Lung density distribution in dynamic CT correlates with oxygenation in ventilated pigs with lavage ARDS

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Background. Fast dynamic computed tomography (dCT) has been used to assess regional dynamics of lung inflation and deflation processes. The aim of this study was to relate ventilation-induced changes in lung density distribution, as measured over several respiratory cycles by dCT, to oxygenation and shunt fraction in a lavage acute respiratory distress syndrome model.

Methods. Six anaesthetized pigs underwent pressure-constant ventilation (P_{I02}=1.0, inspiratory:expiratory ratio=1:1) before and after induction of lung damage by saline lavage. Mean airway pressure (P_{aw}) was varied (8, 13, 18, 23, 28, 33, and 38 cm H²O) in random order. At each P_{aw} level, dCT acquisitions were performed over several respiratory cycles (Somatom Plus4, Siemens; supradiaphragmatic transverse slice; thickness=1 mm; temporal resolution=100 ms). During scanning at each P_{aw}, arterial and mixed venous blood were obtained for blood gas analysis and shunt calculation. In each CT image, fractional areas (FA) of defined density ranges representing ventilated lung and atelectasis were determined by planimetry using dedicated software. The FA data of individual 100 ms scans were averaged over several respiratory cycles, and expressed as mean FA in percentage of total lung area at each P_{aw}. For atelectatic lung parenchyma a quantitative relationship of the respective mean FA to shunt fraction was studied using regression analysis.

Results. Under steady-state conditions, mean FA of atelectasis correlated linearly with the calculated shunt fraction (healthy lungs, r=+0.76; lavaged lungs, r=+0.89). There is a non-linear relationship between mean FA of ventilated lung parenchyma and mean FA of atelectasis with P_{aO2}.

Conclusions. We conclude that dCT allows assessment of the effects of ventilator adjustments and resultant P_{aw}, changes upon lung aeration and oxygenation rapidly, and with good spatial and temporal resolution. This may benefit patients with acute lung injury, whose ventilatory pattern may be optimized as early as during their first diagnostic workup.


Keywords: complications, acute respiratory distress syndrome; lung, lavage; lung, respiratory therapy; measurement techniques, dynamic computed tomography; pig

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In acute respiratory distress syndrome (ARDS), the efficacy of a ventilatory pattern may be determined using several diagnostic approaches, for example arterial blood gas analysis, spirometry or the pressure–volume (PV) relationships. Despite good clinical applicability and reproducibility of these techniques, tailoring ventilator

This study contains parts of the doctoral thesis of Elena Ribel.
settings to an individual pulmonary pathophysiology remains time-consuming. Repetitive trial-and-error-type changes of ventilator settings require multiple diagnostic reassessments. Recent work has shown that dynamic computed tomography (dCT) is not only able to visualize, but also to quantify aeration and recruitment during

**Fig 1** (A) Illustration of image post-processing using predefined density ranges: the ventilated lung area is defined by a density range of –910 to –500 HU by planimetry. The total area of this density range (blue coloured in the right image) is 69.6 cm², which translates to a fraction of 58.1% of the total lung area. Lung planimetry also allows determination of the atelectatic lung area (density range –300 to 200 HU). A prerequisite for applying these density masks in lavage ARDS lungs is a definition of the lung boarders, as the density range for atelectasis does not allow differentiation of surrounding wall structures. This segmentation algorithm is performed using dedicated software, which automatically evaluates the fractional areas of different density ranges in dCT image series. This yields results as shown in (B): illustration of dynamic CT images and the image-derived lung density ranges reflecting ventilated lung and atelectasis during pressure-constant ventilation (PEEP=15 cm H₂O; Pμ=23 cm H₂O; I:E=1:1; FIO₂=1.0).
respiratory manoeuvres and interventions; furthermore, dCT does so with high temporal and spatial resolution. Tokics and colleagues described a correlation between the amount of atelectasis which was present during breath-hold in conventional spiral-CT images, and shunt fraction (i.e. fractional venous admixture to cardiac output). However, the amount of atelectasis is influenced by the airway pressure applied to the lung during imaging. Neumann and colleagues found a significant correlation between shunt and atelectatic lung area in CT images acquired during an inspiratory breath-hold, however, not at end-expiration. It becomes clear from these discrepancies that the analysis of static CT images does not accurately reflect physiological reality during cyclic ventilation. In contrast to static breath-hold imaging, dCT acquisitions allow the assessment of several complete respiratory cycles during continued respiration. Thus, rapid serial CT measurements of the lung can assess the effects of mechanical ventilation on regional lung expansion and collapse.

We hypothesized that dCT was capable of imaging the lung during continuous respiration (i.e. without interrupting the respirator settings), and that density measurements in dCT image series correlated with clinical parameters of lung oxygenation (i.e. the pulmonary shunt-fraction).

In this study using pigs, we therefore compared animals with ventilated, but otherwise healthy lungs, as well as with surfactant-depleted lungs. We assessed dynamic CT-based pulmonary densitometry and calculated pulmonary shunt-fraction from blood gas analysis during controlled pressure

constant ventilation with varied mean airway pressure ($P_{aw}$).

Materials and methods

Animal model

With state animal care committee approval, six pigs (median 29 (range 26–31) kg) were anaesthetized (azaper- one 8 mg kg$^{-1}$ i.m., piritramide 0.6 mg kg$^{-1}$ i.v., thiopental 10–15 mg kg$^{-1}$ h$^{-1}$ i.v.), lungs endotracheally intubated and mechanically ventilated with $F_{\text{IO2}}$=0.3 in air. Intra-arterial and i.v. femoral catheters were inserted for pressure monitoring, blood gas analysis, and drug administration, respectively. A balloon-tipped flow-directed catheter was advanced into a pulmonary artery, guided by pressure waveform characteristics. Monitoring of anaesthesia included electrocardiography, pulse oximetry and continuous display of arterial, central venous and pulmonary arterial pressures.

After instrumentation, the animals were transferred to the CT unit (Somatom Plus 4, Siemens, Erlangen, Germany), positioned supine, and connected to an ICU ventilator (Servo 900 C, Siemens, Erlangen, Germany), and switched to a pressure-constant ventilation (PCV) mode.

In the CT scanner, blood gas status was analysed both in a continuous fashion, using an intra-arterial sensor (Paratrend 7, Philips Inc., Best, The Netherlands) and intermittently by sampling and analysing arterial and mixed venous blood (ABL 500/OSM 3, Radiometer, Copenhagen, Denmark). Both inspiratory and expiratory oxygen and carbon dioxide concentrations were measured using a side-stream gas analyser (Capnomac Ultima, Datex-Ohmeda, Helsinki, Finland).

Imaging

Dynamic CT imaging (multiscan technique) was performed with the following parameters: tube voltage=120 kV, tube current=110 mA, matrix=$512\times512$ mm, and slice thickness=1.0 mm, resulting in a voxel size of $0.34\times0.34\times1.0$ mm. Images were reconstructed using a high-resolution algorithm. An effective temporal resolution of 100 ms was achieved using an overlapping temporal increment (sliding window), with a total x-ray tube rotation time of 750 ms.

Image analysis

In each CT image, the lung parenchyma was detected and differentiated (i.e. segmented) from non-pulmonary tissues automatically using dedicated software. This segmented total cross-sectional lung area was divided into fractional areas of predefined density ranges, which differentiate atelectatic from ventilated lung parenchyma. A density range of $-300$ to $+200$ Hounsfield units (HU) was used to define atelectasis, whereas a density range of $-910$ to $-500$ HU was used to define ventilated lung parenchyma. The area sustained by each density range was expressed as a fraction of the total cross-sectional lung area (fractional area (FA) in %) in order to allow a within-subject comparison of data. Figure 1 illustrates cyclic changes of ventilated and atelectatic lung area during PCV. For each measurement, the FA data of all individual 100 ms scans were averaged over several respiratory cycles, and expressed as mean FA in % of total lung area at the $P_{aw}$ chosen.

Procedure and measurements

The ventilator mode was PCV with an inspiratory:expiratory (I:E) ratio of 1:1, and a fractional inspired oxygen concentration ($F_{\text{IO2}}$) of 1.0. The $P_{aw}$ was set, in random order, to 8, 13, 18, 23, 28, 33, and 38 cm H$_2$O, respectively. This was accomplished by adjusting positive end-expiratory pressure (PEEP) accordingly and keeping the difference between plateau airway pressure and PEEP constant at 16 cm H$_2$O. The ventilatory frequency was allowed to vary, with the goal of maintaining a $P_{\text{aCO2}}$ of 40 (SD 5) mm Hg. After stabilization of haemodynamics and end-expiratory gas concentrations, arterial and mixed venous blood samples were obtained, and a dynamic CT acquisition of 15 s duration (comprising 150 images) was performed.
A surfactant-depletion model of ARDS was induced by repetitive lung lavage with warmed isotonic Ringer's solution until a $P_{A_{O_2}}/F_{I_{O_2}}$ ratio of 100 was achieved. If ionotrophic support was required to maintain stable haemodynamics following lung lavage, a continuous infusion of 3 (SD 2) μg kg⁻¹ h⁻¹ epinephrine was administered.

The above procedure was then repeated in the damaged lungs by changing $P_{A_{O_2}}$ in random order to the seven steps already described.

### Results

The study procedure was completed in all six animals. However, at low $P_{A_{O_2}}$, measurements could not always be obtained because: (i) in some experiments, images had to be excluded from quantitative analysis because of movement of the diaphragm into the imaged slice; and (ii) in most of the animals, no steady-state haemodynamic conditions were achieved after induction of lavage ARDS at $P_{A_{O_2}}$ of 8 and 13 cm H₂O. Hence, data points are missing at 8 and 13 cm H₂O.

### Haemodynamic and arterial blood gas data

Haemodynamic and blood gas results obtained before and after lavage at each $P_{A_{O_2}}$ are shown in Tables 1 and 2.

### Effect of $P_{A_{O_2}}$ on aeration compartments and $P_{A_{O_2}}$

In healthy and lavaged lungs, $P_{A_{O_2}}$ increases were associated with proportionally larger mean ventilated lung area and a decrease in atelectasis. This alveolar recruitment was

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Table 1 Haemodynamics and acid–base status in healthy animals at different airway pressures. Data are median (interquartile range). Comparisons between groups (before and after lung lavages) were made if a minimum of $n=6$ data points were available in each group. *$P<0.05$

<table>
<thead>
<tr>
<th>$n$</th>
<th>1</th>
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<td>8</td>
<td>13</td>
<td>18</td>
<td>23</td>
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<td>33</td>
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<tr>
<td>PEEP (cm H₂O)</td>
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<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>82 (77–88)</td>
<td>85 (82–88)</td>
<td>86 (85–90)</td>
<td>87 (78–91)*</td>
<td>72 (63–91)</td>
<td>69 (63–88)</td>
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<tr>
<td>$CVP$ (mm Hg)</td>
<td>6 (4–11)</td>
<td>6 (3–11)</td>
<td>6 (5–8)</td>
<td>4 (3–11)</td>
<td>9 (6–14)</td>
<td>10 (9–14)</td>
</tr>
<tr>
<td>$P_{A_{O_2}}$ (mm Hg)</td>
<td>281 (178–335)</td>
<td>457 (267–506)</td>
<td>509 (441–552)*</td>
<td>516 (484–544)*</td>
<td>556 (538–581)</td>
<td>586 (559–606)</td>
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<td>$S_{O_2}$ (%)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
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<tr>
<td>Base excess</td>
<td>6.0 (4.3–6.6)</td>
<td>6.1 (4.1–7.2)</td>
<td>5.9 (3.7–7.5)*</td>
<td>7.6 (5.9–9.0)*</td>
<td>8.1 (6.4–8.8)*</td>
<td>7.6 (4.8–6.5)*</td>
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<tr>
<td>Hb (g d⁻¹)</td>
<td>7.6 (7.0–8.2)</td>
<td>7.7 (7.5–8.0)</td>
<td>7.8 (7.1–8.1)</td>
<td>8.1 (7.5–8.9)</td>
<td>7.6 (7.1–8.1)</td>
<td>7.6 (7.1–8.0)</td>
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VF=ventilatory frequency; MAP=mean arterial pressure; CVP=central venous pressure; $S_{O_2}$=arterial oxygen saturation; $P_{A_{O_2}}$=arterial oxygen partial pressure; $P_{A_{CO_2}}$=arterial carbon dioxide partial pressure; $HCO_3$=standard bicarbonate; Hb=haemoglobin concentration.

Table 2 Haemodynamics and acid–base status in lavage-injured animals at different airway pressures. Data are median (interquartile range). Comparisons between groups (before and after lung lavages) were made if a minimum of $n=6$ data points were available in each group. *$P<0.05$

<table>
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<tr>
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<td>18</td>
<td>23</td>
<td>28</td>
<td>33</td>
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<tr>
<td>PEEP (cm H₂O)</td>
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<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
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<tr>
<td>VF (bpm)</td>
<td>58 (52–61)</td>
<td>40 (26–43)</td>
<td>18 (15–49)</td>
<td>34 (23–62)</td>
<td>48 (29–67)</td>
<td>56 (37–69)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>60 (54–62)</td>
<td>68 (57–75)</td>
<td>61 (60–69)*</td>
<td>59 (52–67)</td>
<td>63 (55–66)</td>
<td>56 (54–58)</td>
</tr>
<tr>
<td>$CVP$ (mm Hg)</td>
<td>2 (2–3)</td>
<td>5 (3–7)</td>
<td>6 (4–8)</td>
<td>7 (3–10)</td>
<td>8 (5–10)</td>
<td>5 (4–11)</td>
</tr>
<tr>
<td>$P_{A_{O_2}}$ (mm Hg)</td>
<td>21</td>
<td>46 (40–151)</td>
<td>216 (168–352)*</td>
<td>469 (272–482)*</td>
<td>547 (471–553)</td>
<td>590 (584–610)</td>
</tr>
<tr>
<td>$S_{O_2}$ (%)</td>
<td>8</td>
<td>48 (37–74)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
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<tr>
<td>Base excess</td>
<td>−10.2</td>
<td>−9.4 (−9.8 to −7)</td>
<td>−5.6 (−8.6 to −4.4)*</td>
<td>−6.7 (−7.9 to −5)*</td>
<td>−6.1 (−7.6 to −5.9)*</td>
<td>−8.1 (−9.8 to −6)*</td>
</tr>
<tr>
<td>Hb (g d⁻¹)</td>
<td>9.6</td>
<td>8.3 (7.4–10.2)</td>
<td>9.7 (8.5–10.5)</td>
<td>9 (8.2–10)</td>
<td>8.3 (7.4–9.9)</td>
<td>8.7 (8.3–10)</td>
</tr>
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</table>

VF=ventilatory frequency; MAP=mean arterial pressure; CVP=central venous pressure; $S_{O_2}$=arterial oxygen saturation; $P_{A_{O_2}}$=arterial oxygen partial pressure; $P_{A_{CO_2}}$=arterial carbon dioxide partial pressure; $HCO_3$=standard bicarbonate; Hb=haemoglobin concentration.

The above procedure was then repeated in the damaged lungs by changing $P_{A_{O_2}}$ in random order to the seven steps already described.

### Statistical analysis

Values are given as median, 25th and 75th percentiles. Comparisons between groups (healthy vs lavaged animals) were made using Wilcoxon signed rank test if a minimum of $n=6$ data points were available in each group. Differences were considered to be significant when $P<0.05$. Correlation coefficients between density-specific FA and $Q_s/Q_T$ (shunt) were calculated using linear regression analysis. Mean bias and limits of agreement between mean FA of atelectasis and conventionally calculated shunt were determined according to Bland and Altman.

The study procedure was completed in all six animals. However, at low $P_{A_{O_2}}$, measurements could not always be obtained because: (i) in some experiments, images had to be excluded from quantitative analysis because of movement of the diaphragm into the imaged slice; and (ii) in most of the animals, no steady-state haemodynamic conditions were achieved after induction of lavage ARDS at $P_{A_{O_2}}$ of 8 and 13 cm H₂O. Hence, data points are missing at 8 and 13 cm H₂O.
apparent up to a $P_{aw}$ of 28 cm H$_2$O. Even in lavaged lungs with their much larger atelectatic compartments, when compared with healthy lungs, it was possible to achieve almost complete alveolar recruitment (Fig. 2A and B). As expected, this effect was paralleled by improving oxygenation. At values of $P_{aw}$ higher than 23 cm H$_2$O, $P_{aO_2}$ values in healthy and lavaged lungs were similar. Interestingly, in healthy lungs $P_{aO_2}$ decreased again slightly at the highest $P_{aw}$ of 38 cm H$_2$O (Table 1).

Correlation of CT-based lung compartment $Q_S/Q_T$
In this analysis only measurements under steady-state haemodynamic conditions, i.e. at shunt fractions <40% and at $P_{aO_2}$>80 mm Hg, were included. This reflects the clinically relevant range of $P_{aO_2}/F_{IO_2}$.

Mean fractional area of atelectasis and the calculated shunt fraction each showed a linear correlation in healthy and in lavaged lungs. In healthy and lavaged lungs, a correlation coefficient of $r=+0.76$ and $r=+0.89$, respectively
Fig 3 (A) Bland–Altman analysis of the relationship between atelectatic lung area determined by dCT and shunt fraction determined from blood gas analyses (solid line=bias; dashed lines=limits of agreement, i.e. bias ±2SD). Linear regression analysis showed a good correlation between both methods (healthy lungs, $r=+0.76$; lavaged lungs, $r=+0.89$). (B and C) Non-linear relationship between mean ventilated lung area ($FA_{aer}$), assessed by dCT imaging, and the measured $P_{aO_2}$. (D and E) Mean atelectatic lung area ($FA_{atel}$), assessed by dCT imaging, shows a non-linear negative correlation with measured $P_{aO_2}$ ratio.
were calculated. The CT-based atelectasis fraction overestimated the conventionally calculated shunt fraction systematically by 3.4% (bias) within limits of accuracy of ±7.5% (Fig. 3A).

Mean ventilated lung area and mean atelectatic area showed a non-linear relationship with $P_{aO_2}$, which is illustrated for healthy and lavaged lungs in Figure 3B–E.

**Discussion**

**Dynamic CT imaging**

Dynamic CT imaging used on clinically available spiral CT scanners opens a novel and highly sensitive approach to image-based analysis of the processes of spontaneous respiration and mechanical ventilation. At a fixed table position, and without table movement during imaging, scanning can be performed during continuous respiration. Raw CT data are then reconstructed with a predefined temporal increment (i.e. 100 ms). Whereas during conventional static CT imaging, breath-holding is required to avoid image artefacts, fast dynamic acquisition allows a cine-type visualization of the lung inflation and deflation processes during continued respiration (Fig. 1B). Density measurements in these image series allow quantitative analyses of lung dynamics. In previous CT studies, atelectasis measured by static CT has been correlated with shunt-fractions. However, controversial results have been reported and depend mainly on the study procedure (e.g. imaging at end-expiration vs end-inspiration or the time gap between breath-hold and image acquisition). Dynamic CT is the first clinically available imaging technique, which allows assessment of atelectasis over several respiratory cycles, no matter which ventilatory settings are applied.

In this study, the mean atelectatic lung area showed a linear correlation with shunt-fraction. The mean ventilated lung area (and consequently atelectasis) correlated non-linearly with $P_{aO_2}$. This non-linearity, mainly caused by the buffering effect of haemoglobin, is apparent in the iso-shunt lines (at high shunt-fractions) as described by Nunn and colleagues, and was recently investigated in more detail by Petrots and colleagues. Whereas in these studies $F_{I_O_2}$ was varied, in our study the amount of atelectasis was changed to obtain different $P_{aO_2}$ at a constant $F_{I_O_2}$ of 1.0. In contrast to the data sets underlying Nunn and colleagues’ iso-shunt diagrams, however, our experimental setup made it difficult to produce reliable data points in the low $P_{aO_2}$ range (i.e. with the largest amount of atelectasis), for the following reason: in injured lungs and at low airway pressures, this leads to unstable haemodynamics, which explains that in most animals no steady state was achieved under these conditions.

In this study, dCT images were analysed on an image-by-image basis in order to average density measurements over several respiratory cycles. As we aimed to correlate image-based density measurements with conventional parameters of oxygenation, we produced a range of $P_{aO_2}$ values and shunt fractions as large as possible by studying healthy and surfactant-depleted lungs. The lavage ARDS model is an established animal model, specifically known to induce large amounts of atelectasis. As expected, the amount of atelectasis at low $P_{aw}$ clearly differed before and after saline lavage. However, even in the lavaged lungs, nearly complete recruitment of atelectases occurred at high $P_{aw}$.

Neumann and colleagues compared the response of lung aeration with airway pressure steps in different animal models of ARDS and implied a one-compartmental behaviour of lung aeration. In previous work, we identified two widely separate respiratory time constants in lavage-ARDS, and therefore proposed at least a two-compartment model to discriminate the more rapid aeration process of already open alveoli from slower recruitment of atelectasis in the lavage ARDS model.

As all measurements were performed during $F_{I_O_2}$=1.0, the calculated venous admixture represents a ‘true shunt fraction’. If a mixture of oxygen and nitrogen is used, the resultant $F_{I_O_2}$ has to be taken into account when correlating venous admixture to atelectasis measured throughout an image series.

**Densitometry in CT imaging**

A variety of CT methods to quantify ventilation and atelectasis have already been described in the literature and have been discussed previously. In the current study, we correlated fractional lung areas of different density ranges with $P_{aO_2}$ and shunt. Several studies have demonstrated that specific density windows can be assigned to defined physiological conditions of lung parenchyma, like ventilated lung parenchyma, atelectasis, or overdistension. Other parameters such as mean lung density or total amount of air calculated pixel by pixel as described by Puybasset and colleagues reduce a continuous spectrum of density values or histogram to a single-number descriptor. Such data reduction needs to be controlled for artefacts by an image-by-image radiological interpretation to exclude influences such as barotraumas or pneumothoraces.

In healthy and lavage-ARDS lungs in this study, $P_{aO_2}$ increased with higher mean airway pressures. At a mean airway pressure of 38 cm H₂O, a slight decrease in $P_{aO_2}$ was noted in healthy lungs. This may have been attributable to a decrease in pulmonary blood flow when regional intra-alveolar pressure in overinflated areas exceeded capillary perfusion pressure.

At present, the technique of dCT focuses on the quantification of ventilation, but provides no information on pulmonary perfusion. Thus, the correlation between dynamic lung density distribution and measures of oxygenation described in this study presumes intact pulmonary perfusion. Further development of this technique and/or the additional, independent analysis of regional pulmonary...
perfusion could address regional ventilation–perfusion equilibrium.

A challenge of the method presented is the large number of CT images to be evaluated for quantitative analysis. This problem was addressed by developing a dedicated software tool, which automatically segments the lung in each single CT image. To validate this automated lung segmentation tool, we compared 120 software-based CT evaluations (mean density values of healthy and lavaged lungs) with interactive lung segmentation by a radiologist. There was excellent correlation between both methods with a coefficient $r=0.99$.5

There are some shortcomings of the dCT technique: presently, it allows imaging only in one predefined transverse slice. We selected a supradiaphragmatic slice, which allows scanning of the maximum transverse lung area in this animal model. However, Lu and colleagues15 found an inhomogeneous distribution of PEEP-induced reopening of collapsed alveolar regions, leading to misrepresentation of ventilated lung volume by imaging of a single plane only. Multi-slice scanners, which allow image acquisition with high temporal resolution simultaneously in multiple separate slices are already commercially available. However, these slices are still in close proximity to each other so that no true three-dimensional reconstruction of the lung is possible. With ongoing development of scanner technology, real-time imaging of the ventilation processes throughout the entire lung may be available in the near future.

In native CT imaging, no distinction between blood, tissue and interstitial water can be made, which potentially leads to an error through blood redistribution during the respiratory cycle in positive pressure ventilation.16 However, as intrapulmonary blood volume is ~10% of the total circulatory blood volume (in humans, dogs and rabbits), this influence will not significantly affect quantitative analyses in native dCT imaging.17 The 3–4% overestimation (bias) of shunt by dCT-based atelectasis measurement may be explained by the inability of our setup to separate blood from atelectatic parenchyma.

Finally, dCT evaluations must quantify ventilation indirectly in contrast to other radiological and nuclear medicine techniques that use radioactive or hyperpolarized gases as direct imaging agents. On the other hand, dCT has the ability to visualize lung morphology in high detail, allowing additional quantification of non-ventilated lung areas. Frequent clinical problems in ARDS which could also be evaluated by dCT include pleural effusion, pneumothorax, bullae, and interstitial fibrosis. In addition, ventilator-associated lung injury can also be detected by dynamic CT evaluation (e.g. barotrauma, volutrauma).

CT exposes the patient to radiation, a fact that is also relevant in dCT imaging because of the large number of images necessary for quantitative evaluation. Heussel and colleagues18 measured a radiation exposure of 47 mGy in a dynamic CT measurement of 10 s duration, using the same scanner and acquisition parameters similar to those used in this study. This dose is approximately equivalent to the total dose necessary for a spiral CT of the entire chest. Further investigations will be necessary to optimize imaging procedures, and to reduce radiation exposure during dynamic acquisition.

Alternative imaging techniques

Currently there is no other image-based technique in clinical use for estimating regional lung aeration in patients with ARDS. Electron beam CT (EBCT) reaches a very high temporal resolution (<50 ms for a volumetric assessment of the total lung). However, EBCT uses relatively high radiation doses and suffers from an inferior spatial resolution compared with spiral CT scanning. Because of technical improvement of spiral CT scanners, EBCT is effectively obsolete.19

Conventional ventilation scintigraphy yields only spatial resolution,20 whereas ventilation SPECT (using $^{133}$Xe, $^{127}$Xe or $^{81}$Kr) overcomes this limitation. However, to administer the radioisotope gas, both methods require breathing circuit disconnection, which would lead to alveolar collapse in the patient on continuous high positive pressure ventilation. Positron emission tomography (PET) of the lungs using dissolved injected $^{13}$N$_2$ as a tracer is a promising new radioisotope-based approach to follow regional distribution of both ventilation and perfusion.21 It is still limited by the availability of PET scanners and has not been applied in clinical ARDS. Novel magnetic resonance imaging (MRI) techniques visualizing inhaled hyperpolarized noble gas ($^3$He or $^{129}$Xe) with high temporal resolution (130 ms per image and less),22 allow direct imaging of the ventilation process during a respiratory cycle, and a spatial resolution that is currently unmatched by any nuclear medicine technique. Although these methods have great potential for applications in thoracic radiology and pulmonary physiology, they are not likely to have a significant impact on patients with acute lung injury. In ARDS, the mismatch of ventilation and perfusion is mainly attributable to atelectasis,23 either permanently or cyclically with respiration. Thus, atelectatic lung parenchyma is to be included in quantitative image-based analysis. All techniques using inhaled gas imaging to assess ventilation will miss severely hypoventilated or atelectatic areas. Electric impedance tomography (EIT) represents another relatively new technique that allows quantification and spatial resolution of lung aeration at the bedside without radiation exposure. Kunst and colleagues24 used EIT to determine the lower inflection point and the upper deflection point in an ARDS model. Compared with dCT, EIT still offers considerably less spatial resolution and no direct visualization of atelectasis. Further studies will be necessary to define the potential and clinical significance of both methods.
Clinical implications

In clinical practice, lung aeration is assessed in ventilated ARDS patients by auscultation, chest radiography and arterial blood gas analysis. This approach uses oxygenation failure to quantify the size of the ‘alveolar shunt compartment’ in the three-compartment model of the lung. Hence, the $\text{PaO}_2/\text{FiO}_2$ ratio indirectly indicates the size of the ‘ideal alveolar compartment’ (i.e. the ‘open and perfused’ parts of the lung).

Another, more advanced physiological lung model predicts that, particularly in the diseased lung, an abnormally broad spectrum of ventilation-perfusion ($V_A/Q$) ratios are present. This technique falls short of clinical applicability (e.g. in the assessment of the effect of changes in ventilator settings in the ARDS patient). The multiple inert gas elimination technique (MIGET) uses the different solubilities of six inert gases to calculate fifty different $V_A/Q$ ratios during steady state.\(^2\) Baumgardner and colleagues\(^2\) modified conventional MIGET by incorporating micropore mass inlet spectroscopy (MMIMS-MIGET), which requires much smaller blood samples and allows laboratory analysis at a much more rapid turnover. While the clinical applicability of MMIMS-MIGET holds promise, all MIGET-derived techniques calculate virtual $V_A/Q$ compartments over the whole lung, without spatial or temporal allocation to topographical lung regions.

Image based measurements like dCT and EIT add two interesting factors to conventional lung function tests: high temporal and high spatial resolution. The former offers a new understanding of ventilatory processes during continuous respiration (e.g. the importance of ventilatory frequency on regional lung inflation and deflation processes).\(^1\)\(^2\) If averaged over time, as in this study, dynamic measurements will reflect a more realistic assessment of ventilatory processes than obtained from static measurements, for example the static pressure–volume curve.

Regional lung function tests will be particularly important in inhomogeneous ventilated lungs (e.g. in ARDS), and may be more sensitive than global measurements such as $\text{PaO}_2$ or shunt.

Perspectives

CT-based resolution of cyclic lung density variations during ventilation offers an exact regional quantification of lung aeration in healthy and pathologic pulmonary conditions and offers an additional method to assess oxygenation and shunt fraction without the need to sample mixed venous blood. Furthermore, changes in response to altered ventilator settings (e.g. $P_{\text{aw}}$, ventilatory frequency, and I:E ratio) may be studied. The application of this technology in the clinical arena may allow quantification of the participation of specific lung regions in gas exchange and the definition of the anatomical substrate of gas exchange abnormalities early and rapidly during the diagnostic workup of ARDS patients.

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