Reproduction of MIGET retention and excretion data using a simple mathematical model of gas exchange in lung damage caused by oleic acid infusion

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Rees, S. E., S. Kjærgaard, S. Andreassen, and G. Hedenstierna. Reproduction of MIGET retention and excretion data using a simple mathematical model of gas exchange in seven pigs before and following lung damage caused by oleic acid infusion and subsequently at different levels of positive end-expiratory pressure. The simple model was found to give, on average, a good description of MIGET data, as evaluated by a 2 test on the weighted residual sum of squares resulting from the model fit (P > 0.2). Values of the simple model’s parameters (dead-space volume, shunt, and the fraction of alveolar ventilation going to compartment 2) compared well with the similar MIGET parameters (dead-space volume, shunt, log of the standard deviation of the perfusion, log of the standard deviation of the ventilation), giving values of bias and standard deviation on the differences between dead-space volume and shunt, 0.002 ± 0.002 liter and 7.3 ± 2.1% (% of shunt value), respectively. Values of the fraction of alveolar ventilation going to compartment 2 correlated well with log of the standard deviation of the perfusion (r2 = 0.86) and log of the standard deviation of the ventilation (r2 = 0.92). These results indicate that this simple model provides a good description of lung pathology following oleic acid infusion. It remains to be seen whether physiologically valid values of the simple model parameters can be obtained from clinical experiments varying inspired oxygen fraction. If so, this may indicate a role for simple models in the clinical interpretation of gas exchange.

MATERIALS AND METHODS

Study Protocol

After approval of the local animal ethics committee, seven pigs (weight 27.5 kg, 26.4–31.5, median and range) were anesthetized and mechanically ventilated. After an equilibration period of 45 min, baseline measurements of hemodynamic and ventilatory parameters were taken and a determination of ventilation-perfusion distribution was performed using MIGET. Lung injury was subsequently induced using infusion of oleic acid (further details below). After allowing for a stabilization of the lung injury for 90 min, a series of determinations of V/Q distributions were performed at different PEEP levels and different values of inspiratory-to-expiratory (I:E) ratio.

The study was performed in the experimental laboratory of the Department of Clinical Physiology, Uppsala University Hospital, Uppsala, Sweden.

Anesthesia

As premedication, before transport from the farm, the pigs were given 40 mg of azaperonum (Stresnil, Janssen, Belgium) intramuscularly (im). General anesthesia was induced with 2.2 mg/kg xylazine im (Rompun, Bayer, Leverkusen, Germany) and 6 mg/kg tiletamin/zolazepam im (Zoletil, Boehringer/Ingelheim, Germany).

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The animals were positioned in the supine position and general anesthesia and muscle relaxation was given during the rest of the experiment as a 30 mg·kg\(^{-1}\)·h\(^{-1}\) infusion of ketamine (Veterinaria, Zurich, Switzerland), 2 μg·kg\(^{-1}\)·h\(^{-1}\) fentanyl (Pharmalink), and 50 μg·kg\(^{-1}\)·h\(^{-1}\) pancuronium (Organon Teknika, Boxtel, The Netherlands).

The animals were tracheotomized and ventilated through a cuffed endotracheal tube. Rehydrex (Fresenius Kabi, Uppsala, Sweden) was given at an infusion rate of 10–20 ml·kg\(^{-1}\)·h\(^{-1}\).

A Swan-Ganz catheter and an 18-gauge central venous catheter were introduced in the right internal jugular vein and advanced for measurement of central venous and pulmonary artery pressures. The position of the Swan-Ganz catheter was confirmed using pressure recording. An 18-gauge catheter was introduced in the common carotid artery for measurement of arterial blood pressure. Cardiac output was calculated as the mean of three accepted measurements using the standard thermodilution technique. The measurements of central hemodynamics were performed using a standard monitor (Marquette Electronics, Series 7010, Milwaukee, WI).

**Ventilation**

Volume-controlled ventilation was initiated (Servo 300, Maquet, Solna, Sweden) where tidal volume was set to 10–12 ml/kg. Respiratory frequency was 22/min, I:E ratio was 1:1, and positive end-expiratory pressure (PEEP) was set to 5 cmH\(_2\)O. These settings ensured normocapnia at baseline, i.e., arterial PC\(_{O2}\) was 5.0, 4.5–5.5 kPa (median and range). The settings of tidal volume and respiratory frequency were not changed during the study period.

Inspired and end-tidal values of O\(_2\) and CO\(_2\) were measured continuously by sidestream sampling (gas monitor 1304, Bruel & Kjaer). Mixed expired gases were taken from a gas-mixing chamber, and measurements were taken intermittently.

After stabilization of lung injury, determinations of V\(_{O2}\)/Q\(_{O2}\) distributions were performed at different levels of PEEP, where PEEP was increased from 5 to 10 and 18 cmH\(_2\)O, respectively. On the fourth occasion following lung injury, PEEP was returned to 10 cmH\(_2\)O and the I:E ratio was set to inverse ratio, i.e., 2:1. Thirty minutes after each change in ventilator setting, a new determination of V\(_{O2}\)/Q\(_{O2}\) distribution was performed.

**Lung Injury**

Lung injury was induced by slow (15 min) injection of 0.1–0.15 ml/kg oleic acid (Apoteksbolaget, Gothenburg, Sweden). Titrated doses of adrenaline were used to stabilize arterial blood pressure during the injection.

**V\(_{O2}\)/Q\(_{O2}\) Distribution**

Six inert tracer gases with different solubility in blood (sulfur hexafluoride, ethane, cyclopropane, enflurane, ether, and acetone) were dissolved in isotonic saline and infused in a peripheral vein. Simultaneous samples of mixed venous blood, arterial blood, and mixed expired gas were taken. Inert gases were removed from blood samples by equilibration of blood with nitrogen in a water bath for 45 min, and the concentrations of inert gases in blood and expired gases were measured using gas chromatography (5890, series 2, Hewlett-Packard) in the usual way (21). In addition, mixed venous and arterial blood samples were analyzed for blood gases and acid-base status with the ABL 300 and OSM 3 hemoximeter (Radiometer, Copenhagen, Denmark), and values of mixed expired and end-tidal CO\(_2\) levels were measured in expired gases.

These data were used to obtain the “measured” (m) retention (R\(_{m}\)) and excretion (E\(_{m}\)) of the inert gases (i), where retention is the ratio of the pressure of the inert gas in the arterial (P\(_a\)) to mixed venous (P\(_v\)) blood and excretion is the ratio of the pressure of the inert gas in the mixed expired gases (P\(_{te}\)) to P\(_v\) (19), i.e.,

\[
R_{m}\text{i} = \frac{P_{a}}{P_{v}} \quad \text{and} \quad E_{m}\text{i} = \frac{P_{te}}{P_{v}}
\]

The experimental protocol was approved by the local animal ethics committee, and the study was performed according to the National Research Council guide for “Principles of Laboratory Animal Care.”

**Modeling Methods**

The 50-compartment MIGET model (19) and the simpler model (8) were fitted to measured retention and excretion data obtained from the pig on each of the five different occasions.

**Simple model.** This model, the structure of which is illustrated in Fig. 1, includes parameters describing anatomical dead-space volume (V\(_D\)), pulmonary shunt (shunt), and two compartments receiving both ventilation and perfusion. These two compartments are described by a single parameter (f\(_{A2}\)), which describes the fraction of alveolar ventilation going to compartment 2. The fraction of perfusion to compartment 2 (f\(_{pas2}\)) is fixed at 90% of the nonshunted blood flow to enable the two compartments to simulate a variety of disorders by varying only f\(_{A2}\). By fixing f\(_{pas2}\) at 90%, the ventilation and V\(_{O2}\)/Q\(_{O2}\) ratio of each compartment can be calculated. If the ventilation distribution is also 10 and 90% (i.e., f\(_{A2} = 0.9\)), the model simulates normal gas exchange. The maximal disorder that can be simulated is all ventilation going to 10% of the perfusion (i.e., f\(_{A2} = 0\)). Fixing the perfusion and estimating the ventilation and V\(_{O2}\)/Q\(_{O2}\) ratio is similar to MIGET, where the V\(_{O2}\)/Q\(_{O2}\) of the compartments is fixed and the ventilation and perfusion estimated.

The three parameters of this model (V\(_D\), shunt, and f\(_{A2}\)) can be uniquely identified from retention and excretion data. To do so requires calculation of the V\(_{O2}\)/Q\(_{O2}\) ratio of each of the compartments for the particular value of f\(_{A2}\) and shunt, i.e.,

\[
\frac{V_{O2}}{Q_{O2}} = \frac{V_{A} (1 - f_{A2})}{Q (1 - shunt) (1 - f_{pas2})}
\]

where Q is the cardiac output, and V\(_A\) is the alveolar ventilation, which can be calculated from the respiratory frequency (f) and tidal volume (V\(_T\)) as:

\[
V_{A} = f (V_{T} - V_{D})
\]

Standard equations (19) can then be used to calculate the model-predicted excretion (E\(_{p}\)) and retention (R\(_{p}\)).

![Fig. 1. The structure of the simple model of gas exchange. V\(_D\), dead-space volume; V\(_{O2}\)/Q\(_{O2}\), ventilation/perfusion; f\(_{A2}\), fraction of alveolar ventilation going to compartment 2; f\(_{pas2}\), fraction of perfusion to compartment 2; Q, cardiac output; CvO\(_2\), venous oxygen concentration.](http://jap.physiology.org/)}
where subscripts i and j represent the inert gas and the compartment number, respectively; \( Q_i \), \( V_i \), and \( (V/Q)_i \) are the perfusion, ventilation, and \( V/Q \) ratio, respectively, of compartment j; and \( \lambda_i \) represents the partition coefficient of the inert gas i; \( n \) represents the number of compartments in the model being fitted to the data. For the simple model, \( n = 4 \).

Model fitting is performed using a weighted least squares approach, where values of model parameters were found so as to minimize the difference between measured (m) and model predicted (p) values of excretion and retention according to the following error function:

\[
WRSS = \sum_{i=1}^{6} \frac{(R_{pi} - R_{mi})^2}{\text{var}_i} + \sum_{i=1}^{6} \frac{(E_{pi} - E_{mi})^2}{\text{var}_i}
\]

where \( \text{var}_i \) represents the variance of the measurement error for inert gas i and WRSS represents the weighted residual sum of squares of the model fits.

The standard deviation (SD) and measurement variance of each of the inert gases were calculated from their previously reported (18) coefficient of variations (CV) (sulfur hexafluoride = 5.7%, ethene 2.3%, cyclopropane 1.9%, halothane 2.3%, ether 1.8%, and acetone 2.1%), where

\[
\text{var}_i = \text{SD}_i^2
\]
\[
\text{SD}_i = \text{CV}_i \times (\text{Rm/100})
\]

**MIGET model.** The 50-compartment MIGET model was fitted to the data collected from each pig on each of the five occasions using the standard MIGET computer software (23). The fitting process has been described in detail previously (20) but in brief is similar to that described here for the simple model. The ventilation (\( V_j \)) and perfusion (\( Q_j \)) are considered to be parameters in a model with 50 compartments each with a predefined \( V/Q \) ratio. Instead of fitting to both retention and excretion data, as described here for the simple model, excretion data is used to calculate a second set of retention data. The model is then fitted to the average of these two data sets, with the fitting process taking into consideration the error in measurements of both retention and excretion.

Values of model parameters describing the ventilation and perfusion of the 50 compartments were calculated. These parameters were used to calculate summary statistics describing the mean and log standard deviation (log SD) of the ventilation (log SDV) and perfusion (log SDQ) of the compartments.

**Model-fitting statistics.** The “goodness” of fit of the simple model and the MIGET model to the measured data was determined from the WRSS. To enable comparison between the simple and the MIGET model, the WRSS was calculated from Eq. 6 in both cases. Reporting MIGET errors using Eq. 6 enables transformation of the usual MIGET fitting statistics, i.e., those calculated by fitting retention and transformed excretion, to those describing fit to both retention and excretion. This enables comparison of the simple model with the MIGET model.

For a good fit of a model to data, the average squared difference between measured and model predicted retentions and excretions, i.e., \( (R_{pi} - R_{mi})^2 \) and \( (E_{pi} - E_{mi})^2 \), should be equal to the measurement variance. For six measured retention gases and six measured excretion gases, the expected value (E) of WRSS calculated from Eq. 6 is therefore:

\[
E(\text{WRSS}) = \sum_{i=1}^{6} \frac{(R_{pi} - R_{mi})^2}{\text{var}_i} + \sum_{i=1}^{6} \frac{(E_{pi} - E_{mi})^2}{\text{var}_i} = 12
\]

Any model can be considered a poor fit to retention and excretion data if WRSS is significantly greater than 12. However, the expected value of WRSS is reduced for an increasing number of model parameters. A model with three parameters fitted to retention and excretion data therefore has nine degrees of freedom and an expected WRSS = 12 - 3 = 9. The goodness of fit can then be tested by comparing the value of WRSS obtained from the model fit with that expected using a \( \chi^2 \) test.

For the simple model, the goodness of fit of the model to the data is assessed by performing \( \chi^2 \) test with nine degrees of freedom. For nine degrees of freedom, a WRSS of >16.9 gives a \( \chi^2 \) P value of \( \leq 0.05 \), which is used here as the cutoff value for determining a good model fit.

The MIGET model includes parameters describing each of the 50 compartments included in the model. Due to the large number of parameters a \( \chi^2 \) test has not been performed to assess the goodness of fit of the MIGET models.

Comparisons of values of model parameters before and after lung damage and at various PEEP settings are performed using Kruskal-Wallis tests.

**RESULTS**

Tables 1 and 2 illustrate parameter values and model fitting statistics when fitting the MIGET model (Table 1) and the simple model (Table 2) to retention and excretion data for each pig on each of the five occasions. The goodness of fit is described by the values of WRSS.

For both of the two models, the changes in parameter values during the experiment are as expected. Shunt increases following lung damage (P < 0.05), decreases significantly (P < 0.01) as the PEEP is increased, and returns to a value not statistically different from PEEP = 5 cmH2O when PEEP is returned to 10 cmH2O under inverse-ratio ventilation. \( V_o \) changes very little during the study, being within the range 0.10 to 0.17 liter for all pigs, regardless of occasion or the model being fitted. These rather low values of \( V_o \) do not include apparatus dead space. \( V_o \) never varied more that 0.04 liter during an experiment on any one pig when calculated by either model.

\( V/Q \) mismatch, as indicated by the perfusion dispersion (log SDQ) in the MIGET model, increased significantly after infusion of oleic acid (P < 0.01) and decreased on increased value of PEEP toward normal values at PEEP = 18 cmH2O (P < 0.05). For the simple model, \( V/Q \) mismatch is described by the fA2 parameter. This parameter decreased significantly after infusion of oleic acid (P < 0.01), indicating increased \( V/Q \) mismatch. fA2 increased significantly on increasing the value of PEEP from 5 cmH2O (P < 0.05).

In addition, as illustrated in Fig. 2, values of shunt and \( V_o \) estimated using the simple and the MIGET model are very similar. For \( V_o \), values estimated by the two models are almost identical, with a bias and standard deviation of the difference between these values equal to 0.002 ± 0.002 liter. Shunt estimated from the simple model is higher than that estimated from the MIGET model, with this difference increasing relatively linearly with the value of shunt. The difference can

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1 It has been shown previously (20) that it is possible to uniquely estimate all the parameters included in the MIGET model with the assumption of continuous distributions of flow and perfusion over compartments.
therefore be described as a percentage with a bias and standard deviation, on average 7.3/1000.2.1%.

Figure 3 compares values of MIGET summary parameters with values of fA2, showing linear correlations between log SDV and fA2 ($r^2 = 0.92$) and log SDQ and fA2 ($r^2 = 0.43$). Unlike fA2, log parameters are not obtained by directly fitting to retention and excretion data. Instead, they are a summary of the parameters describing the 50 MIGET compartments using the assumption that ventilation and perfusion are log normally distributed over the compartments. In three situations, shown as crosses on Fig. 3A, perfusion of the MIGET compartments cannot be described as log-normal distributions and the values of log SDQ are rather meaningless. Removing these three points gives a linear correlation between log SDQ and fA2 of $r^2 = 0.86$, and it is likely that a similar correlation would be found between fA2 and other MIGET summary parameters (e.g., DISPR-E), which are not dependent on log-normal distributions of ventilation and perfusion.

On average, the MIGET model is a better fit to the data than the simple model, with an average WRSS equal to 6.7. However, on average, the simple model can also be seen as a good fit to the data, having an average WRSS equal to 9.2, which is not significantly different from the expected value of 9.0 ($P > 0.2$). When the model fits are considered individually, the simple model can be seen as a good fit to the data in all but four occasions, as described by a WRSS not significantly different from 9 at a $P$ value of 0.05. In the four occasions when the simple model was a poor fit to the data, calculated values of shunt exceeded 28%, suggesting that the goodness of fit of the simple model decreases with the severity of the gas exchange abnormality, as illustrated in Fig. 4. No similar relationship was seen for any of the other estimated parameters.

DISCUSSION

MIGET (19) is an experimental method and mathematical model that has become the standard technique when investigating pulmonary gas exchange. Other simple models (6, 8, 9) may provide only a limited view compared with MIGET, but their parameters can be estimated from routine clinical data, making them a possible clinical alternative.

This study has examined the capability of a simpler model to describe MIGET data, i.e., data describing retention and excretion of inert gases in the lungs, in pigs with lung damage.

### Table 1. Values of parameters and WRSS errors when the multiple inert-gas elimination technique model is fitted to inert-gas data

<table>
<thead>
<tr>
<th>Pig</th>
<th>Pig 2</th>
<th>Pig 3</th>
<th>Pig 4</th>
<th>Pig 5</th>
<th>Pig 6</th>
<th>Pig 7</th>
<th>Average Over All Pigs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before</strong></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Shunt, %</td>
<td>4.0</td>
<td>1.5</td>
<td>2.3</td>
<td>1.6</td>
<td>1.1</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Vd, 1</td>
<td>0.13</td>
<td>0.10</td>
<td>0.14</td>
<td>0.11</td>
<td>0.10</td>
<td>0.11</td>
<td>0.12</td>
</tr>
<tr>
<td>Log SDQ</td>
<td>0.63</td>
<td>0.48</td>
<td>0.67</td>
<td>0.56</td>
<td>0.51</td>
<td>0.45</td>
<td>0.45</td>
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<tr>
<td>Log SDV</td>
<td>0.67</td>
<td>0.49</td>
<td>0.76</td>
<td>0.55</td>
<td>0.52</td>
<td>0.45</td>
<td>0.45</td>
</tr>
<tr>
<td>WRSS</td>
<td>7.9</td>
<td>5.9</td>
<td>7.5</td>
<td>2.3</td>
<td>7.7</td>
<td>9.5</td>
<td>8.2</td>
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<tr>
<td><strong>PEEP = 5 cmH2O</strong></td>
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</tr>
<tr>
<td>Shunt, %</td>
<td>45.6</td>
<td>18.1</td>
<td>21.1</td>
<td>7.2</td>
<td>18.1</td>
<td>*</td>
<td>26.2</td>
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<td>Vd, 1</td>
<td>0.16</td>
<td>0.13</td>
<td>0.14</td>
<td>0.14</td>
<td>0.11</td>
<td>0.14</td>
<td>0.15</td>
</tr>
<tr>
<td>Log SDQ</td>
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<td>0.93</td>
<td>0.74</td>
<td>0.69</td>
<td>0.82</td>
<td>*</td>
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<tr>
<td>Log SDV</td>
<td>0.78</td>
<td>0.93</td>
<td>0.67</td>
<td>0.70</td>
<td>0.75</td>
<td>*</td>
<td>0.63</td>
</tr>
<tr>
<td>WRSS</td>
<td>7.1</td>
<td>6.5</td>
<td>6.2</td>
<td>5.8</td>
<td>4.9</td>
<td>*</td>
<td>11.5</td>
</tr>
<tr>
<td><strong>PEEP = 10 cmH2O</strong></td>
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<tr>
<td>Shunt, %</td>
<td>23.4</td>
<td>15.2</td>
<td>15.1</td>
<td>4.5</td>
<td>6.2</td>
<td>37.8</td>
<td>34.9</td>
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<td>0.11</td>
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<td>Log SDQ</td>
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<td>0.84</td>
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<td>Log SDV</td>
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<td>0.73</td>
<td>0.63</td>
<td>0.55</td>
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<td>7.6</td>
<td>3.7</td>
<td>12.8</td>
<td>11.3</td>
<td>13.1</td>
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<td><strong>PEEP = 18 cmH2O</strong></td>
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<td></td>
</tr>
<tr>
<td>Shunt, %</td>
<td>5.3</td>
<td>4.5</td>
<td>2.0</td>
<td>1.9</td>
<td>1.1</td>
<td>21.8</td>
<td>9.2</td>
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<td>0.72</td>
<td>0.46</td>
<td>0.64</td>
<td>0.62</td>
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<td>1.2</td>
<td>15.4</td>
<td>2.2</td>
<td>3.7</td>
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<tr>
<td><strong>PEEP = 10 cmH2O, IE 1:2</strong></td>
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<td></td>
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<tr>
<td>Shunt, %</td>
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<tr>
<td>Log SDQ</td>
<td>0.75</td>
<td>0.63</td>
<td>0.78</td>
<td>0.60</td>
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<td>1.28</td>
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<td>Log SDV</td>
<td>0.68</td>
<td>0.63</td>
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<td>6.2</td>
<td>7.3</td>
<td>13.2</td>
<td>5.9</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Average WRSS, over all pigs and all time points: 6.7

PEEP, positive end-expiratory pressure; Vd, dead-space volume; WRSS, weighted residual sum of square; IE, inspiratory-to-expiratory ratio. *Pig 6, PEEP 5: due to the critical state of the pig, this measurement was not taken.
caused by oleic acid infusion. It has been found that, on average, the simple model is a good fit to the data, in line with the errors expected due to measurement error, and as such the simple model provides an adequate description of lung damage caused by oleic acid infusion. In only 4 of the 34 cases was the model a poor fit, as defined by a $P$ value of $<0.05$. These four cases were within the highest six values of shunt, all with values $>28\%$. This may illustrate that for the most severe gas exchange abnormalities the simple model is not an adequate description of the disorder and that a more complex MIGET type model is required.

Values of parameters estimated by the MIGET and the simple model behaved as expected and in a similar way after lung damage and during changes in PEEP. For VD, values of the two models were almost identical, and for shunt the simple model overestimated shunt by only 7%, meaning that a shunt value of 40.0% would be estimated as 42.8%. Such an error is irrelevant in the clinical context when the patient’s lung function is interpreted and, in the context of this experiment, is very small compared with the changes in shunt seen when PEEP is modified. Values of $fA_2$ correlated well with both log SDV and log SDQ. Indeed, since it is not limited by the assumptions of log normally distributed ventilation and perfusion, it may be a better parameter to summarize the VD abnormalities seen here.

It is important to recognize that, although the simple model provides an adequate description of lung damage caused by

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**Table 2. Values of parameters and WRSS when the simple model is fitted to inert-gas data**

<table>
<thead>
<tr>
<th>Pig</th>
<th>Pig 2</th>
<th>Pig 3</th>
<th>Pig 4</th>
<th>Pig 5</th>
<th>Pig 6</th>
<th>Pig 7</th>
<th>Average, Over All Pigs</th>
<th>$P$ Values of $\chi^2$ Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shunt, %</td>
<td>4.4</td>
<td>1.6</td>
<td>2.5</td>
<td>1.6</td>
<td>1.2</td>
<td>1.9</td>
<td>1.9</td>
<td>2.16</td>
</tr>
<tr>
<td>$V_o$, 1</td>
<td>0.13</td>
<td>0.11</td>
<td>0.13</td>
<td>0.12</td>
<td>0.10</td>
<td>0.12</td>
<td>0.13</td>
<td>0.12</td>
</tr>
<tr>
<td>$fA_2$</td>
<td>0.62</td>
<td>0.73</td>
<td>0.57</td>
<td>0.69</td>
<td>0.71</td>
<td>0.79</td>
<td>0.77</td>
<td>0.70</td>
</tr>
<tr>
<td>WRSS</td>
<td>6.2</td>
<td>1.7</td>
<td>5.1</td>
<td>6.7</td>
<td>7.7</td>
<td>3.2</td>
<td>3.2</td>
<td>4.8</td>
</tr>
</tbody>
</table>

**PEEP = 5 cmH$_2$O**

| Shunt, % | 49.3 | 19.8 | 22.3 | 7.8 | 19.2 | * | 28.3 | 24.5 |
| $V_o$, 1 | 0.16 | 0.13 | 0.14 | 0.14 | 0.12 | * | 0.15 | 0.14 |
| $fA_2$ | 0.54 | 0.48 | 0.64 | 0.60 | 0.57 | * | 0.67 | 0.58 |
| WRSS | 21.5 | 11.8 | 9.4 | 6.9 | 12.6 | * | 18.6 | 13.5 |

**PEEP = 10 cmH$_2$O**

| Shunt, % | 24.7 | 16.5 | 16.2 | 4.7 | 6.7 | 41.8 | 37.3 | 21.1 |
| $V_o$, 1 | 0.16 | 0.13 | 0.14 | 0.14 | 0.12 | 0.14 | 0.15 | 0.14 |
| $fA_2$ | 0.63 | 0.55 | 0.59 | 0.64 | 0.70 | 0.67 | 0.72 | 0.64 |
| WRSS | 8.8 | 7.7 | 11.7 | 8.5 | 12.1 | 17.3 | 17.8 | 12.0 |

**PEEP = 18 cmH$_2$O**

| Shunt, % | 5.7 | 4.93 | 2.14 | 2.06 | 1.21 | 22.9 | 10.0 | 7.0 |
| $V_o$, 1 | 0.17 | 0.12 | 0.15 | 0.15 | 0.13 | 0.14 | 0.16 | 0.15 |
| $fA_2$ | 0.63 | 0.61 | 0.59 | 0.57 | 0.75 | 0.66 | 0.65 | 0.64 |
| WRSS | 8.5 | 5.5 | 9.1 | 8.5 | 10.2 | 1.7 | 7.4 | 7.3 |

**PEEP = 10 cmH$_2$O, IE 1:2**

| Shunt, % | 25.9 | 24.0 | 13.5 | 4.0 | 10.9 | 41.5 | 42.4 | 23.1 |
| $V_o$, 1 | 0.14 | 0.11 | 0.12 | 0.12 | 0.12 | 0.14 | 0.12 | 0.12 |
| $fA_2$ | 0.63 | 0.68 | 0.58 | 0.67 | 0.60 | 0.65 | 0.56 | 0.63 |
| WRSS | 7.6 | 2.6 | 12.0 | 1.9 | 11.7 | 9.9 | 14.8 | 8.6 |

Average WRSS, over all pigs and all time points: 9.2, 0.2

*Pig 6, PEEP 5: due to the critical state of the pig, this measurement was not taken.*

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Fig. 2. Comparison of shunt (left) and $V_o$ parameter (right) estimates from the simple and multiple inert-gas elimination technique (MIGET) model.
oleic acid infusion, there are probably other situations where models of greater complexity are required. The major cause of gas-exchange abnormalities in oleic acid has been shown to be shunt, with some low V/Q ratio, little change in dead space, and a small increase in areas of the lung with a high V/Q ratio (14). It is possible that in other more heterogeneous lung disorders the simple model would be an inadequate representation of MIGET data.

In comparing the ability of the simple and the MIGET model, it is not our intention to suggest that the simple model should be used in preference to the MIGET model in the analysis of multiple inert gas data. Such simple models are not intended to improve our understanding of lung pathophysiology but rather to serve as a tool for describing individual pulmonary gas exchange in patients in situations where limited clinical data are available and models as complex as those included in the MIGET cannot be identified. For example, it has been shown that fA2 and shunt, parameters of the simple model, can be estimated from routine clinical data describing ventilation and blood oxygenation on varying FiO2 (8) and that these can be estimated with reasonable precision from noninvasive measurements in 10–15 min (9, 15). It is possible, therefore, to hypothesize a role for the simple model in quantifying gas-exchange abnormalities in the clinical setting. This role is, however, dependent on the ability of experiments involving variation of FiO2 to characterize gas exchange, and in this context it is necessary to discuss the possible physiological implications of experiments involving variation in FiO2. Variation in FiO2 is known to affect lung physiology, both through absorption atelectasis and hypoxic pulmonary vasoconstriction (HPV). Absorption atelectasis has been shown to occur during anesthesia for preoxygen levels above 80% (5), with oxygenation levels below this not changing the degree of atelectasis substantially. Parameters of the simple model can be identified by varying FiO2 values below 80% (9), and absorption atelectasis should not therefore limit the experimental techniques necessary to estimate the simple model parameters. The effect of FiO2 on HPV and the consequent change in gas exchange is more controversial. Inhibition of HPV has been shown to affect gas exchange either moderately (12) or substantially (2), but HPV inhibition describes a maximal response, and the effects of changes in FiO2 on HPV and gas exchange are likely to be more subtle. Studies using MIGET to investigate the effects of regional or total lung hypoxia have shown only small changes in gas-exchange parameters on varying FiO2 (3, 4). These results are consistent with computer simulations of variations in shunt and log SDQ on varying FiO2 (10, 11), which showed only small changes in shunt (~2–3%) when FiO2 was varied from 0.3 to 1.0 in various patient groups and from 0.4 to 1.0 in acute respiratory distress syndrome. Simulated changes in log SDQ with variation in FiO2 are ~0.2 in all patient groups except acute respiratory distress syndrome, where a variation in FiO2 between 0.4 and 0.7 gives log SDQ variation of a similar order of magnitude, but variation to higher oxygen fraction can give log SDQ changes as much as 0.5. The rationale behind using simple models in the clinic is to quantify lung disorders and monitor patient status from limited changes in FiO2, giving arterial oxygen saturation values in the range of 90–100%. From this perspective, these changes in shunt and log SDQ caused by HPV effects on varying FiO2 could be unimportant.

Further experiments are required to see if the two experimental methods, inert gases or variation in FiO2, give similar values for the simple model parameters. If they do, then model parameters that can be estimated routinely in the clinic by varying FiO2 would be shown to have physiological meaning, at least when describing lung pathology similar to that induced by oleic acid.

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**Fig. 3.** Comparison of the estimated values of log standard deviation of the perfusion (logSDQ; A) and ventilation (logSDV; B) of the compartments with fA2.

**Fig. 4.** Values of weighted residual sum of squares (WRSS) for model fits performed using the simple model, plotted against the estimated shunt values obtained from these fits. The horizontal line indicates a WRSS = 16.9, i.e., the WRSS was associated with a cutoff P value equal to 0.05 on a χ² test with 9 degrees of freedom.

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GRANTS

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