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ORIGINAL RESEARCH

Quantitative computed tomography in comparison with transpulmonary thermodilution for the estimation of pulmonary fluid status: a clinical study in critically ill patients

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Abstract

Extravascular lung water (index) (EVLW(I)) can be estimated using transpulmonary thermodilution (TPTD). Computed tomography (CT) with quantitative analysis of lung tissue density has been proposed to quantify pulmonary edema. We compared variables of pulmonary fluid status assessed using quantitative CT and TPTD in critically ill patients. In 21 intensive care unit patients, we performed TPTD measurements directly before and after chest CT. Based on the density data of segmented CT images we calculated the tissue volume (TV), tissue volume index (TVI), and the mean weighted index of voxel aqueous density (VMWaq). CT-derived TV, TVI, and VMWaq did not predict TPTD-derived EVLWI values ≥ 14 mL/kg. There was a significant moderate positive correlation between VMWaq and mean EVLWI (EVLWI before and after CT) ($r = 0.45$, $p = 0.042$) and EVLWI after CT ($r = 0.49$, $p = 0.025$) but not EVLWI before CT ($r = 0.38$, $p = 0.086$). There was no significant correlation between TV and EVLW before CT, EVLW after CT, or mean EVLW. There was no significant correlation between TVI and EVLWI before CT, EVLWI after CT, or mean EVLWI. CT-derived variables did not predict elevated TPTD-derived EVLWI values. In unselected critically ill patients, variables of pulmonary fluid status assessed using quantitative CT cannot be used to predict EVLWI.

Keywords Extravascular lung water · Pulmonary vascular permeability · Tissue volume · Pulmonary edema

1 Introduction

Extravascular lung water (EVLW) is interstitial, intracellular, alveolar, and lymphatic fluid in the lungs, and thus reflects the amount of water in the lungs outside the pulmonary vasculature not including pleural effusions [1, 2]. In clinical practice, EVLW is indexed to biometric parameters (usually predicted body weight) to be able to use "normal ranges" of extravascular lung water index (EVLWI) despite inter-individual differences in biometric data [3, 4]. Accumulation of EVLW is a hallmark of both acute respiratory distress syndrome (ARDS) and hydrostatic pulmonary edema [1, 5]. EVLW(I) has been demonstrated to have a high predictive value regarding patient outcome in surgical patients [6, 7] and critically ill patients including patients with sepsis and ARDS [8–11].

At the bedside, EVLW can be estimated using single-indicator transpulmonary thermodilution (TPTD) [1]. TPTD is recommended for patients with circulatory shock not responding to initial therapy and shock complicated by

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ARDS [12]. In addition to EVLW, TPTD can be used to assess the pulmonary vascular permeability index (PVPI) that allows differentiating the pathophysiologic reason for increased EVLW [13, 14].

Computed tomography (CT) with quantitative analysis of the density of lung tissue has also been proposed to quantify pulmonary edema [15]. Quantitative CT allows the assessment of organ volumes and computation of the volume of gas, the volume of tissue, and the gas/tissue ratio [15]. CT of the chest has been suggested to quantify pulmonary edema both in experimental and clinical settings [16–18].

Diagnostic CT scans of the thorax are performed in many critically ill patients during intensive care unit (ICU) admission or treatment. To the best of our knowledge, there are no data in unselected ICU patients on the diagnostic value of quantitative CT analysis for the assessment of pulmonary fluid status using CT scans obtained in clinical routine. Therefore, we aimed to compare variables of pulmonary fluid status assessed using quantitative CT and TPTD in a clinical study in unselected critically ill patients.

2 Methods

2.1 Study design and setting

This observational clinical study was performed in patients treated in the medical ICU of a German university hospital (Klinikum rechts der Isar der Technischen Universität München, Munich, Germany). The study was approved by the ethics committee (Ethikkommission der Fakultät für Medizin der Technischen Universität München) and written informed consent was obtained from all patients or their legal representatives. Adult patients were eligible for study inclusion if they (a) were scheduled for CT scanning of the chest and (b) were monitored with TPTD (both for clinical reasons unrelated to the study). According to the study protocol, TPTD measurements (details see below) were performed directly before and after the CT examination.

2.2 Transpulmonary thermodilution measurements

We a priori defined TPTD as the reference method in our study. For TPTD we used the PiCCO system (Pulsion Medical Systems SE, Feldkirchen, Germany) as described previously [19, 20] with a 5-French thermistor-tipped catheter (Pulsiocath PV2015L20; Pulsion Medical Systems SE) placed in the abdominal aorta via the femoral artery. TPTD variables were calculated based on the analysis of the thermodilution curve after injection of 15 mL of iced 0.9% saline in the central venous circulation via a central venous catheter. The injection of the thermal indicator was performed in triplicate and each TPTD value represents the mean of the three consecutive measurements. EVLW was indexed to the predicted body weight resulting in EVLWI. As described previously [13] PVPI was calculated as the ratio of EVLW and pulmonary blood volume.

2.3 Computed tomography and derived calculations

CT was the test method in our study. CT scans were performed using a 64-slice multi-detector CT (Somatom AS, Siemens Healthcare GmbH, Forchheim, Germany). Chest CT was acquired with 120 kVp and automated tube current modulation. Images were reconstructed in transverse plane with a slice thickness of 3 or 5 mm. For this study, the CT scans were analyzed post hoc by two radiologists blinded to the clinical patient data and TPTD-derived parameters.

Manual segmentation was performed using Medical Imaging Interaction Toolkit (MITK) workbench (German Cancer Research Center, Heidelberg, Germany). Regions of interest (ROIs) were prescribed using the software's region growing tool carefully excluding large vessels and extrapulmonary tissue. ROIs were prescribed individually for each axial slice and were initialized in well-ventilated lung tissue. Density of the lungs was determined in Hounsfield Units (HU). A value equal to 0 HU characterizes a voxel with a density equal to that of water and a value of − 1000 HU characterizes a voxel with a density equal to that of air. Based on the density data of the segmented images total lung tissue volume as well as percentages of hyperinflated (< − 900 HU), well-aerated (− 900 to − 500 HU), poorly aerated (− 499 to − 100 HU), and non-aerated (− 99 to + 100 HU) regions were calculated.

As described in detail previously [16] we calculated the tissue volume (TV) as:

$$\begin{aligned} TV = {} & (\text{volume of well-aerated lung tissue} \times 0.3) \\ & + (\text{volume of poorly aerated lung tissue} \times 0.7) \\ & + (\text{volume of non-aerated lung tissue} \times 1.0). \end{aligned}$$

The tissue volume index (TVI) was obtained by indexing TV to predicted body weight.

In addition, we calculated the mean weighted index of voxel aqueous density (VMWaq) as a mathematical assumption of the relative contribution of water in the HU frame:

$$\begin{aligned} VMWaq = {} & ((\text{number (n) of well-aerated lung tissue voxels} \times 0.3) \\ & + (\text{n of poorly aerated lung tissue voxels} \times 0.7) \\ & + (\text{n of non-aerated lung tissue voxels} \times 1.0))/ \\ & \text{total number of voxels.} \end{aligned}$$

2.4 Statistical analysis

Statistical tests were conducted in an exploratory manner on a two-sided 5% significance level. For statistical analyses we used IBM SPSS Statistics for Windows, Version 23 (IBM Corp., Armonk, NY, USA).

Descriptive data are presented as absolute and relative frequencies (categorical data) or as median and 25th and 75th percentile (continuous data).

We used the Spearman correlation coefficient to investigate bivariate correlations of quantitative measurements.

As primary endpoint we investigated the predictive value of the TVI for the prediction of EVLWI values of ≥ 14 mL/kg using receiver operating characteristics (ROC) curve analysis. We chose to use an EVLWI threshold of 14 mL/kg because this cut-off value has repeatedly been shown to be associated with increased mortality [21]. Considering the allocation ratio of 0.62 (mean EVLWI ≥ 14 and < 14 mL/kg), defining "good prediction" as an area under the ROC curve (ROC-AUC) of ≥ 0.80, and applying a 5% significance level, this primary endpoint of our analysis including 21 patients had a post-hoc power of 80%. In addition, we used ROC analysis to assess the predictive value of TV and VMWaq for the prediction of EVLWI values of ≥ 14 mL/kg.

3 Results

3.1 Patients

We included 22 critically ill patients in this study. One patient was excluded from the analysis because of technical problems with the CT analyzing software. Thus, we included 21 patients in the final analysis. The patients' characteristics are presented in Table 1.

Table 1 Patients' characteristics

Basic demographic data	
Sex (female/male)	5/16
Age, years	61 (56–70)
Height, cm	174 (168–180)
Actual body weight, kg	77 (60–85)
Predicted body weight, kg	70 (62–75)
Predicted body surface area, m^2	1.9 (1.7–2.0)
Intensive care unit scores	
Acute physiology and chronic health evaluation II score, points	27 (24–33)
Sequential organ failure assessment score, points	9 (7–12)
Simplified acute physiology score II, points	38 (31–42)
Therapeutic intervention scoring system, points	23 (18–28)
Clinical characteristics on day of study inclusion	
Catecholamine therapy, n (%)	10 (48)
Renal replacement therapy during last 72 h, n (%)	4 (19)
Need for mechanical ventilation, n (%)	14 (67)
Laboratory parameters	
Serum creatinine, mg/dL	1.0 (0.8–1.9)
Blood urea nitrogen, mg/dL	29 (23–44)
Serum bilirubin, mg/dL	0.9 (0.3–2.4)
Aspartate aminotransferase, U/L	43 (25–102)
Leukocyte count, G/L	13.4 (9.5–18.2)
C-reactive protein, mg/dL	6.5 (4.7–11.0)
Reason for ICU admission	
Respiratory insufficiency/pneumonia, n (%)	12 (57)
Acute circulatory failure/hypovolemic shock/septic shock	7 (33)
Acute/acute-on-chronic liver failure, n (%)	1 (5)
Acute pancreatitis, n (%)	1 (5)
Outcome	
Intensive care unit mortality, n (%)	8 (38)
Hospital mortality, n (%)	8 (38)

Data are presented as counts (percentages) or median 25th percentile–75th percentile

3.2 Pulmonary fluid status assessed using quantitative computed tomography

Data from quantitative CT analysis including information on the distribution of hyperinflated, well-aerated, poorly aerated, and non-aerated lung tissue are shown in Table 2 and Fig. 1.

Median TV was 733 (529–804) mL, median TVI was 10.1 (7.0–11.5) mL/kg, and median VMWaq was 0.32 (0.27–0.35).

3.3 Pulmonary fluid status assessed using transpulmonary thermodilution

Data on TPTD-derived EVLW, EVLWI, and PVPI are shown individually for each patient in Table 2.

Median EVLW before and after CT was 627 (526–959) and 751 (601–1100) mL, respectively. Median EVLWI was 10 (8–17) mL/kg both before and after CT.

3.4 Receiver operating characteristics curve analysis

According to ROC-AUC analysis, neither TV nor TVI (primary endpoint) significantly predicted EVLWI values of ≥ 14 mL/kg (Table 3). For VMWaq, ROC analysis yielded ROC-AUCs of 0.76 ($p = 0.062$) and 0.79 ($p = 0.030$) regarding an EVLWI value of ≥ 14 mL/kg before and after CT, respectively (for mean EVLWI ROC-AUC = 0.79, $p = 0.030$) (Table 3). Nevertheless, despite statistical significance, the ROC-AUCs were below the predefined threshold of 0.80.

3.5 Correlation analysis

There was no significant correlation between TV and EVLW before CT ($r = 0.13$, $p = 0.574$), EVLW after CT ($r = 0.05$, $p = 0.823$), or mean EVLW ($r = 0.05$, $p = 0.832$).

There was no significant correlation between TVI and EVLWI before CT ($r = 0.11$, $p = 0.626$), EVLWI after CT ($r = 0.06$, $p = 0.809$), or mean EVLWI ($r = 0.05$, $p = 0.840$).

There was a statistically significant moderate positive correlation between VMWaq and mean EVLWI (EVLWI before and after CT) ($r = 0.45$, $p = 0.042$) and EVLWI after CT ($r = 0.49$, $p = 0.025$) but not EVLWI before CT ($r = 0.38$, $p = 0.086$).

4 Discussion

In this clinical study in unselected critically ill patients, we compared variables of pulmonary fluid status assessed using quantitative CT and TPTD.

CT-derived variables did not predict elevated TPTD-derived EVLWI values. In addition, there was no significant correlation of CT-derived TV and TVI with EVLW and EVLWI assessed using TPTD. Thus, in this study in unselected critically ill patients, variables of pulmonary fluid status assessed using quantitative CT could not be used to predict EVLWI.

Our findings in unselected critically ill patients are in contrast to previous studies that evaluated quantitative CT to estimate pulmonary fluid status under highly standardized conditions in experimental settings.

In an experimental study in 11 spontaneously breathing sheep, Kuzkov et al. [16] demonstrated that CT-derived TVI and EVLWI assessed using TPTD highly significantly correlated ($r = 0.85$, $p < 0.001$). CT scans in this study were performed during a 15-sec breath hold at functional residual capacity.

In a clinical study in 10 ARDS patients, Zhang et al. [18] also reported good correlation ($r = 0.95$, $p < 0.0001$) between TVI and EVLWI. In that study, all patients were mechanically ventilated and CT scans were performed during an end-expiratory pause [18].

In another previous study, Patroniti et al. [22] assessed pulmonary fluid status using double-indicator transpulmonary thermo-dye dilution (TPTDD; with indocyanine green dye in iced dextrose 5%) in 14 patients with ARDS and revealed that these measurements showed good correlation with those by quantitative CT. For our pragmatic clinical study, we deliberately chose to use the single-indicator TPTD method to estimate EVLWI because it is used in clinical practice to estimate EVLWI, has been validated against postmortem lung weight [23], and has been shown to reliably detect even small changes in lung water [24, 25]. One might, however, argue that single-indicator TPTD is not an established reference method to assess EVLWI. Indeed, it is important to understand that the TPTD method—in contrast to the TPTDD method—estimates EVLWI assuming a fixed relation between intrathoracic blood volume and global end-diastolic volume [26].

Given the promising results from these previous studies our aim was to further evaluate the applicability of CT for the assessment of the pulmonary fluid status in critically ill patients. In a previous clinical study in critically ill patients, we observed that the CT-based estimation of EVLWI without analyzing software (qualitative CT) is not accurate compared with TPTD [17].

As a next logical step, in the present study, we used quantitative CT analyses to assess pulmonary hydration under clinical routine conditions in unselected critically ill patients. In these patients, especially in mechanically ventilated patients, diagnostic CT scans are usually performed without an end-expiratory respiratory pause under clinical routine conditions. To evaluate the clinical applicability of

Table 2 Transpulmonary thermodilution measurements and data from computed tomography

ID	Transpulmonary thermodilution-derived hemodynamic variable						Computed tomography										
	EVLW (mL)		EVLWI (mL/kg)		PVPI		TV (mL)	TVI (mL/kg)	VMWaq	$TV_{hyperinflated}$		$TV_{well\text{-}aerated}$		$TV_{poorly\ aerated}$		$TV_{non\text{-}aerated}$	
	Before CT	After CT	Before CT	After CT	Before CT	After CT				(mL)	(%)	(mL)	(%)	(mL)	(%)	(mL)	(%)
1	1156	1220	18	19	2.8	2.5	804	12.5	0.48	15	0.9	930	55.2	697	41.4	38	2.2
2	799	799	13	13	2.9	3.0	1051	17.1	0.25	1112	26.0	2900	67.9	230	5.4	21	0.5
3	619	708	14	16	1.8	2.1	777	17.6	0.35	82	3.7	1790	80.3	270	12.1	52	2.3
4	956	797	12	10	1.6	1.3	544	6.8	0.31	110	6.2	1568	88.0	97	5.4	6	0.3
5	1759	2199	24	30	3.3	4.4	845	11.5	0.37	104	4.5	1734	75.3	408	17.7	40	1.7
6	1709	1709	30	30	5.6	5.6	446	7.8	0.26	371	21.3	1286	73.8	75	4.3	8	0.4
7	462	462	7	7	1.1	1.0	733	11.1	0.27	351	13.1	2242	83.7	74	2.8	9	0.3
8	492	677	8	11	1.6	2.0	348	5.7	0.40	26	3.0	577	67.1	188	21.8	43	5.0
9	1306	1100	19	16	3.6	1.8	652	9.5	0.34	20	1.0	1727	89.2	188	9.7	2	0.1
10	751	751	10	10	2.0	1.8	679	9.0	0.27	534	21.6	1697	68.7	214	8.7	20	0.8
11	601	601	8	8	1.4	1.6	767	10.2	0.31	123	5.0	2173	88.4	156	6.3	6	0.2
12	860	1063	17	21	1.9	3.1	355	7.0	0.38	22	2.3	727	77.0	180	19.1	12	1.2
13	526	451	7	6	1.2	1.1	760	10.1	0.21	1140	32.2	2303	65.0	82	2.3	12	0.3
14	451	601	6	8	0.7	1.1	424	5.6	0.32	56	4.2	1191	88.8	91	6.7	4	0.3
15	570	513	10	9	1.3	1.1	281	4.9	0.43	2	0.4	444	67.7	204	31.2	5	0.7
16	601	751	8	10	1.2	1.6	529	7.0	0.30	122	6.9	1573	88.6	76	4.3	4	0.2
17	627	697	9	10	1.4	1.6	872	12.5	0.30	201	6.9	2556	88.0	129	4.4	15	0.5
18	423	494	6	7	1.2	1.4	759	10.8	0.32	72	3.0	2163	90.5	142	5.9	11	0.5
19	882	1153	13	17	1.4	1.4	644	9.5	0.35	174	9.5	1237	67.8	319	17.5	51	2.8
20	1803	2028	24	27	3.9	4.8	812	10.8	0.35	41	1.8	1924	83.2	291	12.6	31	1.4
21	423	423	6	6	1.5	Missing	1018	14.4	0.22	1289	28.3	3172	69.6	77	1.7	13	0.3
Median (inter-quartile range)	627 (526–956)	751 (601–1100)	10 (8–17)	10 (8–17)	1.6 (1.3–2.8)	1.7 (1.4–2.8)	733 (529–804)	10.1 (7.0–11.5)	0.32 (0.27–0.35)	110 (41–351)		1727 (1237–2173)		180 (90–230)		12 (6–31)	

EVLW extravascular lung water, EVLWI extravascular lung water index, *PVPI* pulmonary vascular permeability index, *TV* tissue volume, *TVI* tissue volume index, *VMWaq* mean weighted index of voxel aqueous density

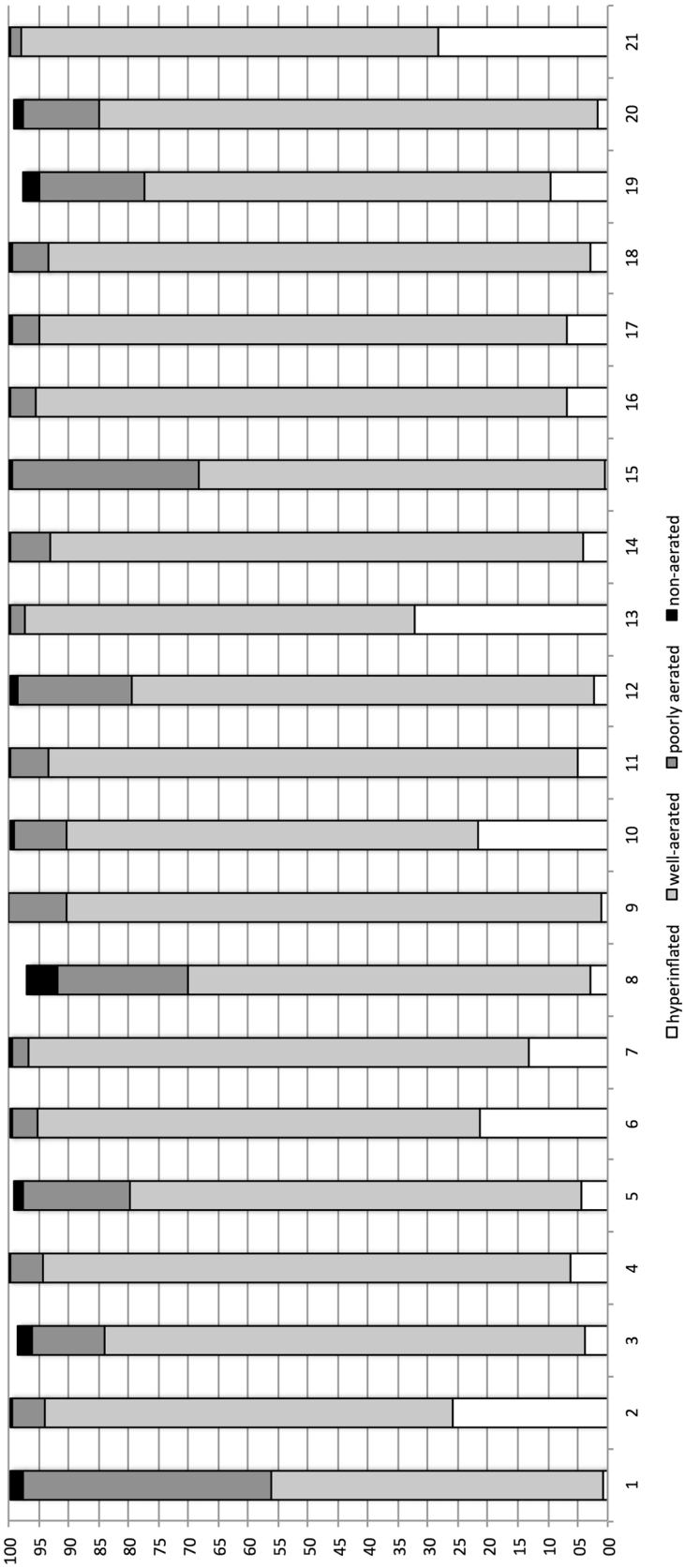

Fig. 1 Distribution of hyperinflated, well-aerated, poorly aerated, and non-aerated lung tissue. Distribution of hyperinflated (white), well-aerated (light gray), poorly aerated (dark gray), and non-aerated (black) lung tissue determined by quantitative computed tomography analysis (some columns do not sum up to 100% because of a small proportion of tissue with > 100 Hounsfield Units)

Table 3 Prediction of extravascular lung water index ≥ 14 mL/kg using receiver operating characteristics curve analysis

	EVLWI ≥ 14 mL/kg					
	EVLWI before CT		EVLWI after CT		Mean EVLWI	
	ROC-AUC	p-value	ROC-AUC	p-value	ROC-AUC	p-value
TV	0.56	0.654	0.53	0.828	0.53	0.828
TVI	0.63	0.332	0.62	0.385	0.62	0.385
VMWaq	0.76	0.062	0.79	0.030	0.79	0.030

EVLWI extravascular lung water index, *TV* tissue volume, *TVI* tissue volume index, *VMWaq* mean weighted index of voxel aqueous density

quantitative CT under clinical routine conditions, we deliberately chose to perform CT scans without an end-expiratory pause and to include both mechanically ventilated and spontaneously breathing patients. To further complicate matters, some of the critically ill patients included in our study had large-volume pleural effusions. Pleural effusions, however, were not included in the CT calculation of lung volumes and pleural effusions do not markedly contribute to TPTD-indicator dilution [2]. All but 2 CT-scans were performed with intravenous contrast agent (some with contrast agent bolus in the arteries/pulmonary arteries).

Therefore, CT-scans in the present study were performed according to clinical routine and not using a standardized protocol for study purposes. In this "clinical reality setting", our results in unselected ICU patients indicate that quantitative CT might not be valuable to assess pulmonary edema (as defined by TPTD-derived EVLWI measurements).

Of note, CT revealed very small lung volumes in some of the patients included in the study. This is in line with the concept of the "baby lung" in patients with ARDS, a concept based on CT images of ARDS patients showing that ARDS not homogeneously involves the entire lung parenchyma but rather the dependent lung regions [27]. It has been shown that in ARDS—besides these dependent lung regions in which gas exchange is markedly impaired—there are normally aerated lung regions [27]. Because these normally aerated lung regions have been demonstrated to have dimensions of a 5- to 6-year-old child (300–500 g aerated tissue) the term "baby lung" was coined [27].

Differences between TV/TVI assessed using CT and TPTD-derived EVLW/EVLWI might also be explained by different measurement principles of the technologies. CT does not differentiate between lung compartments with interstitial fluid, pulmonary tissue, intravascular blood, and edema [16, 18] but detects fluid in the pleural space that is not detected by TPTD [1, 2].

Another explanation could be that the current interpretation of quantitative CT attributes non-aeration mainly to an excess in pulmonary water content. In ARDS, however, increased density and non-aeration also result from atelectasis and aerated areas are not necessarily replaced by fluid. This would also explain that the association of TVI and EVLWI seems to be better in healthy or slightly impaired lungs than in lungs with major pathologies. Under these conditions, non-aeration may result from pulmonary edema as well as atelectasis, e.g., the association of TVI and EVLWI in the animal study by Kuzkov et al. [16] seems to be better before induction of ARDS by oleic acid.

Besides using single-indicator TPTD as the reference method, our study has further limitations. Although the study was performed under routine clinical conditions the limited number of patients and the fact that all patients were treated in an ICU of a single university hospital might limit the generalizability of our findings.

5 Conclusion

In this clinical study in unselected critically ill patients, we compared variables of pulmonary fluid status assessed using quantitative CT and TPTD.

CT-derived variables did not predict elevated TPTD-derived EVLWI values. In addition, there was no significant correlation of CT-derived TV and TVI with EVLW and EVLWI assessed using TPTD. Thus, in this study in unselected critically ill patients, variables of pulmonary fluid status assessed using quantitative CT could not be used to predict EVLWI. To make rigorous conclusions about the value of quantitative CT analysis for the assessment of pulmonary fluid status more clinical data are needed.

Compliance with ethical standards

Conflict of interest Bernd Saugel, Mikhail Kirov, and Wolfgang Huber collaborate with Pulsion Medical Systems SE (Feldkirchen, Germany) as members of the Medical Advisory Board and have received honoraria for giving lectures and refunds of travel expenses from Pulsion Medical Systems SE. All other authors have no conflict of interest to disclose.

Research involving human participants and/or animals All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration

and its later amendments or comparable ethical standards. The study was approved by the ethics committee (Ethikkommission der Fakultät für Medizin der Technischen Universität München).

Informed consent Written informed consent was obtained from all patients or their legal representatives.

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