log SD \(Q_{A}\) (Table 1, Fig. 2), and resulted in reductions of blood flow to lung units with a low \(V_{A}/Q_{A}\) ratio (Fig. 4). Right-to-left shunts were generally small, and no significant effect of tidal volume on shunt was noted (Table 1). Similar results were seen in the ventilation distribution, where during MCh inhalation at high tidal volume (24 ml/kg), mean of \(V_{A}\) was higher and log SD \(V_{A}\) was lower compared with low tidal volume (9 ml/kg) (Table 1). As expected, dead space ventilation was substantially decreased during ventilation at tidal volume of 24 ml/kg compared with tidal volume of 9 ml/kg (1.4 vs. 3.7 l/min, respectively).
Blood flow is calculated by amount of blood flow to lung units with a low V˙A/Q˙ during bronchoconstriction as a function of VT is displayed as a 5-number (PaO2) and arterial oxyhemoglobin saturation were higher than at

between tidal volume groups at given MCh condition (V˙Q, mean of the distribution of perfusion; log SD V˙, 2nd moment of the dead space/tidal volume ventilation; mean of V˙, mean of the distribution of ventilation; log SD Q, 2nd moment of the distribution of perfusion. RSS, residual sum of squares. *Significant difference between tidal volume groups at given MCh condition (P < 0.01).

P < 0.05). Dead space as a percentage of tidal volume (V˙d/V˙t) averaged 66 ± 3% for tidal volume ventilation at 9 ml/kg and 34 ± 2% for tidal volumes at 24 ml/kg (P < 0.01) (Table 1).

Arterial Blood Gas Data and Cardiac Output

Arterial blood gas values and cardiac output are given in Table 2. At tidal volume of 24 ml/kg, arterial partial pressures of oxygen (Pao2) and arterial oxyhemoglobin saturation were higher than at tidal volume at 9 ml/kg, while the alveolar-arterial difference of oxygen partial pressure and PaCO2 were lower.

Cardiac output (Qt) was significantly lower with tidal volumes at 24 ml/kg compared with 9 ml/kg (P < 0.01) during bronchoconstriction (Table 2).

Ventilatory Variables

Ventilatory data are displayed in Table 3. Respiratory rate was controlled at 32 ± 2 breaths/min with tidal volume at 9 ml/kg and 10 ± 2 breaths/min with tidal volume at 24 ml/kg. During MCh-induced bronchoconstriction, Ve was higher with tidal volume at 9 ml/kg compared with tidal volume at 24 ml/kg (5.8 ± 0.2 vs. 4.2 ± 0.4 l/min, respectively; P < 0.05); however, alveolar ventilation (VA) was slightly lower with tidal volume at 9 ml/kg vs. 24 ml/kg (2.0 ± 0.2 and 2.8 ± 0.4 l/min, respectively; P < 0.05). Peak airway pressure was significantly higher during tidal volume at 24 ml/kg than 9 ml/kg ventilation both before and after MCh; however, the difference in absolute pressure was small during MCh (45 ± 1 vs. 39 ± 2 cmH2O, P = 0.003). Dynamic compliance was significantly higher at a tidal volume of 24 ml/kg (10 vs. 5 ml/cmH2O, P < 0.01).

### Table 1. Gas exchange variables before and during bronchoconstriction at tidal volumes of 9 and 24 ml/kg

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before MCh</th>
<th>MCh Inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low V˙A/Q˙, %</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Shunt, %</td>
<td>1.6 ± 0.43</td>
<td>3.2 ± 0.30</td>
</tr>
<tr>
<td>High V˙A/Q˙, %</td>
<td>0.09 ± 0.05</td>
<td>0</td>
</tr>
<tr>
<td>Dead space (V˙d/V˙t), %</td>
<td>52 ± 3</td>
<td>66 ± 3</td>
</tr>
<tr>
<td>Mean of V˙</td>
<td>0.92 ± 0.10</td>
<td>1.37 ± 0.11</td>
</tr>
<tr>
<td>Log SD V˙</td>
<td>0.73 ± 0.08</td>
<td>1.34 ± 0.07</td>
</tr>
<tr>
<td>Mean of Q˙</td>
<td>0.68 ± 0.07</td>
<td>0.16 ± 0.01</td>
</tr>
<tr>
<td>Log SD Q˙</td>
<td>0.45 ± 0.03</td>
<td>1.30 ± 0.11</td>
</tr>
<tr>
<td>RSS</td>
<td>6.1 ± 1.2</td>
<td>2.4 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE. MCh, methacholine; Vt, tidal volume; V˙A/Q˙, ventilation/perfusion; low V˙A/Q and high V˙A/Q, lung units with a low and high V˙A/Q ratio, respectively; shunt, unventilated lung units; dead space (V˙d/V˙t), dead space/tidal volume ventilation; mean of V, mean of the distribution of ventilation; log SD V, 2nd moment of the distribution of ventilation; mean of Q, mean of the distribution of perfusion; log SD Q, 2nd moment of the distribution of perfusion. RSS, residual sum of squares. *Significant difference between tidal volume groups at given MCh condition (P < 0.01).

### Table 2. Blood gas and hemodynamic measures before and during bronchoconstriction at tidal volumes of 9 and 24 ml/kg

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before MCh</th>
<th>MCh Inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.43 ± 0.04</td>
<td>7.26 ± 0.08</td>
</tr>
<tr>
<td>Pao2, Torr</td>
<td>42 ± 2</td>
<td>64 ± 5</td>
</tr>
<tr>
<td>PaCO2, Torr</td>
<td>91 ± 4</td>
<td>33 ± 2</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>95 ± 0.3</td>
<td>39 ± 0.6</td>
</tr>
<tr>
<td>AVdO2, Torr</td>
<td>17 ± 1</td>
<td>65 ± 2</td>
</tr>
<tr>
<td>Mixed venous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.39 ± 0.04</td>
<td>7.23 ± 0.07</td>
</tr>
<tr>
<td>PvcO2, Torr</td>
<td>50 ± 4</td>
<td>71 ± 11</td>
</tr>
<tr>
<td>PvcO2, Torr</td>
<td>41 ± 8</td>
<td>15 ± 5</td>
</tr>
<tr>
<td>SvO2, %</td>
<td>62 ± 11</td>
<td>11 ± 6</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qt, l/min</td>
<td>4.5 ± 0.6</td>
<td>4.3 ± 0.4</td>
</tr>
<tr>
<td>Ppa, Torr</td>
<td>20.3 ± 3.6</td>
<td>47.0 ± 5.9</td>
</tr>
<tr>
<td>Pcwp, Torr</td>
<td>5.0 ± 1.4</td>
<td>5.5 ± 2.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. Pao2 and PvcO2, arterial partial pressure of carbon dioxide and oxygen, respectively; SaO2, arterial oxygen saturation; AVdO2, alveolar-arterial difference of partial pressure of oxygen; PvcO2 and PvcO2, mixed venous partial pressure of carbon dioxide and oxygen, respectively; SvO2, mixed venous oxygen saturation; Qt, total cardiac output; Ppa, mean pulmonary artery pressure; Pcwp, mean pulmonary capillary wedge pressure. *Significant difference between tidal volume groups at given MCh condition (P < 0.01).

### Table 3. Ventilatory measurements and calculations before and during bronchoconstriction at tidal volumes of 9 and 24 ml/kg

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before MCh</th>
<th>MCh Inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT, ml</td>
<td>199 ± 4</td>
<td>179 ± 6</td>
</tr>
<tr>
<td>V tan, ml</td>
<td>97 ± 7</td>
<td>63 ± 5</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>32 ± 2</td>
<td>33 ± 1</td>
</tr>
<tr>
<td>Ve, l/min</td>
<td>6.3 ± 0.1</td>
<td>5.8 ± 0.2</td>
</tr>
<tr>
<td>Va, l/min</td>
<td>3.1 ± 0.2</td>
<td>2.0 ± 0.2</td>
</tr>
<tr>
<td>Peak Paw, cmH2O</td>
<td>14 ± 2</td>
<td>59 ± 2</td>
</tr>
<tr>
<td>Mean Paw, cmH2O</td>
<td>7.2 ± 0.3</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>Cdyn, ml/cmH2O</td>
<td>19 ± 1</td>
<td>5 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SE. Vt, expiratory tidal volume; Vtan, alveolar tidal volume; f, respiratory frequency; Ve (l/min), respiratory minute volume; Va (l/min), alveolar ventilation; peak and mean Paw, peak and mean airway pressure, respectively; Cdyn, dynamic compliance. *Significant difference between tidal volume groups at given MCh condition (P < 0.05). †Significant difference at same tidal volume between MCh conditions (P < 0.05).

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MBW

As expected, before MCh, unimodal distributions of ventilation were observed during both low and high tidal volumes, and increasing tidal volume resulted in a right-shifted mean of the distribution of ventilation (mean of $V_{\text{MBW}}$, Table 4). In contrast, during MCh-induced bronchoconstriction, bimodal distributions of ventilation were observed (Fig. 3), and increasing tidal volume had no effect on the mean of $V_{\text{MBW}}$ or mean of $V_t$ distribution (Table 4). Heterogeneity in the distribution of lung volume (log SD $V_t$) was greater with tidal volume at 24 ml/kg than at 9 ml/kg, in both the constricted and normal (before MCh) lung (Table 4), but the distribution of ventilation (log SD $V_{\text{MBW}}$) was not different between low- and high-tidal-volume ventilation (Table 4). At low tidal volume, MCh reduced PILV from $467 \pm 47$ to $273 \pm 19$ ml ($P < 0.05$) compared with before MCh (Table 4). At high tidal volume, MCh had no significant effect on PILV compared with before MCh ($738 \pm 75$ vs. $680 \pm 44$ ml, respectively) (Table 4). PILV during high-tidal-volume ventilation (24 ml/kg) was also greater than low-tidal-volume ventilation (9 ml/kg), both before and during MCh inhalation (Table 4).

Model Adequacy (RSS)

Indication of adequate fit of the model to the data is an RSS of 5.3 or less in half of the experimental runs (50th percentile) or 10.6 or less in 90% of the experimental runs (90th percentile). In the present experiment, 50th percentile was 2.7 and 2.3 and the 90th percentile was 6.3 and 5.1, for MIGET and MBW analysis, respectively, indicating both good data quality and adequacy of fit to the model.

DISCUSSION

Changes in the Distribution of $V_{\text{A}}/Q_{\text{V}}$ Perfusion at Tidal Volume of 9 or 24 ml/kg

On the basis of the model of Anafi and Wilson (3), a crucial point in the interpretation of the distribution of $V_{\text{A}}/Q_{\text{V}}$ ratios is whether the distribution becomes narrower or simply shifts to the right as tidal volume is increased. If increasing tidal volume resulted in an increase of ventilation to all alveoli, we would expect only a rightward shift in the distribution of $V_{\text{A}}/Q_{\text{V}}$ ratios and that the log SD Q (the second moment of the distribution) would remain unaltered. If, on the other hand, the bistable airway model proposed by Anafi and Wilson had the expected influence as tidal volume was increased, we would expect less $V_{\text{A}}/Q_{\text{V}}$ inequality (i.e., a lowering of log SD Q) and possibly even a conversion from bimodal to unimodal distribution pattern as more poorly ventilated airways pop open with increasing tidal volume and became better ventilated. It is important to note, while Anafi and Wilson’s airway model says nothing about the distribution of blood flow in lung per se, the MIGET analysis reports the distributions of both $V_{\text{A}}$ and Q in relation to $V_{\text{A}}/Q_{\text{V}}$ ratio (Fig. 2). Therefore, as distribution of $V_{\text{A}}$ is altered with bronchoconstriction and with changes in tidal volume, the $V_{\text{A}}/Q_{\text{V}}$ ratio will change accordingly. Since log SD Q is primarily sensitive to changes in the region of low $V_{\text{A}}/Q_{\text{V}}$ (where, by definition, Q exceeds $V_{\text{A}}$), whereas log SD V is primarily sensitive to changes in regions of high $V_{\text{A}}/Q_{\text{V}}$ ratios (because $V_{\text{A}}$ exceeds Q), changes in ventilation distribution in low-$V_{\text{A}}/Q_{\text{V}}$ regions (due to uneven bronchoconstriction and/or increasing tidal volume from 9 to 24 ml/kg) will be reflected primarily by changes in log SD Q.

It is also important to understand the parameters used to describe the distributions of ventilation and perfusion. When any distribution is logarithmically normal and unimodal, and the moments are calculated on a log scale, the first moment (mean of V, mean of Q) gives the mean, median, and mode (all of which are identical), and the second moment (log SD V, log SD Q) the standard deviation (on a log scale). If the distributions are either asymmetrical or consist of two or more modes (as is the case in Fig. 2), the first moment characterizes the log-based mean ($V_{\text{A}}/Q_{\text{V}}$) of the distribution and is a useful outcome parameter that changes as the distribution shifts up or down the x-axis (i.e., $V_{\text{A}}/Q_{\text{V}}$ axis). The second moment, which now cannot be called “standard deviation,” remains a useful parameter describing global dispersion (i.e., heterogeneity of the distribution). Thus the finding that log SD Q became smaller at high-tidal-volume breathing indicates that overall the distribution is narrower and now comprises a more homogeneous population of $V_{\text{A}}/Q_{\text{V}}$ ratios.

We found that $V_{\text{A}}$ was slightly greater with high-tidal-volume (compared with low tidal volume) ventilation during bronchoconstriction, and consequently there was a right shift in the ventilation and perfusion distributions (Table 3), indicating that all airways received some increase in ventilation. However, we also observed improved $V_{\text{A}}/Q_{\text{V}}$ matching, as evidenced by lower log SD Q, as well as considerably lower blood flow in low-$V_{\text{A}}/Q_{\text{V}}$ regions (Table 1 and Fig. 4), and a change in modality (Fig. 2) at high compared with low tidal volume during MCh. This suggests that the increase in ventilation with high tidal volume was not equally distributed among all airways but was especially evident in low-$V_{\text{A}}/Q_{\text{V}}$ regions. These findings are seen to be consistent with the Anafi and Wilson (3) model, but they are also consistent with any mechanism that preferentially augments ventilation in low-$V_{\text{A}}/Q_{\text{V}}$ regions as tidal volume is increased.

There were significant differences in $P_{\text{ACO}}$, between low and high tidal volumes during MCh-induced bronchoconstriction that could have independently altered $V_{\text{A}}/Q_{\text{V}}$. In a previous study using a dog model, Swenson et al. (17) have shown that increases in $P_{\text{ACO}}$ worsen $V_{\text{A}}/Q_{\text{V}}$ matching (i.e., increases log SD Q). In that study, a 10-Torr increase in CO₂ from 34.1

Table 4. MBW parameters obtained before and during bronchoconstriction at tidal volumes of 9 and 24 ml/kg

<table>
<thead>
<tr>
<th></th>
<th>Before MCh</th>
<th>MCh Inhalation</th>
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<tbody>
<tr>
<td></td>
<td>9 ml/kg Vt</td>
<td>24 ml/kg Vt</td>
</tr>
<tr>
<td>PILV, ml</td>
<td>467±47</td>
<td>680±44*</td>
</tr>
<tr>
<td>Mean of $V_{\text{MBW}}$</td>
<td>0.28±0.06</td>
<td>0.62±0.09</td>
</tr>
<tr>
<td>Log SD $V_{\text{MBW}}$</td>
<td>0.76±0.21</td>
<td>0.70±0.07</td>
</tr>
<tr>
<td>Mean of $V_t$</td>
<td>0.14±0.01</td>
<td>0.17±0.04</td>
</tr>
<tr>
<td>Log SD $V_t$</td>
<td>0.53±0.24</td>
<td>1.59±0.20*</td>
</tr>
<tr>
<td>High $V_{\text{MBW}}/V_t$ ratio, %</td>
<td>57±4.7</td>
<td>54±2.2</td>
</tr>
<tr>
<td>RSS</td>
<td>4.29±0.41</td>
<td>3.34±0.29</td>
</tr>
</tbody>
</table>

Values are means ± SE. MBW, multiple breath washout; PILV, preinspiratory lung volume; mean of $V_{\text{MBW}}$, mean of distribution of ventilation; log SD $V_{\text{MBW}}$, log SD of ventilation; mean of $V_t$, mean of distribution of lung volume; log SD $V_t$, log SD of lung volume; high $V_{\text{MBW}}/V_t$ ratios are defined as $V_{\text{MBW}}/V_t$ ratios > 100. *Significant difference between tidal volume groups at each MCh condition (P < 0.05).
to 44.0 Torr) increased log SD Q by 0.07 units (from 0.58 to 0.65) (17). Thus the 8-Torr decline we observed in Paco2, when going from low to high tidal volume might itself be expected to produce a small (~0.05 unit) decline in log SD Q. That during MCh-inhalation we saw a much larger decline in log SD Q (1.30 to 1.09; a decrease of 0.21) suggests that the small difference in Paco2 between low- and high-tidal-volume ventilation is only likely to explain a small portion of the decline in log SD Q.

The pigs were also more hypoxemic during low- than high-tidal-volume ventilation during bronchoconstriction (Table 2). Greater hypoxic pulmonary vasoconstriction (HPV) may thus have existed during low-tidal-volume ventilation. This is supported by the greater pulmonary artery and capillary wedge pressures (albeit not statistically significant) we measured during low- compared high-tidal-volume ventilation during MCh inhalation (Table 2). If there was significant HPV during low-tidal-volume ventilation, our data likely underestimated the improvement in Vlah/Q ratio with high-tidal-volume ventilation. This is because HPV at low tidal volume would have reduced blood flow in low-Vlah/Q regions, thereby improving their Vlah/Q ratio and lessening overall Vlah/Q inequality. Thus the effect of high tidal volume might actually have been larger if not for hypoxic pulmonary vasoconstriction.

While improved Vlah/Q matching (i.e., lower log SD Q and reduction in low Vlah/Q units) and a change to unimodal distributions are consistent with the expected behavior of the bistable airway model, these findings do not preclude other explanations. It could be that severe airway constriction is clustered throughout the lung periphery (19), not just in terminal airways as described by Anafi and Wilson (3). This could also lead to a substantial portion of the lung being underventilated but still well perfused (as seen in Fig. 2, top). Increasing tidal volume could amplify the distending forces that are imposed throughout the airway tree, so that the MCh-stimulated airway smooth muscle cannot exert sufficient force against this load to maintain the airways constricted. This might also result in a reduction in poorly ventilated units and/or dead space ventilation (improving Vlah/Q matching) and may explain the increase in alveolar ventilation and the rightward shift in the mean of V (Table 1). Therefore, while the MIGET data indicates that Anafi and Wilson’s bistable airway model is consistent with our findings, it cannot be concluded that this is the only possible mechanism for the observed responses.

Changes in the Distribution of Vlah/Vl at Tidal Volume of 9 or 24 ml/kg

Ventilation distributions in experimentally bronchoconstricted or occluded lungs are well described and typically display a bimodal distribution (2, 4, 11, 15, 22). In this study, as expected, we also observed bimodal distributions of ventilation with bronchoconstriction (Fig. 3). On the basis of the bistable model, a decrease in ventilatory inhomogeneity (i.e., smaller log SD Vlahsw) would have been expected as constricted airways pop open with the application of a higher tidal volume, and perhaps even a change from bimodal toward a more unimodal distribution. While there was a tendency for log SD Vlahsw to decrease with tidal volume at 24 ml/kg compared with tidal volume at 9 ml/kg, this was not statistically significant. Moreover, that this was seen in both the control (before MCh) and constricted lung (Table 4) suggests any potential difference is log SD Vlahsw did not occur in relation to bronchoconstriction per se, as would be expected in Anafi and Wilson’s model (3). We also saw no change in modality of the ventilation distribution when changing tidal volume from 9 to 24 ml/kg (Fig. 3). This argues against Anafi and Wilson’s bistable terminal airway model.

At first glance, the apparent discordant finding between MIGET (which appears to support the model) and MBW analysis (which appears to not support the model) may seem paradoxical. However, it should be noted that the MBW analysis reflects the ratio of ventilation to lung volume (i.e., Vlah/Vl), whereas the MIGET analysis reflects the ratio of ventilation to blood flow (i.e., Vlah/Q), and therefore the two methods reflect the distribution of ventilation with respect to two very different parameters, i.e., lung volume (MBW) and blood flow (MIGET). Thus it is conceivable that each analysis could yield different results.

We did not anticipate the changes that occurred in the PILV with the application of high tidal volume during MCh inhalation. In retrospect, it is not surprising that PILV increased with the application of larger tidal volume, both before and during MCh inhalation (Table 4). However, with low-tidal-volume ventilation, there was a (42%) fall in PILV during bronchoconstriction compared with baseline (273 vs. 467 ml, respectively, P < 0.05), while there was no significant change in PILV with high-tidal-volume ventilation (baseline 680 vs. 738 ml, respectively) (Table 4). During low-tidal-volume ventilation, the decrease in PILV with bronchoconstriction could be explained by a large proportion of airways poorly communicating with conducting airways (i.e., substantial number of airways positioned in a nearly closed state and essentially unventilated and not visible to the MBW). On the basis of the bistable airway model, if increasing tidal volume were to convert airways from a nearly closed to popped open position, it would also be expected that bronchoconstriction would not have the same effect on PILV when ventilating at high tidal volumes, because most airways would already be popped open (due to the higher tidal volume). That PILV was much greater with high than low tidal volume, and that PILV did not change with high-tidal-volume ventilation before and during MCh-induced bronchoconstriction, seems to be consistent with the bistable airway model. The fact that large increases in lung compliance also occurred with increasing tidal volume likely reflects the greater gas volume in the lung with high tidal volume. However, if pleural pressure was more positive during MCh inhalation, this could have led to an overestimate of transpleural pressure and therefore an underestimate of dynamic lung compliance we calculated.

In short, the changes in PILV can be taken to support Anafi and Wilson’s bistable airway model (3) despite no significant changes in the ventilation/volume distribution. Given that ventilation inhomogeneity we report using MBW technique is in relation to lung volume (i.e., Vlah/Vl), it may be that the resulting changes in Vl altered the distribution of ventilation in a manner more complex than we originally predicted. However, it could also be that these findings might be explained by bronchoconstriction in distal airways (not just terminal airways as in Anafi and Wilson’s model) occurring in discrete pockets and unevenly throughout the lung (19). Thus, even if our data
are generally consistent with Anafi and Wilson’s bistable terminal airway model, they do not provide proof that the bistable airway model is solely responsible for the responses observed.

Anafi et al. (2) have also examined ventilation inhomogeneity in humans (assessed by 16-breath MBW) exposed to increasing doses of MCh inducing bronchoconstriction. In those data, curvature of the inert gas washin and the phase III slope (i.e., alveolar plateau) increased as MCh concentration increased and followed the pattern predicted by the bistable airway model (3). In our data, a similar assessment of ventilatory inhomogeneity using curvature of washin (i.e., slope ratio) and phase III slope would be confounded by the large difference in PILV between low and high tidal volume used in the constricted lung (7, 8, 10).

Summary

On the basis of the bistable terminal airway model proposed by Anafi and Wilson (3), where terminal airways in the bronchoconstricted lung exist either in a stable well-open or a nearly closed condition, we predicted that switching from low (9 ml/kg) to high (24 ml/kg) tidal volume would improve V˙A/Q˙ inequality. While Anafi and Wilson’s bistable airway model (3). In our data, a similar assessment of ventilatory inhomogeneity using curvature of washin (i.e., slope ratio) and phase III slope would be confounded by the large difference in PILV between low and high tidal volume used in the constricted lung (7, 8, 10).

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GRANTS

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