Bedside Estimation of Nonaerated Lung Tissue Using Blood Gas Analysis*

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Objectives: Studies correlating the arterial partial pressure of oxygen to the fraction of nonaerated lung assessed by CT shunt yielded inconsistent results. We systematically analyzed this relationship and scrutinized key methodological factors that may compromise it. We hypothesized that both physiological shunt and the ratio between PaO2 and the fraction of inspired oxygen enable estimation of CT shunt at the bedside.

Design: Prospective observational clinical and laboratory animal investigations.

Setting: ICUs (University Hospital Leipzig, Germany) and Experimental Pulmonology Laboratory (University of São Paulo, Brazil).

Patients, Subjects and Interventions: Whole-lung CT and arterial blood gases were acquired simultaneously in 77 patients mechanically ventilated with pure oxygen. A subgroup of 28 patients was submitted to different FiO2. We also studied 19 patients who underwent repeat CT. Furthermore we studied ten pigs with acute lung injury at multiple airway pressures, as well as a theoretical model relating PaO2 and physiological shunt. We logarithmically transformed the PaO2/FiO2 to change this nonlinear relationship into a linear regression problem.

Measurements and Main Results: We observed strong linear correlations between Riley’s approximation of physiological shunt and CT shunt (R² = 0.84) and between logarithmically transformed PaO2/FiO2 and CT shunt (R² = 0.86), allowing us to construct a look-up table with prediction intervals. Strong linear correlations were also demonstrated within-patients (R² = 0.95). Correlations were significantly improved by the following methodological issues: measurement of PaO2/FiO2 during pure oxygen ventilation, use of logarithmically transformed PaO2/FiO2 instead of the “raw” PaO2/FiO2, quantification of nonaerated lung as percentage of total lung mass and definition of nonaerated lung by the [-200 to +100] Hounsfield Units interval, which includes shunting units within less opacified lung regions.

Conclusion: During pure oxygen ventilation, logarithmically transformed PaO2/FiO2 allows estimation of CT shunt and its changes in patients during systemic inflammation. Relevant intrapulmonary shunting seems to occur in lung regions with CT numbers between [-200 and +100] Hounsfield Units. (Crit Care Med 2013; 41:732–743)

Key Words: atelectasis; blood gas analysis; mechanical ventilation; pulmonary gas exchange; respiratory failure; spiral computer-assisted tomography

*See also p. 912.
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Proper estimation of the amount of nonaerated lung at the bedside could help clinicians to optimize ventilator settings, for instance by providing an estimate of the lung fraction unavailable for ventilation. Physicians could thus better “size” the lung and choose individualized ventilator settings (1–4). Another application would be the assessment of lung recruitment in response to an increase in airway pressures (5–7), which could help in evaluating the effect of higher positive end-expiratory pressure (PEEP) or recruitment maneuvers.

The amount of nonaerated lung relative to the total lung size may be precisely quantified by CT (1, 8–10); alternatively, it could be inferred from measurements of pulmonary shunt assuming blunted hypoxic pulmonary vasoconstriction. In clinical practice, assessment of pulmonary shunt has often been replaced by measuring the ratio of PaO₂ to FIO₂, which can less invasively be obtained with standard monitoring equipment (11–16). The suitability of both pulmonary shunt and PaO₂/FIO₂ for this purpose, however, is controversial because studies trying to correlate PaO₂/FIO₂ to the pulmonary shunt or to the amount of nonaerated lung quantified by CT shunt yielded inconsistent results (5, 12, 14–23). Differences in regional perfusion (10, 24–27), the nonlinear relationship between PaO₂/FIO₂ and pulmonary shunt (28–31), the use of different FIO₂ (12, 32–40), and the differences in CT methods (1, 12, 18, 27, 41, 42) could help explain some of these inconsistencies.

This study aimed to test the suitability of PaO₂/FIO₂ as a bedside indicator of nonaerated lung in mechanically ventilated patients in the acute inflammatory phase of disease. We studied theoretical, experimental, and clinical data from a heterogeneous cohort of mechanically ventilated patients. We hypothesized that strong correlations exist between pulmonary shunt and CT shunt and between PaO₂/FIO₂ and CT shunt, provided that key methodological issues, not systematically addressed in previous studies, are considered. Demonstration of these relationships would allow estimating the amount of nonaerated lung from simple PaO₂/FIO₂ measurements.

Some results of this study have been previously reported as abstracts (43, 44).

**MATERIALS AND METHODS**

Because we suspected that important methodological issues have impared previous attempts to show a good correlation between PaO₂/FIO₂ and CT shunt, we scrutinized potential sources of error, such as the nonlinear relationship between PaO₂/FIO₂ and pulmonary shunt, PaO₂/FIO₂ measurement at nonstandardized FIO₂, use of the traditional “percent-volume” variable instead of the “percent mass” of nonaerated lung to quantify CT shunt, and failure of the traditional CT-definition, that is, [–100 to +100] Hounsfield Units (HU), to detect all relevant nonaerated and thus shunting lung units (18–20, 27, 42, 45).

Further details on methods (i.e., handling of patients, CT scanning, animal experiments, and theoretical model) are presented as supplemental data (Supplemental Digital Content 1, http://links.lww.com/CCM/A553).

**Definitions**

**Physiological Shunt.** It refers to the venous admixture calculated by standard formulae using measured oxygen contents of mixed venous and arterial blood, during 100% oxygen ventilation, in order to eliminate the influence of poorly ventilated areas (18, 33, 37, 38, 46–50).

**Riley’s Approximation to Physiological Shunt.** When mixed venous blood is unavailable, empirical values for the arterio-venous difference in oxygen content (∆CₐᵥO₂, proposals ranging from 3.5 to 5 mL/dL) provide an approximation of venous admixture (30, 47, 51–53). We used a fixed ∆CₐᵥO₂ = 4.3 mL/dL as suggested by Riley (53).

**CT Shunt.** It refers to the CT-quantified percentage of nonaerated lung, where pulmonary shunting is supposed to occur. We avoided the term anatomical shunt (5), not wanting to conflict with classical definitions of shunt through bronchial or Thebesian veins (47, 52–54).

**Rationale and Hypotheses**

We test one main hypothesis and four subhypotheses. Assuming blunted hypoxic pulmonary vasoconstriction during systemic inflammation and pure oxygen ventilation (24–26), our main hypothesis was the existence of a strong, linear correlation between physiological shunt and CT shunt, which are surrogates of the nonaerated lung fraction. To test this main hypothesis in a large database where mixed venous blood gases were unavailable, we had to use Riley’s approximation instead of physiological shunt. Consequently, we had to confirm a strong correlation between Riley’s approximation and physiological shunt during pure oxygen ventilation (first subhypothesis). We studied the latter relationship using a theoretical model simulating variable clinical conditions, as well as experimental data (pigs with acute lung injury) representing varying amounts of nonaerated lung and cardiac output.

If ∆CₐᵥO₂ is nearly constant, the variability in Riley’s approximation during pure oxygen ventilation should be mainly explained by changes in the alveolar-capillary gradient (diffusion component) or in the capillary-arterial gradient (venous admixture component) in the partial pressure of oxygen, both of which are reflected by the PaO₂/FIO₂ if the PaCO₂ is close to normal. Consequently, given a strong correlation between Riley’s approximation and CT shunt (second subhypothesis), there should be a strong relationship between PaO₂/FIO₂ (pure oxygen) and CT shunt. Due to the shape of the oxygen–hemoglobin dissociation curve, variations in physiological shunt cause negative nonlinear (near exponential) variations in PaO₂/FIO₂ (29–31). Thus, our third subhypothesis was that the natural logarithmic transformation of PaO₂/FIO₂ (lnPaO₂/FIO₂) could roughly linearize the relationship to physiological shunt. As a result of transforming this nonlinear relationship into a linear regression problem, we should be able to demonstrate a strong linear relationship between lnPaO₂/FIO₂ (pure oxygen) and CT shunt (fourth subhypothesis [12, 55]).

**Modeling the Relationship Between Physiological Shunt and PaO₂**

Based on Berggren’s equation and Fick’s principle, we built a model that allowed determination of PaO₂ (theoretical data)
from physiological shunt and other variables (see Supplemental data, Supplemental Digital Content 1, http://links.lww.com/CCM/A553).

Animal Experiments
The animal experiments complied with the NIH guidelines and were approved by the animal care committee of the University of São Paulo Medical School (56). We studied 10 anesthetized pigs with lung injury due to surfactant washout and subsequent injurious mechanical ventilation. Arterial and mixed venous blood gases were obtained at different airway pressures (decremental 2 cm H2O PEEP steps from 25 to 5 cm H2O after a recruitment maneuver), resulting in varying amounts of nonaerated lung and cardiac output.

Patients
After approval by the Institutional Ethics Committee (University Hospital Leipzig, reference numbers 202/2003 and 311/2007), we analyzed physiological, demographic, and CT data of 77 patients, which were automatically entered into our electronic database during routine clinical management at the University Hospital Leipzig. Because data entry was anonymous and no additional interventions were required, the need for informed consent was waived. Ten or more minutes before CT, pure oxygen was applied. All other ventilator settings were maintained. Arterial blood gases were analyzed in close temporal proximity to CT. There was a subgroup in which, during unchanged mechanical ventilation, the FiO2 had been decreased because of sufficient oxygenation shortly after CT. In these 28 of the 77 patients, the PaO2/FiO2 was measured again (time interval of approximately 10 min) at FiO2 of 0.5.

Patients with severe refractory hypotension (mean arterial pressures below 60 mm Hg), heart failure, severe pulmonary embolism, large (occupying more than one quadrant of the lung in the CT image) pneumothorax, hemothorax, or pleural effusion or chronic impairment of gas exchange (e.g., fibrosis) were not included.

Additional data from repeat CT taken after either a short (30–60 min; 11 patients with acute respiratory distress syndrome [ARDS] originally published by Borges et al [12]) or longer interval (1–11 days; eight patients from our institution) were available.

Quantitative CT Analysis
All CT images covering the entire lungs were segmented manually using anatomical landmarks (Osiris software, University Hospital of Geneva, Switzerland). Major hilar vessels and bronchi, pneumothoraces, pleural fluids, and gross motion artifacts were excluded. We chose window levels and widths appropriate for the lung parenchyma (~500/1500 HU) or the mediastinum (50/250 HU). Volume and mass variables characterizing the total lung or its differently aerated compartments were calculated as previously described (1, 9, 12, 57). All percentages of the volume (%Volume) or mass (%Mass) of lung within different HU intervals (expressed within brackets) were calculated relative to the total lung volume or total lung mass, respectively. The following HU intervals were used to separate differently aerated compartments: poorly aerated, [−101 to −500] HU; normally aerated, [−501 to −900] HU; and hyperaerated, [−901 to −1000] HU. The %Mass of nonaerated lung was calculated using the traditional [−100 to +100] HU interval and also including subsequent 100 HU intervals below −100 HU, that is, [−200 to +100] HU and so on, down to [−500 to +100] HU.

Statistical Analysis
Results are expressed as median (minimum–maximum). Relationships between variables were analyzed by linear regression. When prediction intervals are provided from linear regression, homoscedasticity was tested using the Breusch-Pagan test (58). Dummy variables were included into multiple linear regression models to account for between-patient differences in analyses of repeated measurements or for between-patient differences such as administration of contrast material (55). Changes when going from one regression model to another were described by changes in the coefficients of determination (R2) and tested with the J-test (59). An increase in R2 corresponds to the additional percentage of variance in the dependent variable explained by the model. The statistical software packages SPSS 15.0 (SPSS GmbH, Munich, Germany), GraphPad Prism 5 (GraphPad Software, La Jolla, CA), and R (version 2.14.0, http://www.R-project.org) were used. Significance was assumed at p < 0.05. Confidence interval or prediction interval (95%, 75%) are reported where appropriate.

RESULTS
Patient characteristics are given in Table 1. Additional results are presented as supplemental data (Supplemental Digital Content 1, http://links.lww.com/CCM/A553).

Physiological Shunt vs. Riley’s Approximation
Using theoretical and experimental data obtained during pure oxygen ventilation, with varying levels of hemoglobin, cardiac output, ΔCaw, O2, and airway pressures, we observed a strong correlation between Riley’s approximation and physiological shunt (first subhypothesis, Fig. 1). Riley’s approximation minimally degraded (less than 5%) the information that might be obtained by the more laborious and invasive measurement of physiological shunt.

Riley’s Approximation vs. CT Shunt
In patients ventilated with pure oxygen, the strong linear correlation between Riley’s approximation and CT shunt confirmed our second subhypothesis (Fig. 2). In particular, quantification of CT shunt as %Mass of nonaerated lung and the inclusion of the %Mass [−200 to −100] HU improved the correlation.

PaO2/FiO2 vs. Physiological Shunt
Using theoretical and experimental data (pure oxygen ventilation), we confirmed that the relationship between PaO2/FiO2 and physiological shunt was extremely nonlinear, with an exponential-decay appearance. The lnPaO2/FiO2 corrected...
this nonlinearity substantially (Fig. 3). Similarly, the lnPaO$_2$/FiO$_2$ corrected the nonlinearity of the relationship between PaO$_2$/FiO$_2$ and Riley’s approximation (Supplemental Fig. 1, Supplemental Digital Content 2, http://links.lww.com/CCM/A554). These observations support our third subhypothesis assuming that the correlation between PaO$_2$/FiO$_2$ and CT shunt has to be tested using an appropriate transformation.

**Oxygenation vs. CT Shunt**

In the heterogeneous cohort of 77 mechanically ventilated patients (pure oxygen), we observed a strong negative linear relationship between lnPaO$_2$/FiO$_2$ and different shunt estimates (fourth subhypothesis, Figs. 4 and 5). The strength of this correlation improved significantly with every correction of a potential source of error.

**Contribution of Potential Sources of Errors**

Using theoretical simulations, we observed that lnPaO$_2$/FiO$_2$ measurement during ventilation with an inspired oxygen concentration below 100% impairs the correlation between shunt estimates and lnPaO$_2$/FiO$_2$ (Supplemental Fig. 2, Supplemental Digital Content 3, http://links.lww.com/CCM/A555). Supplemental Figure 3 (Supplemental Digital Content 4, http://links.lww.com/CCM/A556) also illustrates the poorer performance of lnPaO$_2$/FiO$_2$ measured at 50% oxygen in the 28 patients for whom we had lnPaO$_2$/FiO$_2$ measurements for both 50% and 100% oxygen. Similar findings were observed for the correlation between Riley’s approximation and CT shunt (Supplemental Fig. 3, Supplemental Digital Content 4, http://links.lww.com/CCM/A556).

When considering all 77 patients, we observed stepwise increments in the strength of the correlation between oxygenation

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**Table 1. Patient Data**

<table>
<thead>
<tr>
<th></th>
<th>Single CT</th>
<th>Repeat CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (female)</td>
<td>77 (17)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Number of CTs/patient</td>
<td>1</td>
<td>2 (2–4)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>45 (15–82)</td>
<td>30 (17–75)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25.7 (20.2–37.0)</td>
<td>24.3 (19.9–29.7)</td>
</tr>
<tr>
<td>Multiple trauma patients (%)</td>
<td>61 (79 %)</td>
<td>7 (87%)</td>
</tr>
<tr>
<td>Other patients (%)</td>
<td>16 (21 %)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Patients with ARDS (%)</td>
<td>34 (44 %)</td>
<td>5 (63 %)</td>
</tr>
<tr>
<td>Time to first CT (h)</td>
<td>2.0 (0.75–437)</td>
<td>1.7 (1.3–120.0)</td>
</tr>
<tr>
<td>Time to repeat CT (h)</td>
<td>–</td>
<td>29 (7–334)</td>
</tr>
<tr>
<td>Contrast medium</td>
<td>69 (90%)</td>
<td>8 (75 %)</td>
</tr>
<tr>
<td>PEEP (cm H$_2$O)</td>
<td>10 (6–20)</td>
<td>10 (10–20)</td>
</tr>
<tr>
<td>PIP (cm H$_2$O)</td>
<td>25 (19–37)</td>
<td>23 (16–37)</td>
</tr>
<tr>
<td>PaO$_2$/FiO$_2$ at CT (mm Hg)</td>
<td>327 (54–664)</td>
<td>301 (48–592)</td>
</tr>
<tr>
<td>PaCO$_2$ at CT (mm Hg)</td>
<td>46.7 (273–128.0)</td>
<td>48.8 (32.4–78.1)</td>
</tr>
<tr>
<td>Delta PaO$_2$/FiO$_2$ (mm Hg)</td>
<td>–</td>
<td>113 (13–441)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.6 (5.5–15.3)</td>
<td>10.0 (8.9–14.5)</td>
</tr>
<tr>
<td>Total lung weight (g)</td>
<td>992 (636–3019)</td>
<td>1381 (783–3017)</td>
</tr>
<tr>
<td>Total lung volume (mL)</td>
<td>3738 (1568–6213)</td>
<td>3715 (2078–6351)</td>
</tr>
<tr>
<td>%V$_{100}$</td>
<td>3.5 (0.1–53.7)</td>
<td>5.4 (0.3–45.9)</td>
</tr>
<tr>
<td>%V$_{500}$</td>
<td>7.0 (1.8–43.6)</td>
<td>19.5 (5.6–35.6)</td>
</tr>
<tr>
<td>%M$_{100}$</td>
<td>12.0 (0.7–78.8)</td>
<td>142 (0.8–63.7)</td>
</tr>
<tr>
<td>%M$_{200}$</td>
<td>15.8 (1.3–82.5)</td>
<td>20.8 (1.6–71.5)</td>
</tr>
<tr>
<td>%M$_{500}$</td>
<td>15.6 (5.4–50.8)</td>
<td>28.9 (10.3–44.5)</td>
</tr>
</tbody>
</table>

Body mass index = weight in kilograms divided by the square of the height in meters; ARDS = all patients with acute respiratory distress syndrome defined according to reference 65; time to first CT = median time between commencement of mechanical ventilation and CT; time to repeat CT = median time between two consecutive CTs; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure during pressure controlled mechanical ventilation; %V = lung volume within the given range of Hounsfield Units expressed as percentage of the total lung volume; %M = calculated accordingly and expressed as percentage of the total lung mass.

Table 1 lists descriptive, physiological, and quantitative CT data. Data are given as median (minimum–maximum).
Figure 1. Correlations between Riley’s approximation and physiological shunt for theoretical data from model simulations and data from an experiment in pigs. Data points for both analyses were obtained during or simulated for 100% oxygen ventilation. For the definition of different shunt entities, the reader is referred to the section Materials and Methods. The red dashed lines correspond to the least squares regression lines. $R^2 = \text{coefficient of determination.}$ The regression equations are Riley’s approximation = $2.34 + 0.87 \times$ physiological shunt (95% confidence intervals [CIs] 2.04–2.65 and 0.86–0.87) for theoretical data and Riley’s approximation = $4.22 + 0.75 \times$ physiological shunt (95% CIs 3.43–5.00 and 0.72–0.78) for experimental data. The $p$ values for both $R^2$ values were less than 0.0001.

Figure 2. Regression of Riley’s approximation to shunt on different estimates of CT shunt in mechanically ventilated patients in the acute phase of disease. Data of the 77 patients with single data points were included in these analyses. For the definition of different shunt entities, the reader is referred to the section Materials and Methods. %Volume [–100 to +100] HU (left panel) refers to the lung volume within the given interval of Hounsfield Units (HU) expressed as percentage of the total lung volume, %Mass [–100 to +100] HU (middle panel) and [–200 to +100] HU interval (right panel), respectively, and expressed as percentage of the total lung mass. The thick red dashed lines correspond to the least squares regression lines and the black dashed lines mark the 95% confidence intervals (CIs) of the regression line. $R^2 = \text{coefficient of determination.}$ The regression equations are Riley’s approximation = $13.98 + 0.71 \times$ CT shunt (%Volume [–100 to +100] HU) increased from 0.57 to 0.74 ($p < 10^{-12}$).

When the %Mass of nonaerated lung [–100 to +100] HU replaced the %Volume [–100 to +100] HU as the independent variable, the $R^2$ for the correlation with CT shunt increased from 0.74 to 0.82 ($p < 10^{-6}$, Figs. 4 and 5).

Finally, as shown in Figures 4 and 5 and Table 2, the correlation between lnPaO2/FiO2 and CT shunt improved again significantly after extending the HU interval from –100 HU to –200 HU now including parts of the lung compartment traditionally defined as poorly aerated ($R^2$ increased from 0.82 to 0.86; $p < 10^{-6}$, Figs. 4 and 5). The $R^2$ improved again marginally but statistically significantly when the HU interval was extended to –300 HU ($R^2 = 0.87$, $p = 0.009$). The $R^2$ did not improve further when the HU interval was extended below –300 HU (Fig. 5).

In a final regression analysis relating PaO2/FiO2 and CT shunt (%Mass [–200 to +100] HU, this choice of interval is justified in the discussion), we choose PaO2/FiO2 as the independent variable since that will be used to estimate CT shunt (see Supplemental data, Supplemental Digital Content 1, http://links.lww.com/CCM/A553; and Supplemental Fig. 4, Supplemental Digital Content 5, http://links.lww.com/CCM/A557; and Supplemental Fig. 5, Supplemental Digital Content...
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Figure 3. Regression of PaO₂/Fio₂ or the logarithmically (ln) transformed PaO₂/Fio₂, respectively, on physiological shunt for theoretical data obtained by model simulations (A, upper panels) and for experimental data measured in pigs with acute lung injury (B, lower panels). For the definition of different shunt entities see section Materials and Methods. The thick red dashed lines correspond to the least squares regression lines and the black dashed lines mark the 95% confidence intervals (CIs) of the regression line. R² = coefficient of determination. The regression equations are lnPaO₂/Fio₂ = 6.291 – 0.044 × physiological shunt (95% CIs 6.263–6.318 and –0.045 to –0.044) for the upper right panel and lnPaO₂/Fio₂ = 6.271 – 0.044 × physiological shunt (95% CIs 6.209–6.333 and –0.047 to –0.042) for the lower right panel. No equations are given for the regression lines in the left panels because basic assumptions of linear regression are not fulfilled. The p values for all R² values were smaller than 0.0001.

6, http://links.lww.com/CCM/A558). Table 3 relates PaO₂/Fio₂ and the predicted amounts of CT shunt in the form of a look-up table.

Repeated CT Exams Within the Same Patients

Heterogeneous Cohort of Mechanically Ventilated Patients. The within-patient regression (repeat CTs) of lnPaO₂/Fio₂ on CT shunt also showed a strong negative linear relationship. As before, the R² improved when replacing %Mass [–100 to +100] HU by %Mass [–200 to +100] HU (0.93–0.95, p = 0.03). Inclusion of additional HU intervals beyond –200 HU did not improve or even impaired the R². Supplemental Figure 6 (Supplemental Digital Content 7, http://links.lww.com/CCM/A559) shows that decreases in CT shunt always resulted in proportional lnPaO₂/Fio₂ increments except for one patient who had a large intrapulmonary hematoma. Intraindividual changes in CT shunt between two successive measurements were linked to predictable changes in lnPaO₂/Fio₂ (Fig. 6, R² = 0.97).

Cohort of Patients With ARDS. In this dataset (11 patients with ARDS, 7–8 repeated measurements per patient, see reference 12), the within-patient regression of lnPaO₂/Fio₂ on CT shunt also showed a strong, negative correlation (Supplemental Fig. 6, Supplemental Digital Content 7, http://links.lww.com/CCM/A559). Again, the R² improved when we considered the %Mass of nonaerated lung, instead of the %Volume (R² from 0.84 to 0.90, p < 10⁻¹³). The R² increased further when extending the HU interval to –200 HU (R² from 0.90 to 0.91, p = 0.07), although marginally significant due to the small sample size with many measurements per patient. Inclusion of HU intervals beyond –200 HU did not improve the R². Again, within-patient changes in CT shunt between successive CTs were associated with predictable changes in lnPaO₂/Fio₂ (R² = 0.82, Fig. 6).

Clinical Variables and CT Shunt

As shown in Table 2, clinical variables, such as the use of contrast material, the body mass index, the baseline diagnosis,
and the ventilation variables, might explain part of the variability of lnPaO₂/Fio₂ in univariate models. However, they added little or no information beyond that already conveyed by CT shunt (%Mass [-200 to +100] HU) to multivariate models. Of note, CT shunt, alone, explained ~87% of the variability in lnPaO₂/Fio₂.

DISCUSSION

We demonstrated a strong linear relationship between arterial oxygenation and the CT-quantified amount of nonaerated lung provided that the PaO₂/Fio₂ values were logarithmically transformed and measured during pure oxygen ventilation. This was shown by whole-lung CT in a clinically relevant cohort of mechanically ventilated patients with different amounts of nonaerated lung. A strong correlation was shown not only for patients with single measurements but also for patients with repeat CT. The between-patients and within-patient consistency of this relationship indicated its potential usefulness for the bedside estimation of the amount of nonaerated lung. We identified a distinct CT-defined lung compartment, encompassing parts of the lung traditionally defined as poorly aerated, whose mass showed a strong negative correlation with the lnPaO₂/Fio₂, and explained up to 86% of its variance.

Arterial blood gas measurement is relatively simple and inexpensive, available at the bedside, and provides important information (16). Many previous studies tried to infer the magnitude of CT shunt based on simple PaO₂ measurements. The results, however, were inconsistent (5, 10, 12, 14, 17–23, 27, 60–62). Some investigators suggested that this relationship was so unreliable that it could not be analyzed without information about regional pulmonary perfusion and they concluded that prediction of CT shunt by blood gas analysis is virtually impossible (5, 16, 17).

Our results, however, suggest that both single measurements of PaO₂/Fio₂ and changes between two PaO₂/Fio₂ measurements are highly significantly correlated to CT shunt after an appropriate transformation. This is in accordance with several small studies using CT or positron emission tomography (PET), which support a strong correlation between CT shunt and both, PaO₂/Fio₂ and physiological shunt (10, 12, 14, 18–23, 27, 60–64). Our study indicates that PaO₂/Fio₂ measurement (pure oxygen) may be clinically useful for bedside assessment of the amount of
nonaerated and potentially recruitable lung, for example, using Table 3. According to the 75% prediction intervals in Table 3, PaO2/FIO2 values of 200 mm Hg or 100 mm Hg indicate that at least 21% or 36%, respectively, of the lung are nonaerated. A PaO2/FIO2 of 500 mm Hg instead means that less than 10% of the lung is nonaerated. In our opinion, such information is clinically useful. We performed preliminary validation tests of the prediction of the amount of nonaerated lung from PaO2/FIO2 values using data of 12 patients with ARDS (65). The true amount of %Mass [−200 to +100] HU calculated from CT fell within the 75% prediction intervals for 10 of 12 patients (see Supplemental data, Supplemental Digital Content 1, http://links.lww.com/CCM/A553).

When viewing our study in perspective, it appears that despite some variation of regional perfusion and hypoxic pulmonary vasoconstriction, a good correlation between PaO2/FIO2 and CT shunt exists, at least during pure oxygen ventilation in hemodynamically stabilized patients with systemic inflammation. As suggested by our analysis, several potential sources of methodological error may explain conflicting results of previous studies on the relationship between PaO2/FIO2 and CT shunt.

The relationship between PaO2/FIO2 and physiological shunt or CT shunt is nonlinear because of the shape of the hemoglobin binding curve, as clearly demonstrated in Figure 3 and suggested by others (12, 19, 21, 28–31). Although some studies reported a linear correlation already between PaO2/FIO2 and CT shunt (14, 20, 22, 63), our data indicates that use of a logarithmic transformation of PaO2/FIO2 markedly improves the linear correlation if a broad range of lung conditions is analyzed. From a physiological perspective, a linear correlation between physiological shunt and CT shunt during ventilation with pure oxygen (main hypothesis) appears more plausible than between PaO2/FIO2 and CT shunt (Fig. 2) (19–21, 60). The clinically more practical relationship between CT shunt and PaO2/FIO2 must be considered a development of the relationship between CT shunt and physiological shunt (12, 19, 21, 65).

Pure oxygen ventilation for PaO2/FIO2 measurement may reduce the impairment of the correlation between lnPaO2/FIO2 and physiological shunt or CT shunt by regions with low ventilation-to-perfusion ratios as previously pointed out by others and reproduced in our study (5, 12, 18, 19, 27, 35, 37, 47, 48, 67–69). Additionally, pure oxygen ventilation may blunt hypoxic pulmonary vasoconstriction which may increase the sensitivity of lnPaO2/FIO2 for assessing CT shunt (26, 69).

High PaCO2 levels may cause an underestimation of PaO2/FIO2 (12). Our study confirmed this finding. However, many patients had normal PaCO2, so its effect in the regression model was limited (Table 1).

### TABLE 2. Regression Results

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Univariate Analysis</th>
<th>Multivariate Model</th>
<th>p</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Partial Correlation</td>
<td>Attributable Variance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%M−100 to +100 HU</td>
<td>−0.90 &lt;0.0001</td>
<td>81.5% &lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%M−200 to −100 HU</td>
<td>−0.65 &lt;0.0001</td>
<td>5.7% &lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%M−300 to −200 HU</td>
<td>−0.50 &lt;0.0001</td>
<td>− 0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%M−400 to −300 HU</td>
<td>−0.32 0.004</td>
<td>− 0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%M−500 to −400 HU</td>
<td>−0.11 0.36</td>
<td>− 0.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%M−600 to −500 HU</td>
<td>−0.42 &lt;0.0001</td>
<td>− 0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaCO2</td>
<td>−0.51 &lt;0.0001</td>
<td>1.2% 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.17 0.15</td>
<td>− 0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEEP</td>
<td>−0.39 &lt;0.0001</td>
<td>− 0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIP</td>
<td>−0.48 &lt;0.0001</td>
<td>− 0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>−0.37 0.001</td>
<td>0.7% 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lung weight</td>
<td>−0.58 &lt;0.0001</td>
<td>− 0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma vs. others</td>
<td>0.39 0.001</td>
<td>0.8% 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contrast material</td>
<td>0.24 0.04</td>
<td>− 0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best multivariate model</td>
<td>− −</td>
<td>89.3% &lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

%M = lung mass within the given range of Hounsfield Units (HU) expressed as percentage of the total lung mass; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure during pressure controlled mechanical ventilation; body mass index = weight in kilograms divided by the square of the height in meters.

Attributable variance refers to the percentage of variance in the logarithmically transformed PaO2/FIO2 explained by the independent variables shown. It corresponds to the R2 change resulting from inclusion of the indicated variable into the preadjusted model. Only the variables in bold font were included in the multivariate model. Table 2 lists the results of univariate and multivariate regression analyses involving variables potentially explaining differences in the logarithmically transformed PaO2/FIO2 in patients with single CT.
Weights can be more reliably measured by CT than volumes (70). Thus, information contained in CT numbers can be degraded when using %Volume. For example, if we consider two voxels with −99 HU and +99 HU, respectively, they would add the same volume to the analyzed lung compartment while their mass contribution would vary by more than 10%. More importantly, however, a large portion of the lung parenchyma is composed of capillaries and blood. Therefore, ~2–3 times more capillaries are present per voxel in a collapsed compartment than in a normally aerated one. Because a nonaerated voxel has the same volume as a normally aerated one, but two to three times its mass, it is understandable why the %Volume of nonaerated lung underestimates physiological shunt (Supplemental Fig. 7, Supplemental Digital Content 8, http://links.lww.com/CCM/A560) (12, 45). Our results support the superiority of the %Mass estimate for the quantification of CT shunt.

Due to the limited spatial resolution of CT, it is conceivable that regions with densities below −100 HU are responsible for significant amounts of physiological shunt and resulting changes in PaO$_2$/FiO$_2$ (18–20, 27, 42, 45, 71). This can occur at the transition from nonaerated to aerated lung regions (45, 71) or within regions where nonaerated and aerated alveoli coexist in a speckled pattern (intravoxel heterogeneity). Theoretically, the correlation of PaO$_2$/FiO$_2$ and CT shunt could be improved by reducing partial-volume artifacts in high-resolution CT. However, we recently demonstrated that high-resolution CT potentially introduces artifacts rather than improving density resolution (72).

The traditional [−100 to +100] HU interval is based on a sound rationale (71, 73) and has been widely accepted to represent nonaerated lung regions in which shunting is supposed to occur. However, our results and several other studies support the notion that inhomogeneously distributed nonaerated lung regions (as, e.g., in ARDS) are better detected by a threshold below −100 HU (19, 20, 27, 42, 45, 71). Malbouisson et al (18) found an improved correlation of changes in PaO$_2$/FiO$_2$ with the amount of air entering the broader [−500 to +100] HU interval compared with the correlation with the [−100 to +100] HU interval. A broader HU interval is also supported by PET studies showing that gas fractions below 0.3 (corresponding to regions with ≥ −300 HU in CT) represent lung regions that comprise shunting lung units (27, 42). The gain in information provided by extensions of the HU interval, however, seems to reach a threshold beyond which shunt may be overestimated (19, 27).

Our study suggests that an extension of the HU interval to include −200 or even −300 HU brings a significant improvement, the major part of which is contained in the [−200 to +100] HU interval. Considering that others discussed an overestimation of shunt already at −300 HU, we chose to err on the side of caution and use the [−200 to +100] HU interval (19).

**Limitations**

The use of contrast material could have influenced the HU threshold (74). Besides the fact that contrast material would increase rather than decrease lung density, no effect of contrast material on the volume of nonaerated lung could be demonstrated (75). However, the slightly higher correlation with %Volume compared to %Mass may be due to partial-volume artifacts (72).

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**TABLE 3. Look-up Table for Prediction of CT Shunt From PaO$_2$/FiO$_2$ Values**

<table>
<thead>
<tr>
<th>PaO$_2$/FiO$_2$</th>
<th>Predicted CT Shunt (%)</th>
<th>75% Prediction Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>62.1</td>
<td>46.5–75.5</td>
</tr>
<tr>
<td>50</td>
<td>60.3</td>
<td>44.7–74.1</td>
</tr>
<tr>
<td>60</td>
<td>58.5</td>
<td>42.9–72.6</td>
</tr>
<tr>
<td>70</td>
<td>56.7</td>
<td>41.2–71.1</td>
</tr>
<tr>
<td>80</td>
<td>54.9</td>
<td>39.4–69.6</td>
</tr>
<tr>
<td>90</td>
<td>53.1</td>
<td>37.7–68.0</td>
</tr>
<tr>
<td>100</td>
<td>51.3</td>
<td>36.0–66.3</td>
</tr>
<tr>
<td>120</td>
<td>47.6</td>
<td>32.7–62.9</td>
</tr>
<tr>
<td>140</td>
<td>44.0</td>
<td>29.6–59.4</td>
</tr>
<tr>
<td>160</td>
<td>40.4</td>
<td>26.6–55.8</td>
</tr>
<tr>
<td>180</td>
<td>36.9</td>
<td>23.9–52.1</td>
</tr>
<tr>
<td>200</td>
<td>33.5</td>
<td>21.3–48.4</td>
</tr>
<tr>
<td>220</td>
<td>30.3</td>
<td>19.0–44.8</td>
</tr>
<tr>
<td>240</td>
<td>27.3</td>
<td>16.8–41.2</td>
</tr>
<tr>
<td>260</td>
<td>24.5</td>
<td>14.9–37.6</td>
</tr>
<tr>
<td>280</td>
<td>21.9</td>
<td>13.1–34.3</td>
</tr>
<tr>
<td>300</td>
<td>19.5</td>
<td>11.5–31.0</td>
</tr>
<tr>
<td>320</td>
<td>17.3</td>
<td>10.1–28.0</td>
</tr>
<tr>
<td>340</td>
<td>15.3</td>
<td>8.9–25.1</td>
</tr>
<tr>
<td>360</td>
<td>13.5</td>
<td>7.7–22.4</td>
</tr>
<tr>
<td>380</td>
<td>11.9</td>
<td>6.7–20.0</td>
</tr>
<tr>
<td>400</td>
<td>10.4</td>
<td>5.9–17.7</td>
</tr>
<tr>
<td>420</td>
<td>9.1</td>
<td>5.1–15.7</td>
</tr>
<tr>
<td>440</td>
<td>8.0</td>
<td>4.4–13.9</td>
</tr>
<tr>
<td>460</td>
<td>6.9</td>
<td>3.9–12.2</td>
</tr>
<tr>
<td>480</td>
<td>6.1</td>
<td>3.3–10.7</td>
</tr>
<tr>
<td>500</td>
<td>5.3</td>
<td>2.9–9.4</td>
</tr>
<tr>
<td>520</td>
<td>4.6</td>
<td>2.5–8.2</td>
</tr>
<tr>
<td>540</td>
<td>4.0</td>
<td>2.2–7.2</td>
</tr>
<tr>
<td>560</td>
<td>3.5</td>
<td>1.9–6.3</td>
</tr>
<tr>
<td>580</td>
<td>3.0</td>
<td>1.6–5.5</td>
</tr>
<tr>
<td>600</td>
<td>2.6</td>
<td>1.4–4.8</td>
</tr>
</tbody>
</table>

This table lists values of CT shunt and the respective 75% prediction interval (PI), which were predicted from PaO$_2$/FiO$_2$ values. For a future patient, the 75% PI specifies the range within which a single CT shunt value that was predicted from a PaO$_2$/FiO$_2$ value will lie with 75% certainty. Such a PI should not be confused with the somewhat unconventional 75% PI was chosen to provide the clinician with an interval narrow enough to suggest a course of action but broad enough to include a good majority of the expected values. The equation for regression relating PaO$_2$/FiO$_2$ and CT shunt found in our study was used for calculation. This regression equation was

\[
\ln \left( \frac{\text{CT shunt}}{100 \%- \text{CT shunt}} \right) = 0.79 - 0.00735 \times \text{PaO}_2 / \text{FiO}_2
\]

The 95% CIs for coefficient and intercept in the regression equation were −0.0081 to −0.0068 and 0.52–1.05, respectively. The calculations shown in this table are only valid for 100% oxygen ventilation. CT shunt is given as percentage of the total lung mass for [−200 to +100] Hounsfield Units (HU). For further information, the reader is referred to Supplemental Fig. 4, Supplemental Digital Content 5, http://links.lww.com/CCM/A557; and Supplemental Fig. 5, Supplemental Digital Content 6, http://links.lww.com/CCM/A558.

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material could be detected by multiple linear regression analysis. We assumed that nonaerated lung predominantly consists of perfused septa, perhaps with some interstitial edema. If intra-alveolar edema predominates, the applicability of our results might be limited (75). Routine CT scans were taken during ongoing ventilation. Consequently, CT data may have been averaged over different phases of the respiratory cycle. However, because PaO2 measurement also averages respiratory fluctuations (19, 76), we believe that this apparent limitation was in fact an advantage. Although we recommend pure oxygen ventilation only for short PaO2 measurement periods, even short periods may promote atelectasis and increase shunt. However, it has been shown that moderate to high PEEP as used in this study prevents significant atelectasis formation (38–40, 48, 50, 77). Our results apply to patients showing a systemic inflammatory reaction, who were recently submitted to mechanical ventilation. It is likely that in later disease stages, the intensity of inflammation and the hypoxic pulmonary vasoconstriction will vary, which can weaken the correlations shown in our work (69). Only 44% of our 77 patients had ARDS, and their median lung weight was within the normal range (1, 9, 78). Therefore, as recently proposed by our group, the mechanism of nonaerated lung was probably atelectasis rather than inflammatory consolidation in a considerable number of patients (9). Consequently, our results must be cautiously applied to ARDS patients. However, we believe that restricting our analysis to ARDS patients would entail withholding clinically relevant information. Patients with a PaO2/Fio2 ratio between 300 and 400 mm Hg may have relevant amounts of nonaerated lung and thus have a high risk of developing ARDS or ventilator-associated lung injury (79, 80).

**CONCLUSION**

The lnPaO2/Fio2 measured during a short period of pure oxygen ventilation strongly correlates with physiological shunt and CT estimates of nonaerated lung in hemodynamically stabilized patients with systemic inflammation who were recently placed on mechanical ventilation (acute phase of disease). Changes in lnPaO2/Fio2 were best explained by variations in the mass of nonaerated lung with CT numbers between [–200 and +100] HU. Measurement of PaO2/Fio2 may thus enable a clinically useful bedside assessment of the amount of nonaerated lung or of potentially recruitable lung, for example, using the table presented in this paper. Nevertheless, it seems important to acknowledge that arterial blood gas analysis can neither predict the anatomic distribution of nonaerated lung nor identify other complications such as lung hyperinflation or barotrauma and can thus in no way be a substitute for CT scan analysis in ARDS patients.

**ACKNOWLEDGMENT**

We thank Henning Starke (Department of Anesthesiology and Intensive Care Medicine, University Hospital Leipzig, Leipzig, Germany), who helped analyzing the CT data.

**REFERENCES**


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**Figure 6.** Correlation between changes (delta, Δ) in the logarithmically (ln) transformed PaO2/Fio2 and changes in CT shunt in the acute phase of disease. CT shunt is calculated as %Mass [–200 to +100] HU and expressed as percentage of the total lung mass. Patients with repeat CT from the present study (left panel) and the study by Borges et al (right panel), see reference 12, were included. The **thick red dashed lines** correspond to the least squares regression lines; the **black dashed lines** mark the 95% confidence intervals (CIs) of the regression line. The regression equations are ΔlnPaO2/Fio2 = −0.036 × ΔCT-shunt – 0.152 (95% CIs –0.041 to –0.031 and –0.291 to –0.013) for the left panel and ΔlnPaO2/Fio2 = −0.021 × ΔCT-shunt – 0.024 (95% CIs –0.024 to –0.019 and –0.096 to 0.049) for the right panel. The p values for all R² values were less than 0.0001.


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