Effect of changes in arterial-mixed venous oxygen content difference ($C(a-\bar{v})O_2$) on indices of pulmonary oxygen transfer in a model ARDS lung²,²²

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Many indices are used to quantify pulmonary oxygen transfer. Indices that use only measurements from arterial blood and inspired gas assume a constant $C(a-\bar{v})O_2$. Though variations in $C(a-\bar{v})O_2$ are recognized, indices such as $P_aO_2/F_IO_2$ remain popular and are often considered the best measure of pulmonary oxygen transfer in critically ill patients. This study estimated the effect of within-subject variations in $C(a-\bar{v})O_2$ and $F_IO_2$ on venous admixture ($Qs/Qt$), the calculated oxygen content difference between end-capillary and arterial blood ($Cc'-O_2-CaO_2$), the alveolar–arterial oxygen tension gradient ($P(A-a)O_2$) and $P_aO_2/F_IO_2$, using a validated lung model of acute respiratory distress syndrome (ARDS). All four indices showed changes with $F_IO_2$ and $C(a-\bar{v})O_2$, although the magnitude of changes in $Qs/Qt$ was clinically unimportant (<2%). The other three indices showed larger variations that may potentially be misleading. At an $F_IO_2$ of 0.7, $P_aO_2/F_IO_2$ varied between 18 and 10 kPa and at an $F_IO_2$ of 0.9 the ratio varied between 22 and 8 kPa. These changes, which were unrelated to underlying lung pathology, are sufficiently large to result in misclassification on the gas exchange scale suggested by the American European Consensus Conference on ARDS. This study shows there is no reliable alternative to $Qs/Qt$ to quantify pulmonary oxygen transfer in critically ill patients.

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Several oxygen tension and content-based indices are used to quantify pulmonary oxygen transfer. Tension-based indices include the alveolar–arterial oxygen tension gradient ($P(A-a)O_2$), the ratio ($P_aO_2/F_IO_2$) between arterial oxygen tension ($P_aO_2$) and fractional inspired oxygen ($F_IO_2$), the respiratory index ($P(A-a)O_2/PaO_2$) and the arterial–alveolar oxygen tension ratio ($P_aO_2/PaO_2$). Indices such as venous admixture ($Qs/Qt$), the estimated shunt fraction (which gives the arterial–mixed venous oxygen content difference a fixed value) and the calculated content difference between end-capillary and arterial blood ($Cc'-O_2-CaO_2$) are based on oxygen content. The relationship between partial pressure and oxygen content in blood is non-linear and therefore indices that use oxygen tension may be disproportionately dependent on $F_IO_2$, particularly in patients with intrapulmonary shunting.¹⁻³ The relationship between $Qs/Qt$ and $F_IO_2$ is also not straightforward. Douglas et al. showed that $Qs/Qt$ was largest with $F_IO_2=0.21$, least with $F_IO_2$ from 0.4 to 0.6 and increased again for $F_IO_2>0.6$.⁴ Gowda et al. showed that variations in $Qs/Qt$ related to $F_IO_2$ were directly proportional to the fraction of cardiac output perfusing alveolar units with a low ventilation/perfusion ratio ($V/Q$).⁵

The difference in oxygen content between arterial and mixed venous blood ($C(a-\bar{v})O_2$) is an important variable in the assessment of pulmonary oxygen transfer. Although considerable within- and between-patient variability is


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common in critical illness, indices such as $P_{aO_2}/F_{IO_2}$ remain popular for clinical and research purposes. Furthermore, the inclusion of $P_{aO_2}/F_{IO_2}$ in the American European Consensus Conference recommendations on acute respiratory distress syndrome (ARDS) has led to the widespread impression that the $P_{aO_2}/F_{IO_2}$ ratio is the preferred method of assessing pulmonary oxygen transfer in clinical studies. For example, in a recent multicentre trial on inhaled nitric oxide, the efficiency of pulmonary oxygen transfer was assessed over several days using $P_{aO_2}/F_{IO_2}$, no data or comment being provided on variations in mixed venous oxygen content that may have influenced the findings. This approach compromises the critical evaluation of the effects of a given intervention on pulmonary oxygen transfer.

Direct assessment of the effect of $C(a\text{-}\overline{V}_O_2)$ involves manipulation of the delicate physiological balance that is frequently seen in critically ill patients, and raises difficult ethical issues. Mathematical models have therefore been considered appropriate tools to address similar problems. Such models require formal validation if conclusions are to receive wider acceptance.

This study was therefore undertaken, with the following objectives: (i) to describe and validate a mathematical model of an ARDS lung; and (ii) to use the above model in a theoretical study evaluating the effect of $C(a\text{-}\overline{V}_O_2)$ and $F_{IO_2}$ on four commonly used indices of pulmonary oxygen transfer.

Materials and methods

The study was carried out in two stages: in stage 1 a lung model of ARDS was described and validated, and stage 2 consisted of a theoretical appraisal of four commonly used indices of pulmonary oxygen transfer.

Stage 1: lung model of ARDS

To derive a lung model of ARDS, a multicompartment model of a normal lung was modified by incorporating data on shunt, dead space and $V/Q$ scatter obtained by Dantzker et al. in patients with ARDS (Appendix 1). Validity of the model was verified using new data collected from 10 consecutive patients treated for ARDS in our intensive care unit. After institutional approval had been obtained, between four and seven sets of arterial and mixed venous blood gas measurements and cardiac output estimations were obtained from each patient. The following measurements were recorded: $P_{aO_2}$, $P_{aCO_2}$, arterial haemoglobin saturation ($S_{aO_2}$), mixed venous oxygen tension ($P_{vO_2}$), mixed venous carbon dioxide tension ($P_{vCO_2}$), mixed venous haemoglobin saturation ($S_{vO_2}$), haemoglobin concentration (Hb), venous admixture ($Q \text{/}Qt$), cardiac output and fractional inspired oxygen ($F_{IO_2}$). The position of the pulmonary artery catheter was confirmed radiologically and all blood gas/cardiac output measurements were made by trained nursing staff. The blood gas machine and co-oximeter (BGE and IL282 respectively; Instrumentation Laboratory, Milan, Italy) were calibrated according to the manufacturer’s guidelines. Cardiac output, $Qs/Qt$, Hb, $P_{vO_2}$, $S_{vO_2}$, $P_{vCO_2}$ and $F_{IO_2}$ for each set of readings were used as input variables to obtain a predicted $P_{aO_2}$ through an iterative process.

$P_{aO_2}$ predicted by the model and the true (measured) $P_{aO_2}$ were compared by analysis of covariance (ANCOVA) to determine the within-subject correlation coefficient ($r$). Agreement was assessed using the intraclass correlation coefficient ($r_i$) and Bland–Altman analysis.

Stage 2: evaluation of indices of pulmonary oxygen transfer

After validation, the lung model was used to derive four commonly used indices of pulmonary oxygen transfer ($Qs/Qt$, $C(a\text{-}\overline{V}_O_2)$, $P(a\text{-}\overline{a})_O_2$ and $P_{aO_2}/F_{IO_2}$) as $F_{IO_2}$ was varied between 0.21 and 1.0. We assumed constant minute ventilation, temperature (37°C), acid–base balance (base excess=0) and respiratory exchange ratio (RER=0.85) and a normal oxygen dissociation curve ($P_{50}=3.6$ kPa). The oxygen content of arterial blood ($C(aO_2)$) was determined by weighting of compartmental perfusion and ventilation. Mixed venous oxygen content ($C(vO_2)$) was derived from $C(aO_2)$ and peripheral oxygen extraction. End-capillary oxygen content was derived in the customary fashion using the alveolar gas equation. The process was repeated for three fixed $C(a\text{-}\overline{V}_O_2)$ values: 22.0, 35.6 and 49.2 ml litre$^{-1}$. This range represents the mean ± two within-subject standard deviations for $C(a\text{-}\overline{V}_O_2)$ in critically ill patients. Patient data used for validation of the model were not used in deriving any of the indices.

Results

Stage 1: lung model

Blood gas data from the 10 ARDS patients used in the validation of the model are given in Appendix 2. Figure 1 shows the distribution of $V/Q$ in the model lung. Shunt ($V/Q < 0.005$) and dead space ($V/Q > 100$) were 40.7 and 28.8% respectively. Approximately 10% of cardiac output perfused units with $V/Q < 0.1$. ANCOVA returned $r=0.93$ ($r^2=0.86$, $P<0.001$). Intraclass correlation assessed by $r_i$ was 0.91. Bland–Altman analysis showed a bias (measured minus predicted) of 1 kPa with limits of agreement of −2 to +4 kPa.

Stage 2: evaluation of indices of pulmonary oxygen transfer

Venous admixture ($Qs/Qt$)

Figure 2 shows changes in $Qs/Qt$ when $F_{IO_2}$ was altered from 0.21 to 1.0. In the entire range of $F_{IO_2}$, the maximum
difference noted in $\dot{Q}s/\dot{Q}t$ due to variation in $C(a-\overline{v})_O2$ was approximately 1%, with lesser changes noted at higher $FIO_2$ ($FIO_2=0.5-0.9$). At constant $C(a-\overline{v})_O2$, the change in $\dot{Q}s/\dot{Q}t$ due to $FIO_2$ was less than 2%, and these differences were also less at higher $FIO_2$.

Difference between end-capillary and arterial oxygen content ($C(\alpha-\overline{v})_O2-CaO2$)

Figure 3 shows the changes in $C(c'-\overline{v})_O2-CaO2$. All three curves showed a similar trend, with a reduction in $C(c'-\overline{v})_O2-CaO2$ by a maximum of 1.1 ml litre$^{-1}$ when $FIO_2$ was increased from 0.21 to 1.0. Approximately 90% (1.0 ml litre$^{-1}$) of this change occurred in the $FIO_2$ range 0.21-0.5. However, the difference between the curves at different levels of $C(a-\overline{v})_O2$ was up to 19 ml litre$^{-1}$.

Ratio of $PaO_2$ to $FIO_2$

Figure 4 shows the relationship between $PaO_2/FIO_2$, $FIO_2$, and $C(a-\overline{v})_O2$. When $FIO_2$ was increased from 0.21 to 0.9 the corresponding ratio decreased from 29 to 11 kPa ($C(a-\overline{v})_O2=35.6$ ml litre$^{-1}$). The curves tended to flatten out in the $FIO_2$ range of 0.5-0.8, changes being less than 5 kPa for all three curves. The relationship with $FIO_2$ was more complex when $C(a-\overline{v})_O2$ was low (22 ml litre$^{-1}$), as the ratio increased again when $FIO_2>0.7$.

Alveolar–arterial oxygen tension gradient ($P(A-a)O2$)

Figure 5 summarizes the relationship between $P(A-a)O2$, $FIO_2$, and $C(a-\overline{v})_O2$. The changes in $P(A-a)O2$ due to $C(a-\overline{v})_O2$ ranged between 2.1 and 12.2 kPa. The changes with $FIO_2$ were considerable, increased $FIO_2$ resulting in a proportionate increase in $P(A-a)O2$.

Discussion

The inability to define a unique continuous distribution of $V/Q$ scatter using inert gas elimination is well recog-
Nevertheless, multicompartment models represent the extensive spread of $V/Q$ scatter seen in disease states satisfactorily and are accepted tools in pulmonary research. Measured $Q_s/Q_t$ in the data used for validation of the model (Appendix 2) includes true shunt and a further contribution due to $V/Q$ mismatch. This fraction was considered equal to the true shunt in each patient as it was not possible to separate the two components. Because $F_{IO_2}$ was always >0.5, any contribution from $V/Q$ mismatch to measured $Q_s/Q_t$ is expected to be minimal. This explains the good correlation between measured and predicted $P_{aO_2}$ ($r=0.93$).

The model does not account for effects of $F_{IO_2}$ on pulmonary vascular autoregulation, which is an important physiological compensatory mechanism and may account for the underestimation of $P_{aO_2}$ by the model. The effects of metabolic acidosis/alkalosis, temperature and 2,3-diphosphoglycerate (2,3-DPG) on the oxyhaemoglobin dissociation curve and the effects of abnormal forms of haemoglobin on pulmonary oxygen transfer have also not been modelled. The above factors may account for the relatively wide limits of agreement seen in the study. In spite of these limitations, the model is sufficiently accurate ($r=0.93, r_i=0.91, \text{bias}=+1 \text{ kPa}, \text{SD}=1.5 \text{ kPa}$) to justify its use. The difficulties in measuring high $P_{aO_2}$ using standard oxygen electrodes is well known. However, the range of $P_{aO_2}$ values in our patients (3.3–27 kPa) was well within the stipulated measuring range for the blood gas machine.

**Fig 3** $C(a-ar{v})_{O_2}$ as a function of $F_{IO_2}$.

**Fig 4** $P_{aO_2}/F_{IO_2}$ as a function of $F_{IO_2}$. 
(0–106 kPa). Therefore, measurement errors are unlikely to have contributed to any of the observed discrepancies. In deriving the indices of pulmonary oxygen transfer, a fixed shunt (true shunt) was assumed despite changes in $F_{\text{IO}_2}$. It is well recognized that in patients with a large contribution from areas with $V/Q$ mismatch, changes in $F_{\text{IO}_2}$ lead to changes in $Q_s/Q_t$. Our model describes these changes well (Fig. 2). The absorption atelectasis that may occur in the presence of high $F_{\text{IO}_2}$, on the other hand, may lead to increased shunting. However in order to quantify the effects of extrapulmonary factors such as $F_{\text{IO}_2}$ and $C(a-v)O_2$, it was necessary to hold the intrapulmonary factors (shunt, $V/Q$ scatter and dead space) constant. Absorption atelectasis was therefore not included in the present model.

Oxygen tension based indices

Indices based on $P_{\text{aO}_2}$ may be popular because they are simple. In patients with normal lungs, stable cardiovascular status and constant peripheral oxygen extraction, good correlation has been demonstrated between $Q_s/Q_t$ and $P_{\text{aO}_2}/F_{\text{IO}_2}$, or $P(A-a)O_2$. In a theoretical study, Rasanen et al. demonstrated the relationship between $Q_s/Q_t$ and these three indices to be non-linear and greatly influenced by $F_{\text{IO}_2}$ and $C(a-v)O_2$. The range of $C(a-v)O_2$ used by Rasanen et al. (20–80 ml litre$^{-1}$) was, however, arbitrary and therefore the study failed to convince many clinicians of the disadvantages of indices such as $P_{\text{aO}_2}/F_{\text{IO}_2}$. We have therefore revisited the subject to determine whether the range of variation that is known to occur within individual patients is small enough to justify the continued use of indices such as $P_{\text{aO}_2}/F_{\text{IO}_2}$.

The disadvantage of using $P(A-a)O_2$ to quantify pulmonary oxygen transfer is evident from Fig. 5. On the other hand, $P_{\text{aO}_2}/F_{\text{IO}_2}$ is a simple index and has gained widespread acceptance for clinical and research purposes. A review of the literature shows conflicting data on the accuracy with which $P_{\text{aO}_2}/F_{\text{IO}_2}$ reflects $Q_s/Q_t$. Some studies have shown good correlation in groups of critically ill patients, and the evidence presented forms the basis for its current popular use. Other studies, however, show poor correlation. Because of the inclusion of multiple readings obtained from individual patients with a variety of illnesses, the correlation coefficients cited in studies comparing $P_{\text{aO}_2}/F_{\text{IO}_2}$ and $Q_s/Q_t$ may be erroneously high and not reflect the true relationship between the two indices. Nevertheless, there is no doubt that $P_{\text{aO}_2}/F_{\text{IO}_2}$ is a useful clinical parameter as long as the underlying assumptions are appreciated and regularly evaluated. In the present study most of the observed $F_{\text{IO}_2}$-related variations were at low $F_{\text{IO}_2}$, and in the 0.5–0.8 range variability was less than 5 kPa. The relationship between $P_{\text{aO}_2}/F_{\text{IO}_2}$ and $C(a-v)O_2$ is more complex when $C(a-v)O_2$ is low (22 ml litre$^{-1}$), a condition likely in septic patients with a hyperdynamic circulation. Under these circumstances, $P_{\text{aO}_2}/F_{\text{IO}_2}$ increases when $F_{\text{IO}_2}>0.7$. The problem may be compounded by changes in $C(a-v)O_2$ at the same time. For example, when $F_{\text{IO}_2}=0.7$ the ratio varied between 18 and 10 kPa with changes in $C(a-v)O_2$, and when $F_{\text{IO}_2}=0.9$ the ratio varied between 22 and 8 kPa. These changes are large enough to result in misclassification on the gas exchange scale suggested by the American European Consensus Conference. Despite this, a recent review quoting Gowda et al. states that the $P_{\text{aO}_2}/F_{\text{IO}_2}$ ratio is ‘the preferred method of assessing gas exchange in clinical trials’. The group of patients represented by Gowda et al. in their theoretical models, in reality, represents patients likely to require many interventions that lead to changes in $C(a-v)O_2$. This limits the usefulness of $P_{\text{aO}_2}/F_{\text{IO}_2}$.
in this patient group. What is not disputed is that $P_{aO_2}/FIO_2$ is not an objective marker of pulmonary oxygen transfer in patients with haemodynamic and metabolic instability. It therefore follows that $P_{aO_2}/FIO_2$ in ARDS should be interpreted with caution, particularly when pulmonary oxygen transfer is assessed over several days.

Indices based on oxygen content

$Q_s/Qt$ derived at the clinically chosen $FIO_2$ is a widely used method and has been used as the gold standard measure of pulmonary oxygen transfer.\textsuperscript{6,7,19,23} By comparing calculated $Q_s/Qt$ at $FIO_2$ of 0.5 and 1.0, Gowda et al. demonstrated that the variability in $Q_s/Qt$ (related to $FIO_2$) was directly proportional to the fraction of cardiac output perfusing alveolar units with $V/Q$ ratios of less than 0.1.\textsuperscript{5} Therefore, the relative contribution to $Q_s/Qt$ from shunt and areas of low but finite $V/Q$ is an important determinant of the variability in $Q_s/Qt$ with $FIO_2$. In the present study, although approximately 10% of cardiac output perfused alveolar units with $V/Q \leq 0.1$, the magnitude of changes in $Q_s/Qt$ due to variation in $C(a-V)O_2$, or $FIO_2$ was small (<2%) and clinically unimportant. Rossaint et al.\textsuperscript{17} demonstrated a similar distribution of ventilation and perfusion in a study of 12 ARDS patients (shunt, 35%; flow to areas of lung with $V/Q < 0.1$, 10%; dead space, 34%). In a more recent study, Santos et al. confirmed that the primary mechanism for impaired pulmonary oxygen transfer in patients with acute lung injury was right-to-left shunt and blood flow to alveolar units with $V/Q < 0.1$ less than 10%.\textsuperscript{28} In the absence of mixed venous blood samples, Kerr in 1975\textsuperscript{29} and Drummond and Zhong in 1983\textsuperscript{30} used $Cc'O_2-Cao_2$ to quantify pulmonary oxygen transfer in clinical studies conducted in stable patients over relatively short periods. The present study confirms that variation in $C(a-V)O_2$ limits its clinical application.

The ventilation/perfusion distribution shown in our model has important implications in the management of patients with ARDS. Simply increasing $FIO_2$ beyond 0.5 may not achieve worthwhile improvements in arterial oxygen content, because the contribution of $V/Q$ mismatch to $Q_s/Qt$ is almost completely eliminated at an $FIO_2$ of approximately 0.5.\textsuperscript{3} If right-to-left shunting is the dominant cause of abnormal pulmonary oxygen transfer, then further increases in $FIO_2$ do not compensate for this defect.\textsuperscript{3} Measures that are intended to achieve a reduction in shunt, such as higher positive end-expiratory pressure and prone position, are more appropriate and should be considered early in patients with ARDS if adequate arterial oxygen content is not achieved with $FIO_2$ above 0.5.

In conclusion, in ARDS there may be marked cardio-respiratory and metabolic abnormalities resulting from the underlying disease and/or interventions. In such patients, there is no reliable substitute for $Q_s/Qt$ to quantify defects in pulmonary oxygen transfer. There is also a need to clarify the criteria used in research in which interventions that may influence pulmonary oxygen transfer are assessed over relatively long periods. We believe that the inclusion of $P_{aO_2}/FIO_2$ in the American European Consensus Conference recommendations without qualification may lead to its inappropriate use.

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**Appendix 1: ARDS lung model**

**Modelling of pulmonary oxygen transfer**

A numerical method based on the early work on this subject by Wallace Fenn et al. and described in greater detail by West\textsuperscript{31} was used to calculate gas exchange in individual lung compartments. The oxygen–carbon dioxide ($O_2–CO_2$) diagram and the ventilation/perfusion ratio $V/\dot{Q}$ line (where $V$ is the alveolar ventilation and $\dot{Q}$ is the pulmonary capillary blood flow), which describes all possible alveolar compartments that can exist within a lung at any given time, forms the cornerstone of this model. In order to derive the ventilation/perfusion ratio line, it is necessary to solve the following $V/\dot{Q}$ ratio equation:\textsuperscript{32}

$$\frac{V}{\dot{Q}} = \frac{6.6(CvCO_2 - CCO_2^{*})}{PA_{CO_2}}$$

where $CvCO_2$ and $CCO_2^{*}$ refer to the carbon dioxide concentration of mixed venous blood and end-capillary blood respectively, in units of ml dl\textsuperscript{-1}, and $PA_{CO_2}$ is the alveolar partial pressure of carbon dioxide in mm Hg. In solving the above equation it is necessary to take into account the Haldane and Bohr effect, whereby the relationship between partial pressure and the end-capillary concentrations of carbon dioxide and oxygen in the blood draining from each compartment alters with changes in $V/\dot{Q}$. Because the equations defining the oxygen and carbon dioxide dissociation curves are non-linear and interdependent, an iterative procedure incorporating a root-finding algorithm based on bracketing and bisection\textsuperscript{33} was used in deriving the solution. The method was used to find a common solution for compartmental ventilation, compartmental blood flow and the end-capillary concentration of oxygen and carbon dioxide in the blood draining from each of the compartments. This iterative process was stopped when the oxygen saturation on the oxygen and carbon dioxide dissociation curves agreed within 0.001%.

The oxygen dissociation curve was described by the Hill function:\textsuperscript{34}
Reference values of $n=2.7$ and $P_{50}=3.576$ kPa (26.8 mm Hg) were used, based on the work of Siggard-Anderson.\cite{35,36}

The alveolar oxygen tension $P_{A\text{O}_2}$ in each of the compartments for the respiratory exchange ratio (R) associated with each $V_{A}/Q_{C}$ and $P_{A\text{CO}_2}$ was calculated from the alveolar gas equation:\cite{32}

$$SO_2 = \frac{P_{O_2}^n}{P_{O_2}^n + P_{50}^n} \times 100$$

(where $SO_2$ is the haemoglobin oxygen saturation (%) and $P_{O_2}$ is the partial pressure of oxygen in the blood).
In deriving the oxygen saturation of end-capillary blood, the transformation described by Kelman\(^3\) was used to calculate a value of \(P_{50}'\) (\(P'_{50}\)) for the oxygen dissociation curve to account for different values of saturation and partial pressure of carbon dioxide in the blood (\(PcO_2\)) from the equation:

\[
P'_{50} = P_{50} \times 10^{-[0.4(pH -7.4)+0.06(ln 40-ln Pco2)]}
\]

where pH is calculated from the equation:

\[
pH=7.59+0.0031 \times Hb(1-SO_2)-0.2741 \times ln(PCO/20)
\]

The shape of the curve was assumed to be invariant under this translation and the effects of pH caused by metabolic changes, temperature and 2,3-DPG were omitted from the equation. Similar Kelman transformations for the CO\(_2\) dissociation curves were carried out for each alveolar compartment.\(^3\) Because oxygen saturation is not known, it was calculated, for each alveolar compartment, by an iterative process designed to terminate when the values of oxygen content, carbon dioxide content, \(P_{CO_2}\), \(P_{O_2}\) and oxygen saturation satisfy both the oxygen and carbon dioxide dissociation curves.

**Distribution of lung compartments in the model**

For each lung compartment, alveolar ventilation may be described by the logarithmic normal distribution function\(^3\) multiplied by a scaling constant:

\[
f(x) = k \frac{1}{\sigma \sqrt{2\pi}} e^{-\frac{1}{2} \left(\frac{x - \mu}{\sigma}\right)^2}
\]

(where \(f(x)=\bar{V}_A, x=\ln(V_A/QC), \mu\) is the log mean value and \(\sigma\) is the log standard deviation of the ventilation/perfusion distribution with scaling constant \(k\)).

Based on the data provided by Dantzker et al.,\(^12\) the following values were used to describe the ARDS lung: \(\sigma=0.43, \mu=2.921\) and \(k=2.13\). Alveolar ventilation of 9.28 litres (dead space 3.75 litres) and cardiac output of 6.65 litres (shunt 2.71 litres) were derived from Dantzker et al.\(^12\). Following Lee et al.,\(^15\) the lung compartments were spaced evenly on a logarithmic scale of 0.1 log\(_{10}\) units from \(-2\) to +2, which covers the range of \(V_A/QC\) from 0.01 to 100 in 41 compartments. Shunt and dead space were included as two separate compartments, resulting in a total of 43 compartments in the entire model. Because for each compartment the ventilation \(V_A\) is known and \(V_A/QC\) is known, the corresponding \(QC\) may be derived from equation 6. Thus, the weighted sum of the end-capillary oxygen concentration for each lung compartment with the associated \(V_A/QC\), \(R\), \(P_{ACO_2}\), \(P_{AO_2}\) and \(CcO_2\) from all the compartments accounts for the gas exchange from the entire lung model.

**Appendix 2. Data used to validate ARDS lung model**

Data used to validate the ARDS lung model are given in Table 1.
Indices of pulmonary oxygen transfer

Measured \( P_aO_2 \) and \( P_aCO_2 \) predicted from ARDS lung model (kPa) are shown in Table 2.

References