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Radiographic lung density assessed by computed tomography is associated with extravascular lung water content

V. V. KUZKOV[1,2], E. V. SUBOROV[1,2], M. Y. KIROV[1,2], K. WÆRHAUG[1], R. MORTENSEN[3], V. N. KUKLIN[1], K. C. NORDHUS[3] and L. J. BJERTNÆS[1]

[1]*Departments of Anaesthesiology and Intensive Care Medicine, Institute of Clinical Medicine, Faculty of Health Sciences, University of Tromsø and University Hospital of North Norway, Tromsø, Norway,* [2]*Department of Anaesthesiology and Intensive Care Medicine, Northern State Medical University, Arkhangelsk, Russian Federation and* [3]*Department of Radiology, University Hospital of North Norway, Tromsø, Norway.*

Background: We hypothesized that in acute lung injury (ALI), the volume of pulmonary tissue with aqueous density, as determined by spiral computed tomography (CT), is associated with extravascular lung water content. Our aim was to compare tissue volume index, as assessed by CT, before and after oleic acid-induced ALI, with extravascular lung water indexes (EVLWI), determined with single transpulmonary thermodilution ($EVLWI_{STD}$), thermal-dye dilution ($EVLWI_{TDD}$), and postmortem gravimetry ($EVLWI_G$).

Methods: Seven instrumented sheep received an intravenous infusion of oleic acid 0.08 ml/kg (OA group) and four animals had vehicle only (Control group). The day before, and immediately after the experiment, sheep were anesthetized to undergo quantitative CT examinations during a short breath hold. Hemodynamics, oxygenation, $EVLWI_{STD}$, and $EVLW_{TDD}$ were registered. Linear regression analysis was used to assess the relationships between $EVLWI_{STD}$, $EVLW_{TDD}$, $EVLWI_G$, and lung tissue volume index (TVI_{CT}) determined with CT.

Results: In the OA group, total lung volume increased compared with Controls. Poorly and non-aerated lung volumes increased a 3.6- and 4.9-fold, respectively, and TVI_{CT} almost doubled. $EVLWI_{STD}$, $EVLWI_{TDD}$, and TVI_{CT} were associated significantly with $EVLWI_G$ ($r = 0.85$, 0.90, and 0.88, respectively; $P < 0.001$). TVI_{CT} deviated from the reference $EVLWI_G$ values to the greatest extent with a mean bias ± 2SD of 4.0 ± 6.0 ml/kg.

Conclusions: In ovine oleic acid-induced ALI, lung tissue volume, as assessed by quantitative CT, is in close agreement with EVLWI, as determined by indicator dilution methods and postmortem gravimetry, but overestimates lung fluid content.

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ACCUMULATION of extravascular lung water (EVLW) is a hallmark of acute lung injury (ALI) of various etiologies.[1] Therefore, quantification of EVLW might provide valuable therapeutic guidance to providers of intensive care.[2] Among the various methods for the determination of EVLW, the single transpulmonary thermodilution has become one of the most widespread techniques at the bedside.[3] Several investigators have compared the prognostic value of hemodynamic and volumetric measurements using the dilution techniques in experimental and clinical studies.[3–6] However, ambiguity exists regarding the accuracy of EVLW determined with single transpulmonary thermodilution (Appendix 1).[2,7] Investigators have raised concerns about the precision of the measurements that might be influenced by the type and homogeneity of lung injury, the presence of shunts, the concordance of intrathoracic blood compartments, and the degree of lung aeration.[5–9] For these reasons, EVLW determined with single transpulmonary thermodilution requires verification with other available methods. Among the different diagnostic tools, quantitative computed tomography (CT) is a versatile method for examination of patients with suspected pulmonary oedema. CT scanners provide a rapid and reliable estimation of organ volumes and differentiate between volumes of gas and tissue.[10,11]

The ability of CT to detect and estimate matter of aqueous density can be an essential diagnostic supplement in cases of inhomogeneous ALI, a

morphological change that affects considerably the evenness of both pulmonary perfusion and ventilation.[12,13] Intravenously infused oleic acid has been used to mimic the pulmonary blood flow disturbances typical of ALI.[5,14,15] Corresponding to clinical ALI, the loss of lung aeration in this model can result in the fast accumulation of EVLW, which can progress into alveolar flooding.[14,15]

Thus, we hypothesized that the volume of lung tissue with aqueous density assessed by spiral CT is associated with the severity of pulmonary oedema in ALI. Our aim was to compare tissue volume index (TVI), as assessed by CT, before and after oleic acid-induced ALI, with EVLW, determined with single transpulmonary thermodilution ($EVLWI_{STD}$), thermal-dye dilution ($EVLWI_{TDD}$), and postmortem gravimetry ($EVLWI_G$) as the reference method.

Methods

The Norwegian Experimental Animal Board approved the study protocol, according to the regulations of the European Council and to the most recent version of the Helsinki Declaration.

Animal instrumentation

Thirteen yearling sheep of body weight 33.7 ± 2.7 kg, whereof two were excluded, underwent general anesthesia and instrumentation with introducers in the left external jugular vein and common carotid artery, as described previously.[10,16] After 2–4 days of recovery, sheep were placed in an experimental pen and a balloon-tipped catheter (7.0 F, F131HF7; Edwards Life Sciences, Irvine, CA) was placed in the pulmonary artery via the venous introducer. A fiberoptic thermal-dye dilution catheter (4 F, PV2024L; Pulsion Medical Systems, Munich, Germany) and a thermodilution catheter (5 F, PV2015L20; Pulsion Medical Systems) were inserted into the aorta via the arterial introducer, and connected to a Cold Z–021 and a PiCCO*plus* monitor (Pulsion Medical Systems), respectively. The TDD- and the pulmonary artery catheters were connected to pressure transducers (Transpac® III, Abbott, North Chicago, IL, USA).

Measurements and derived calculations

Spiral lung CT (Siemens Somatom Sensation 16, Erlangen, Germany) was carried out twice: 12–24 h before and 2 h after the induction of ALI. Before transportation to the CT suite, sheep received 500 ml of Ringer's lactate and were sedated with ketamine 5–7 mg/kg and midazolam 0.3–0.6 mg/kg intravenously followed by titrated bolus injections to preserve adequate sedation and spontaneous breathing (FiO_2 0.21).

With the sheep resting in the prone position (head first), spiral CT (120 KV, 120 mAs, rotation time 0.5 s, slice collimation 0.75 mm, isotropic voxel size 0.5 mm, feed 15 mm) was performed during a 15-s breath hold at functional residual capacity (FRC) allowing analysis of 400 lung sections. Breath hold was achieved by a top-up dose of ketamine 3 mg/kg injected intravenously, while one of the investigators watching the diaphragm closed the nostrils of the animal with two fingers to secure breath hold during the pause between expiration and inspiration. The purpose of this maneuver was to provide a period of apnea at a lung volume as close to FRC as possible during the CT scanning. Contrary to most anesthetics, ketamine does not reduce FRC.[17] Images were displayed at lung window settings of 1500 Hounsfield units (HU) width and −600 HU levels. In total, the CT examination and the transportations to and from the CT suite took 15–20 min.

The acquisition and analysis of lung CT data were performed using Syngo software (Siemens) following a manual delineation of the lung contour and calculation of lung volume excluding heart and large extra- and intrapulmonary vessels. Percentages of well-aerated (radiographic attenuation between −1000 and −500 HU), poorly aerated (−499 to −100 HU), and non-aerated (−99 to +100 HU) regions were computed, as reported previously.[10,11,18] An independent analysis of over-inflated areas (−900 to −1000 HU) was neglected because the animals breathed spontaneously without positive end-expiratory pressure without signs of pulmonary obstruction.[19] This interval of radiographic density was merged with well-aerated zones, which resulted in overlapping frames from −500 to −1000 HU.

Assuming that the densities of air (−1000 HU) and tissue (0 HU) correspond to 0 and 1 g/ml, respectively, it is possible to compute lung regions of interest for total volume, volume of gas, volume and weight of tissue, and the gas/tissue ratio.[10,11,19] This implies that the average radiographic density of a region can be estimated by assuming that the simple mean attenuation expressed in HU is uniformly and inversely related to the physical

density as:

$$1 - \left[\frac{(HU_{max} + HU_{min})/2}{1000}\right]$$

Hence, in the present study, TVI_{CT} was calculated by means of a simplified equation as the sum of the average radiographic densities multiplied by the volume of the corresponding regions[10]:

$$TVI_{CT} = (V_{WA} \times 0.25) + (V_{PA} \times 0.7) + (V_{NA} \times 1.0)$$

where TVI_{CT} is the CT-derived relative lung tissue volume index (ml/kg); V_{WA} is volume of well-aerated lung tissue (ml/kg); V_{PA} is volume of poorly aerated lung tissue (ml/kg); V_{NA} is volume of non-aerated lung tissue (ml/kg).

In addition, two derived parameters have been calculated: (1) the lung volume index (LVI_{CT}) calculated as the absolute volume of both lungs indexed to its actual weight and (2) lung tissue density (LD_{CT}) computed as TVI_{CT}: LVI_{CT}.

Hemodynamic measurements were performed hourly (baseline, 1 h, and 2 h). Heart rate, mean systemic arterial pressure, mean pulmonary arterial pressure (PAP), mean pulmonary artery occlusion pressure (PAOP), and mean right atrial pressure were registered using a Patient Data Monitor (565A, Kone, Espoo, Finland) and continuously recorded using a Gould 6600 Polygraph (Gould Instruments, Cleveland, OH).

Volumetric parameters were computed as an average of triple boluses of ice-cold solutions of indocyanine green (1 mg/ml, 6 ml) for TDD (COLD Z–21) and dextrose (50 mg/ml, 10 ml) for single thermodilution (PiCCO*plus*). The indicators were injected into the right atrium via the proximal port of the pulmonary artery catheter. Using TDD and single thermodilution, we determined cardiac index (CI), extravascular lung water index (EVLWI), global end-diastolic volume index (GEDVI), and intrathoracic blood volume index (ITBVI). For single thermodilution, $ITBVI_{STD}$ was assumed to be equal to $GEDVI_{STD} \times 1.25$ (Appendix 1). Pulmonary blood volume index was measured by thermal-dye dilution ($PBVI_{TDD}$) only. Systemic and pulmonary vascular resistance indexes (SVRI and PVRI, respectively) were calculated using standard equations. Blood samples were drawn from the systemic (a) and the pulmonary ($\bar{v}$) arteries and analyzed for pH, blood gases, hemoglobin, and hematocrit. Venous admixture (Q_S/Q_T) was calculated.

Experimental protocol

Lung CT was performed 24 h before, and immediately after the experiment. Two sheep were excluded because of corruption of the CT imaging files (rendering data processing impossible). The experiments were carried out on spontaneously breathing, awake standing sheep. After baseline at time 0 h, the animals were randomly assigned either to a Control group ($n = 4$) with no interventions or to an oleic acid (OA) group ($n = 7$). In the OA group, sheep received an intravenous infusion over 30 min of oleic acid (Sigma Chemical, St. Louis, MO) 0.08 ml/kg, which was mixed with the animal's own blood, amounting to a total volume of 50 ml. The Control group received an equivalent volume of saline. All the animals were breathing room air (FiO_2 0.21) and received an infusion of Ringer's lactate (10 ml/kg/h) aimed to maintain the intravascular volume at baseline, as evaluated by GEDVI. The duration of the whole experiment, excluding the final CT examination, was 2 h. After euthanasia with an intravenous injection of pentobarbital 100 mg/kg followed by potassium chloride 300 mmol, 40 ml of blood was sampled from the left ventricle and the lungs were harvested for quantification of $EVLWI_G$, as described by earlier investigators and our own group.[5,20–22]

Statistical analysis

Data were presented as mean ± standard deviation (SD). Within-group analysis was performed using ANOVA followed by *post hoc* Scheffe's test, when appropriate. For intergroup comparisons of two independent variables, Mann–Whitney's U-test was used. The intragroup changes in repeated CT variables were compared using Wilcoxon's test. For each continuous variable, the distribution of data was checked using Shapiro–Wilk's test. TVI_{CT}, $EVLWI_{STD}$, and $EVLWI_{TDD}$ were compared with $EVLWI_G$ using linear regression (Pearson r), and presented as scatter diagrams and Bland–Altman's plots, respectively. Calculation of biases ± 95% confidence intervals, and regression equations were performed. For all tests, we considered $P < 0.05$ to be statistically significant.

Results

All animals survived until the end of the experiments. At baseline, we found no significant differ-

ences between the groups, as shown in Figs 1 and 2 and Tables 1 and 2.

Computed tomography

Figure 1 depicts percentages of well-, poorly, and non-aerated lung tissues. We found no changes in the Control group. In the OA group, the volumes of poorly and non-aerated lung tissue increased 3.6- and 4.9-fold, respectively, compared with intragroup baseline and the Controls ($P < 0.001$).

In the Control group, TVI_{CT}, LVI_{CT}, and LD_{CT} remained unchanged throughout the experiment (Table 1). In contrast, in the OA group, TVI_{CT} increased by 84% compared with baseline ($P < 0.05$). At the second CT examination, TVI_{CT}, LVI_{CT}, and LD_{CT} were significantly higher in the OA group compared with the Controls.

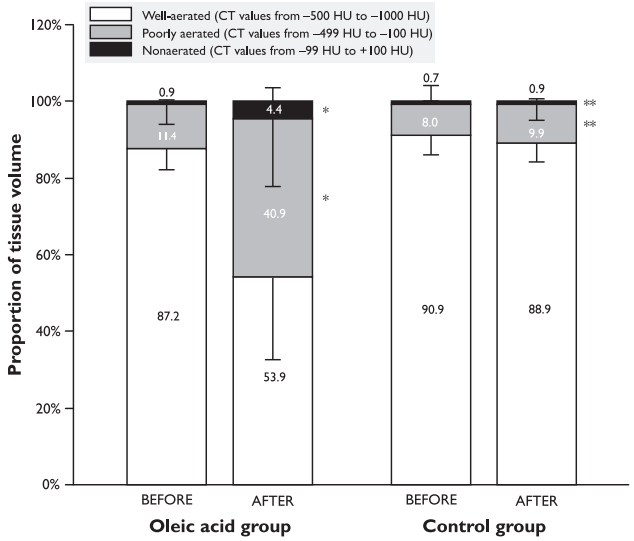

*Fig. 1. Distribution of well-, poorly, and non-aerated lung compartments in sheep, as determined by computed tomography before and after oleic acid-induced lung injury, and before and after the experiment in a sham-operated Control group without lung injury.*P < 0.05 within the oleic acid group compared with initial computed tomography (Wilcoxon's test); **P < 0.05 between the groups (Mann–Whitney's U-test).*

Hemodynamics and gas exchange

In the OA group (Table 2), PAP and PVRI increased both in comparison with intragroup baseline and between the groups, while PAOP increased transiently and CI declined compared with baseline ($P < 0.05$). All the latter variables remained unchanged in the Control group. In the OA group, PaO_2 decreased ($P < 0.01$), while $PaCO_2$ and Q_s/Q_T increased ($P < 0.05$) compared with the Controls. pH in the OA group decreased transiently at 1 h ($P < 0.05$) (not shown).

Single thermodilution and TDD measurements

Figure 2 demonstrates changes in EVLWI. In the OA group, $EVLWI_{STD}$ (a) and $EVLWI_{TDD}$ (b) increased by 69% and 127%, respectively, in comparison with the Control group ($P < 0.001$). Preload markers including ITBVI and GEDVI determined by both single and TDD did not change significantly (not shown). By 2 h, PBVI (Table 2) tended to be higher in the OA group, albeit not significantly ($P = 0.073$).

Postmortem gravimetry

Mean lung weight amounted to 678 ± 89 and 318 ± 50 g, while $EVLWI_G$ was 14.3 ± 2.0 and 5.2 ± 0.5 ml/kg in the OA and the Control groups, respectively ($P < 0.0001$).

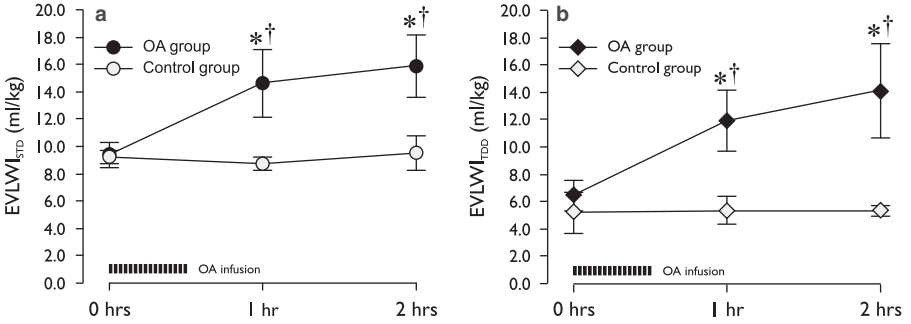

*Fig. 2. Extravascular lung water indexes determined with single thermodilution (a) and thermal-dye dilution (b) in sheep subjected to oleic acid-induced lung injury vs. sham-operated Controls. $EVLWI_{STD}$, extravascular lung water index determined by single thermodilution; $EVLWI_{TDD}$, extravascular lung water index determined by thermal-dye dilution; OA, oleic acid; *P < 0.05 between groups; †P < 0.05 within the group.*

Physiological correlations and validation of techniques

Figure 3 depicts Bland–Altman's plots with regression equations validating the investigated *in vivo* methods *vs*. $EVLWI_G$ as the 'gold standard.' $EVLWI_{STD}$ ($r = 0.85$) and $EVLWI_{TDD}$ ($r = 0.85$) proved to be associated with $EVLW_G$ with bias ± 2 SD of 2.4 ± 5.2 and -0.2 ± 4.6 ml/kg, respectively. In parallel, $EVLWI_{STD}$ and $EVLWI_{TDD}$ were correlated with PaO_2 ($r = -0.68$ and -0.73, respectively, $P < 0.05$).

Table 1

Quantitative lung computed tomography in sheep subjected to oleic acid-induced lung injury.

Parameter	Group	Initial CT	Repeated CT
TVI_{CT} (ml/kg)	Oleic acid ($n = 7$)	10.0 ± 1.6	18.5 ± 4.8*,†
	Control ($n = 4$)	9.8 ± 1.4	8.9 ± 1.1
LVI_{CT} (ml/kg)	Oleic acid ($n = 7$)	33.2 ± 8.4	40.1 ± 8.8*
	Control ($n = 4$)	34.0 ± 7.1	29.9 ± 5.6
LD_{CT} (g/ml)	Oleic acid ($n = 7$)	0.307 ± 0.026	0.465 ± 0.102*,†
	Control ($n = 4$)	0.290 ± 0.024	0.300 ± 0.022

Data presented as the mean ± standard deviation of the mean. TVI_{CT}, tissue volume index calculated according to expected density of radiographic attenuation areas and indexed for actual body weight; LVI_{CT}, lung volume index calculated as the volume of both lungs combined, and indexed to the animal's actual weight; LD_{CT}, lung tissue density computed as $TVI_{CT} : LVI_{CT}$.
*$P < 0.05$ between the groups.
†$P < 0.05$ within group compared with initial CT.

The final CT examination revealed that TVI_{CT} was associated with $EVLWI_{STD}$ ($r = 0.69$), $EVLWI_{TDD}$ ($r = 0.72$), and $EVLWI_G$ ($r = 0.88$; $CI_{95\%}$ -1.8 to 9.8 ml/kg; bias ± 2 SD of 4.0 ± 6.0 ml/kg). In addition, TVI_{CT} was associated with PaO_2 ($r = -0.90$) and LVI_{CT} ($r = 0.62$).

Discussion

The present investigation has shown that pulmonary tissue volume of aqueous density, estimated from the mean CT attenuation values after oleic acid-induced lung injury is associated with the values of EVLWI determined simultaneously with single transpulmonary thermodilution, TDD, and, finally, is in agreement with reference EVLWI values determined by gravimetry.

In this study, quantitative spiral CT showed that after oleic acid-induced ALI, the total lung volume increases despite a decrease in lung aeration. These changes resulted mainly from the expansion of poorly and non-aerated lung compartments in agreement with other experimental and clinical investigations.[11,14,23] TVI also increased in parallel with oedema evolvement and increase in lung weight, as assessed by CT. The latter findings are consistent with recent observations in patients with ALI.[11]

Table 2

Hemodynamic, volumetric, and gas exchange variables in sheep subjected to oleic acid-induced lung injury.

Parameter	Group	Time		
		Baseline	1 h	2 h
PAP (mmHg)	Oleic acid ($n = 7$)	17 ± 1	29 ± 5*,†	27 ± 4*,†
	Control ($n = 4$)	16 ± 1	17 ± 2	17 ± 2
PAOP (mmHg)	Oleic acid ($n = 7$)	7 ± 2	14 ± 4*,†	12 ± 3
	Control ($n = 4$)	9 ± 1	10 ± 2	10 ± 1
CI_{PA} (l/min/m^2)	Oleic acid ($n = 7$)	5.85 ± 1.27	4.58 ± 0.66†	4.62 ± 0.88†
	Control ($n = 4$)	4.67 ± 1.25	4.81 ± 1.13	4.88 ± 0.70
PVRI (dynes × s/cm^5/m^2)	Oleic acid ($n = 7$)	143 ± 49	262 ± 87†	249 ± 53*,†
	Control ($n = 4$)	141 ± 69	124 ± 74	105 ± 33
$PBVI_{TDD}$ (ml/m^2)	Oleic acid ($n = 7$)	240 ± 30	225 ± 54	206 ± 35
	Control ($n = 4$)	232 ± 24	212 ± 38	260 ± 38
PaO_2 (mmHg)	Oleic acid ($n = 7$)	98.0 ± 13.1	60.6 ± 8.7*,†	62.0 ± 12.9*,†
	Control ($n = 4$)	92.3 ± 12.2	84.2 ± 4.3	90.3 ± 8.4
$PaCO_2$ (mmHg)	Oleic acid ($n = 7$)	37.0 ± 2.6	44.6 ± 6.0*,†	41.6 ± 3.5*
	Control ($n = 4$)	35.0 ± 1.7	37.4 ± 2.5	35.8 ± 1.2
Q_S/Q_T	Oleic acid ($n = 7$)	0.046 ± 0.026	0.140 ± 0.062*,†	0.127 ± 0.089*,†
	Control ($n = 4$)	0.030 ± 0.012	0.024 ± 0.015	0.021 ± 0.016

Data presented as the mean ± standard deviation of the mean.
*$P < 0.05$ between the groups.
†$P < 0.05$ within a group compared with baseline.
PAP, mean pulmonary artery pressure; PAOP, mean pulmonary artery occlusion pressure; CI_{PA}, cardiac index determined in pulmonary artery (thermal-dye dilution); PVRI, pulmonary vascular resistance index; $PBVI_{TDD}$, pulmonary blood volume index determined by thermal-dye dilution; PaO_2, partial pressure of oxygen in the arterial blood; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; Q_S/Q_T, venous admixture.

Quantitative CT has demonstrated a great potential for controlling the effects of recruitment maneuvers, PEEP application, and patient positioning in ALI.[10,17,24] Recent experimental and clinical investigations have revealed that CT-derived pulmonary tissue volume is associated with EVLWI and pulmonary thermal volume determined with TDD.[11,23] In the present study, we observed associations between TVI_{CT} and EVLWI determined by both indicator dilution techniques and *postmortem* gravimetry. Notably, we found that TVI_{CT}, as determined after careful manual delineation of the lung contour, followed by the calculation of lung volume and radiologic density, was in close agreement with $EVLWI_G$ with a mean bias of 4 ml/kg. This overestimation might be due to additive effects of several factors. For the first, it is important to bear in mind that CT does not differentiate between lung compartments with interstitial fluid, pulmonary tissue, or residual intravascular blood.[25] For the second, CT unveils fluids in the alveoli and pleural space that might elude detection with indicator dilution methods.[26] Evidently, the OA-induced oedema included a visible alveolar component, but no pleural effusions were observed at autopsy. Technical artifacts including 'beam hardening'and 'partial volume' effects, as well as movements of the heart, vessels, and lungs, may also augment the net radiographic attenuations.[27] In oleic acid-induced ALI, the preservation of spontaneous breathing may improve lung aeration and accelerate the resolution of oedema,[28] which can explain the outliers in the present study. Hence, we cannot exclude the possibility that mild improvements might have occurred during transportation from the animal laboratory to the CT suite. It is also a possibility that hemoglobin-rich fluid extravasated because of hemorrhagic alveolar oedema.[5,15] Notably, postmortem gravimetry does not distinguish between intra- and extravascular blood, thus, calculating all the hemoglobin as if belonging to the intravascular content and falsely excluding the hemoglobin-containing extravasated fluid from the computation.

After infusion of oleic acid, we observed substantial increases in PAP and PVRI paralleled by

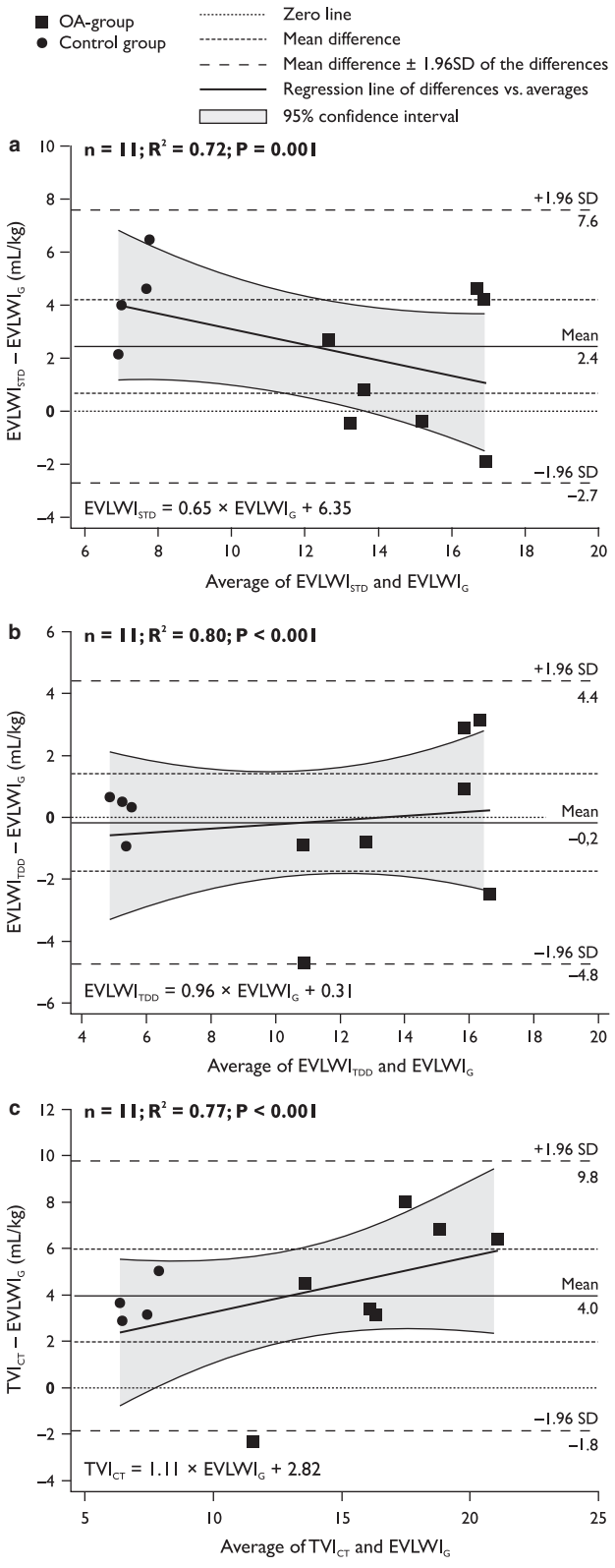

Fig. 3. Bland–Altman's plots showing the associations between extravascular lung water index determined by postmortem gravimetry with extravascular lung water indexes determined by single thermodilution (a), thermal-dye dilution (b), and tissue volume index derived from CT attenuations (c). $EVLWI_G$, extravascular lung water index determined by postmortem gravimetry; $EVLWI_{STD}$, extravascular lung water index determined by single thermodilution; $EVLWI_{TDD}$, extravascular lung water index determined by thermal-dye dilution; TVI_{CT}, tissue volume index estimated by quantitative computed tomography.

the evolvement of pulmonary oedema and significant derangement of gas exchange. We registered increases in EVLWI with both the dilutional techniques. Our findings agree with those of previous investigators studying oleic acid-induced ALI.[4,5,8,29] Following oleic acid, we also observed an inhomogeneous pattern of ALI, including alveolar flooding. However, the hemodynamic and respiratory derangements regressed rapidly, as was also observed in other CT-controlled studies.[14,28]

We found an association between TVI_{CT} and EVLWI, as determined by STD, TDD, and *postmortem* gravimetry. However, in spite of lower absolute biases, the agreement between $EVLWI_G$, as the reference value, and $EVLWI_{STD}$ and $EVLWI_{TDD}$, respectively, proved to be similar to the agreement between TVI_{CT} and $EVLW_G$. By implication, this finding confirms the results of other investigations demonstrating that the accuracy of STD and TDD also depends on the aetiology and the degree of ALI homogeneity, and may be particularly compromised in pathological conditions associated with inhomogeneously distributed pulmonary perfusion.[6,8] The uneven pattern of injury induced by OA may prevent the thermal indicator from interfering uniformly with the oedematous zones because blood flow diverts to less injured areas.[30,31] The latter is consistent with the finding that the dilution methods may yield misleading results after exposure to direct lung injury produced by instillation of hydrochloric acid into the airways.[8] In clinical settings where inhomogeneously distributed ALI is a prominent feature, quantitative CT might provide valuable additional information about lung tissue volumes and relative density. Thus, CT might be a supplementary tool for assessment of lung tissue consolidation and oedema, in addition to the quantification of oedema by dilutional techniques. Therefore, further progress in the development of automated algorithms for analysis of the spiral CT data may provide a key to indirect quantification of pulmonary oedema.

We speculate that inhomogeneous pulmonary perfusion affecting the distribution of both the dye and the thermal indicators could be secondary to hypovolemia, hypoxic vasoconstriction, or pulmonary embolism. All these factors may limit heat exchange that can result in the underestimation of EVLW.[31,32] The mild decline in PBVI that we observed might rather be explained by restricted capacity of the pulmonary vascular bed due to regional vasoconstriction and/or intravascular occlusion due to generation of thrombi.[33,34] Drops of non-emulsified oleic acid also could shape emboli that directly occlude the capillary bed.[35] Therefore, future studies should address the question to what extent factors such as inhomogeneity of lung perfusion, reduction of pulmonary blood flow, and severity of oedema can limit heat exchange and compromise the accuracy of current methods for measuring EVLW content.

Limitations of the study

The experimental study design and the small number of animals may restrict a direct extrapolation of its results to patients with ALI or ARDS. It might not be guaranteed that CT scanning was performed under the condition of complete apnea and at the level of FRC in the non-intubated spontaneously breathing animals. Because the animals were spontaneously breathing, an independent analysis of the hyperinflated areas of the lung tissue (-900 to -1000 HU) was neglected. We believe that hyperinflated zones did not contribute significantly to the resulting value of the TVI_{CT} in this particular experimental setting.[19] However, neglecting the hyperinflated compartment of lung tissue may limit the clinical significance of this study if applied on patients with bronchial obstruction and/or pulmonary emphysema.

Conclusion

As evaluated by postmortem gravimetry, extravascular lung water index assessed by indicator dilution techniques and pulmonary tissue volume estimated by quantitative computed tomography track the extent of pulmonary oedema with an acceptable accuracy. Although the tissue volume index determined with quantitative CT overestimates the values of EVLW, this index might provide supplementary information about the contribution of pulmonary oedema to lung damage in ALI.

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Address:
Prof. *Lars J. Bjertnaes*
Departments of Anaesthesiology and
Intensive Care Medicine
Institute of Clinical Medicine
Faculty of Health Sciences
University Hospital of North Norway
9038 Tromsø
Norway
e-mail: lars.bjertnaes@uit.no

Appendix 1: Volumes derived from transpulmonary dilution techniques

Thermal-dye dilution (TDD) and single thermodilution (STD) calculate cardiac output (CO) based on transpulmonary thermodilution curve according to Stuart-Hamilton principle.

TDD determines the distribution volumes of the thermal and the dye indicators between the point of injection in the right atrium and the point of detection in the aorta by using a combination of thermal and dye indicators (ice-cold indocyanine green (ICG) solution). This technique works by exchanging cold (temperature) extravascularly, whereas ICG binds to intravascular albumin. Therefore, Intrathoracic Thermal Volume (ITTV) and Intrathoracic Blood Volume (ITBV) are calculated as CO $\times$ Mean Transit time (MTt) of the thermal indicator and CO $\times$ MTt of the dye indicator, respectively. The difference between ITTV and ITBV gives extravascular lung water (EVLW).

STD only utilizes a temperature indicator (usually, ice-cold 5% dextrose solution). STD cannot measure ITBV directly, but calculates pulmonary thermal volume (PTV) by multiplying cardiac output with the down-slope (curve exponential decay) time assuming PTV to be the largest mixing volume for the thermal indicator made up by the pulmonary blood volume (PBV) and EVLW volume. The difference between ITTV and PTV gives the maximum end-diastolic volume of the four heart chambers, i.e. global end-diastolic volume (GEDV). Because STD assumes a constant relationship between PBV and GEDV = 1 : 4, ITBV is estimated as GEDV+PBV = 1.25 $\times$ GEDV (Fig. A1). The difference between ITTV and derived ITBV gives EVLW.

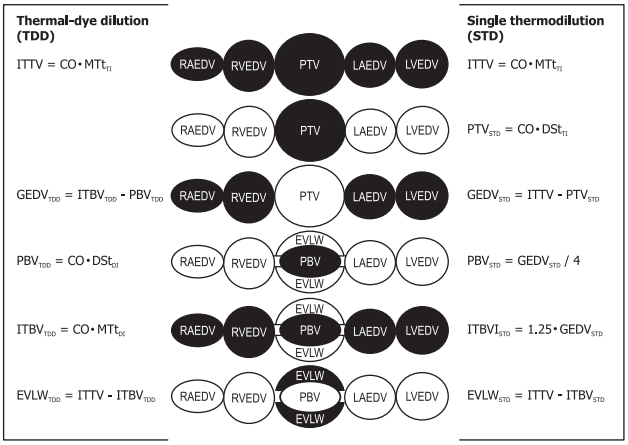

Fig. A1. Methodology of transpulmonary indicator dilution techniques TDD, thermal-dye dilution; STD, single thermodilution; MTt, indicator mean transit time; DSt, indicator down-slope (exponential decay) time; TI, thermal indicator; DI, dye indicator.

Calculated volumetric parameters*: CO, cardiac output; ITTV, intrathoracic thermal volume; ITBV, intrathoracic blood volume; GEDV, global end-diastolic volume; PTV, pulmonary thermal volume; PBV, pulmonary blood volume; EVLW, extravascular lung water.*

Heart volumes*: RAEDV, right atrial end-diastolic volume; RVEDV, right ventricular end-diastolic volume; LAEDV, left atrial end-diastolic volume; LVEDV, left ventricular end-diastolic volume.*