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Comparing transpulmonary thermodilution monitoring to lung ultrasound during pneumonia: an observational study

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Abstract

Introduction: Monitoring of lung function during pneumonia is essential for the evaluation of the effectiveness of therapy in ICU patients. Among various bedside techniques, two particularly interesting are the lung ultrasound and the transpulmonary thermodilution technique. In this observational single center study we wanted to assess the correlation between the lung ultrasound examination (LUS) and transpulmonary thermodilution volumetric parameters such as extravascular lung water index (EVLWI) and pulmonary vascular permeability index (PVPI).

Material and methods: We analyzed data obtained from medical history of twelve patients requiring mechanical ventilation and hemodynamics monitoring with PICCO catheter due to newly diagnosed pneumonia. We compared lung ultrasound examination performed on the first and third day of new antimicrobial therapy with results of transpulmonary thermodilution examination made on the same day. We also calculated the difference between values obtained on first and third day to compare the trends.

Results: We did not find any association between tested variables, except a correlation between PVPI and EVLWI, both measured at the same day (Rho = 0.3; 95%CI –0.02–0.59; p = 0.03), and trends in the period of 3 days (Rho = 0.6; 95%CI 0.2–0.8; p = 0.005).

Conclusions: The results of the study indicate that volumetric values achieved using the PiCCO method as well as lung ultrasound should be interpreted with care and related to the clinical state of a patient, keeping in mind that no correlation between the result achieved and the actual state of inflammatory changes in the lungs may be possible.

Key words: pneumonia, transpulmonary thermodilution, lung ultrasound

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Introduction

Pneumonia, either acquired during ventilation, or being a cause of ventilation, is still one of the most common types of infection in the intensive care unit (ICU). Inflammation process involving the lungs causes damage to parenchyma and pulmonary vessels, which results in increased extravascular lung water (EVLW) [1]. The equilibrium between fluid transudation/exudation and lymphatic drainage of the lungs has been estimated to be approx. 7 ml/kg, therefore, it has been suggested that the EVLW index (EVLWI) in undamaged lungs is less than 10 ml/kg. It constitutes physiological extravascular lung water present in the interstitial tissue, pulmonary alveoli and the lymphatic system of the lungs [2]. Clinical symptoms of pulmonary infection are characteristic and the purpose of many clinical trials was to summarize them and create a universal scale for diagnostics. For example, the Clinical Pulmonary Infection Score (CPIS) is a well-known score based on the variables such as superficial body temperature, PaO_2/FiO_2, leukocyte count, tracheal secretions character, chest radiographs and bacteriological tests [3]. Its poor sensitivity

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and specificity preclude its use as a single diagnostic scale, and only changes in PaO_2/FiO_2 and WBC count have an impact on eventual mortality [4]. Although the clinical evaluation of the ventilated patient is essential in the ICU, many new techniques allow physicians to measure the level of lungs dysfunction. One of the most useful is transpulmonary thermodilution with the analysis of the pulse wave contour (Pulse index continuous cardiac output, PICCO). Due to the pathophysiology of pneumonia, a considerable advantage of PiCCO is a possibility of determining volumetric parameters, such as the volume of extravascular lung water (EVLW) and pulmonary blood volume (PBV). In addition, the ratio of EVLW to PVB called the pulmonary vascular permeability index (PVPI) may be useful for the differentiation of pulmonary edema etiology — in ARDS, the cut-off value is 3 [5]. Apart from physical examination, laboratory tests and invasive monitoring, physicians have a number of diagnostic imaging tools. While the accuracy of auscultation is estimated to be approx. 36% for consolidation and 55% for alveolar-interstitial syndrome, and one of a chest radiograph is 75% and 72% respectively, the diagnostic accuracy of lung ultrasound is 97% for consolidation and 95% for alveolar-interstitial syndrome [6], and it closely correlates to the lungs air volume acquired by CT [7]. Bedside ultrasound technique is precise, repeatable and based mainly on the analysis of artefacts developing while ultrasound waves travel through centres with different physicochemical properties [8]. Unlike high-resolution computed tomography (HRCT), which is currently the "gold standard" of lung imaging, ultrasound does not require critically ill patients to be transported.

Bedside lung ultrasound examination performed in our ICU is typically based on the assessment of 8 quadrants of the lungs [8]. They are limited by the parasternal line, anterior axillary line, posterior axillary line, and the line that runs in the middle of the distance between the diaphragm and the clavicle and the top of the axilla both on the right and left side of the thorax (Fig. 2). Visualization of the specific artefacts determine the degree of quadrant aeration, which can be categorized as follows: N (properly aerated) — the movement of the lung was clearly visible against the pleural cavity and A-line or single (< 3), narrow, and properly defined B-lines occur; B1 (moderately non-aerated, moderate interstitial syndrome) — multiple (> 3), regular, and clearly visible B-lines, no A-line; B2 (alveolar-interstitial syndrome) — diffuse B-lines, unclearly defined, occurring at uneven distances < 3 mm; C (consolidation) — "lung hepatization syndrome" with air or fluid bronchogram, no A-line or B-line, impaired movement trace of the lung against the pleural cavity. Pictures are presented in Figure 3.

The aim of this study was to estimate correlation between the values of EVLWI, PVPI and lung ultrasound examination (LUS) during treatment of pneumonia. Secondary, we compared the trends of measured parameters between the pathogen directed therapy (PDT) or inappropriate empirical therapy (ET).

Material and methods

In this observational study we collected information from the medical history of patients admitted to the SPSK no 7 GCM ICU between May and December 2016. Specific ethical approval was not required as all obtained data were collected as part of the standard assessment, and a retrospective analysis included non-identifiable patient data. No interventions on cohort were made. We preliminarily assessed for eligibility 58 patients with respiratory failure due to pneumonia. Twelve

Table 1. Three days trend — differences between first and third day of antimicrobial therapy

Three days trend	Inappropriate empirical treatment (ET) n = 10	Pathogen directed therapy (PDT) n = 10	p
WBC (10^3/ul)	–3,7 (IQR 5,2; –5,4 to – 0,1)	1,37 (IQR 12,1; –7,7 to 4,4)	0,7
CRP (mg/l)	11,4 (SD 119,9; –74,4 to 97,1)	32,38 (SD123,4; –55,9 to 120,7)	0,7
PaO_2/FiO_2 (mm Hg)	-8,6 (SD 57,3; –49,6 to 32,4)	2,7 (SD 91,3; –62,6 to 68,0)	0,7
EVLWI (ml/kg)	0,8 (IQR 1,1; 0,4 to 1,5)	0,1 (IQR 3,7; –0,7 to 3,0)	0,5
PVPI	0,09 (SD 0,3; –0,1 to 0,3)	0,13 (SD 0,5; –0,3 to 0,5)	0,8
LUS	1,1 (SD 6,2; –3,3 to 5,5)	1,0 (SD 3,3; –1,3 to 3,3)	0,9

IQR: interquartile range; SD: standard deviation; WBC: white blood cells; CRP: c-reactive protein; EVLWI: extravascular lung water index; PVPI: pulmonary vascular permeability index; lung ultrasound examination

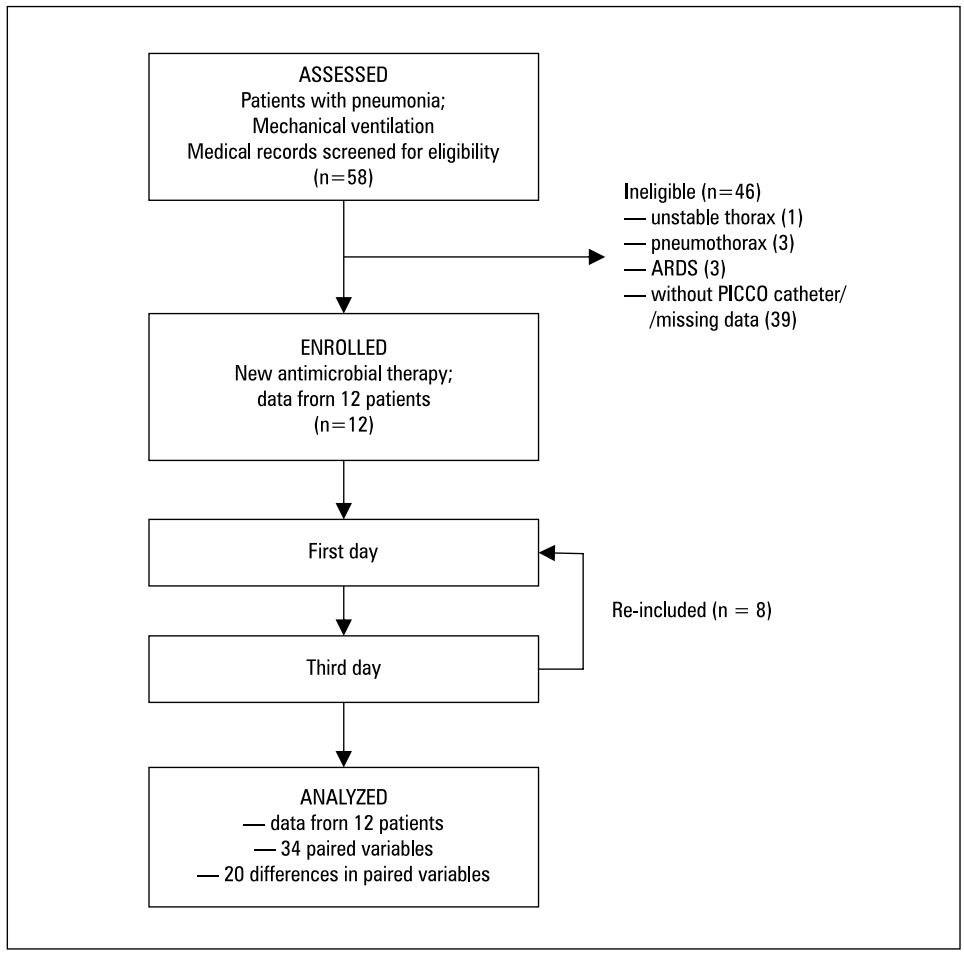

Figure 1. Flow chart

patients were eligible when data of transpulmonary thermodilution and lung ultrasound were available from the same day and they fulfilled inclusion criteria: newly diagnosed pneumonia (hospital- or community-acquired pneumonia), mechanical ventilation, transpulmonary thermodilution monitoring (PICCO), data from the first and third day of new antibiotic therapy. We excluded from the analysis data of 46 patients without PICCO monitoring or other missing data (39), patients with unstable thorax with drainage (1), tension pneumothorax with drainage (3) or ARDS (3). Flow diagram is presented in Figure 1.

LUS examinations were performed by two anesthesiologists with ultrasonography certificates and clinical experience in lung ultrasound and echocardiography. The description of ultrasound lungs examination was converted into the numerical scale that assesses the degree of atelectasis, where the normally aerated lungs (N) scores 0 pts, B1 pattern (B1) = 1 pt, B2 pattern (B2) = 2 pts, consolidation (C) = 3 pts. Then the Lung Ultrasound Score (LUS) was calculated as the total sum of points achieved in individual quadrants — LUS = 0–24 pts. Because of the technical issues and probability of bias, the absolute values of EVLW was manually indexed for ideal body weight calculated according to the Lemmens formula, which is identical for both genders (IBW = height (meter)^2 × 22).

All statistical calculations were made with StatsDirect (StatsDirect Ltd, Cambridge, UK). A minimum sample size to find moderate correlation was estimated 30 ($r = 0.5, \alpha = 0.05, \beta = 0.8$). We analyzed a total number of 34 values of LUS, EVLWI and PVPI obtained from 12 patients at the first and third day of the new antimicrobial therapy. Subsequently, we calculated the difference between the values obtained on the first and third day to assess the trends. Depending on the results of bronchoalveloar lavage specimens we divided these data in two groups — the pathogen directed therapy (PDT, n = 10) or inappropriate empirical therapy (ET, n = 10). Data were analyzed in terms of the type of variable distribution using the Shapiro-Wilk test and visualization of

quantile-quantile plot. For the normally distributed variables, the results are presented as mean, standard deviation (SD) and 95% CI of the mean [95% CI] while for non-normal variables, these were presented as median with interquartile range (IQR) and quartiles [lower quartile–upper quartile]. Categorical variables were presented as proportion and percentage. Depending on data distribution, either Pearson (R) or Spearman correlation coefficient (Rho) was determined. The differences between the groups were analyzed with t-Student test or Mann-Whitney test. The $p < 0.05$ was considered significant.

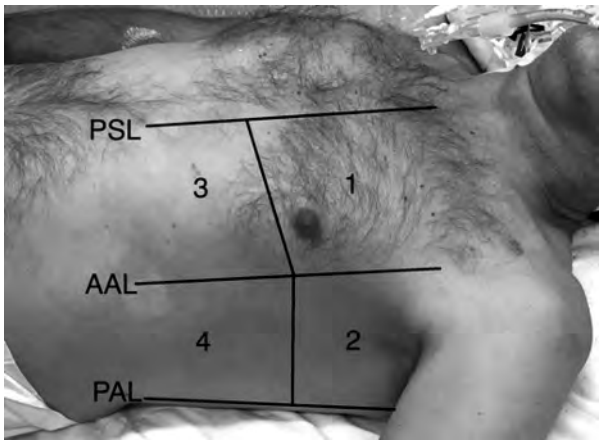

Figure 2. Left lung divided into 4 quadrants. PSL: parasternal line; AAL: anterior axillary line; PAL: posteriori axillary line

Results

We analyzed data acquired from the medical history of four women and eight men aged 71.5 (range 63–79). They were admitted to ICU from the surgical ward (4/12, 33.3%), neurology ward (3/12, 25%), internal medicine ward (2/12, 16.7%), cardiology ward (1/12, 8.3%), psychiatry ward (1/12, 8.3%) and directly from the emergency department (1/12, 8.3%). The patients were diagnosed as follows: ventilator-associated pneumonia (5/12, 41.7%), hospital-acquired pneumonia (4/12, 33.3%), aspiration pneumonia (3/12, 25%). Nine patients suffered from CVD, including history of myocardial infarction (3/12, 25%), atrial fibrillation (5/12, 41.7%) and mild mitral valve regurgitation (1/12, 8.3%). Five subjects required renal replacement therapy during hospitalization (5/12, 41.7%). The median hospitalization time was 9 days (IQR10), but all patients died during their stay in the intensive care unit. The bacteriological result of BAL specimen was

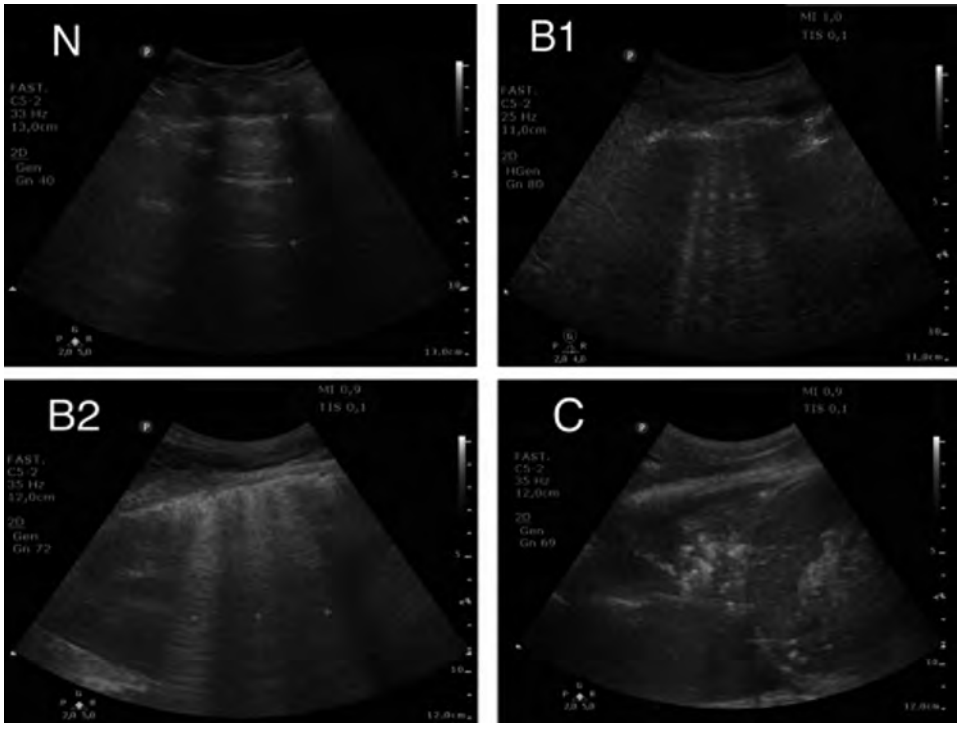

Figure 3. Lung ultrasound patterns, degree of lung aeration. **N** (properly aerated): the movement of the lung was clearly visible against the pleural cavity and A-line or single (< 3), narrow, and properly defined B-lines occur; **B1** (moderately non-aerated, moderate interstitial syndrome): multiple (> 3), regular, and clearly visible B-lines, no A-line; **B2** (alveolar-interstitial syndrome): diffuse B-lines, unclearly defined, occurring at uneven distances < 3 mm; **C** (consolidation): "lung hepatization syndrome" with air or fluid bronchogram, no A-line or B-line, impaired movement of the lung against the pleural cavity

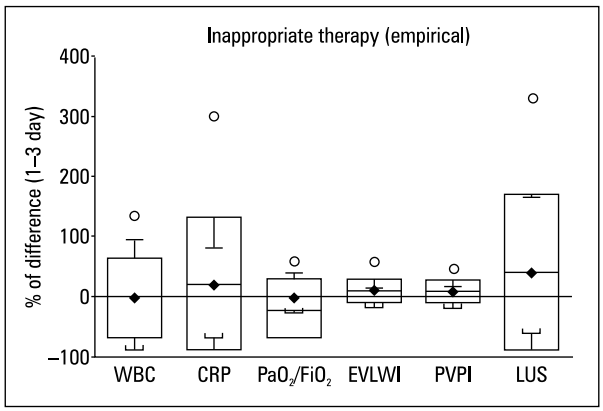

Figure 4. Differences in variables between first and third day of inappropriate empirical therapy

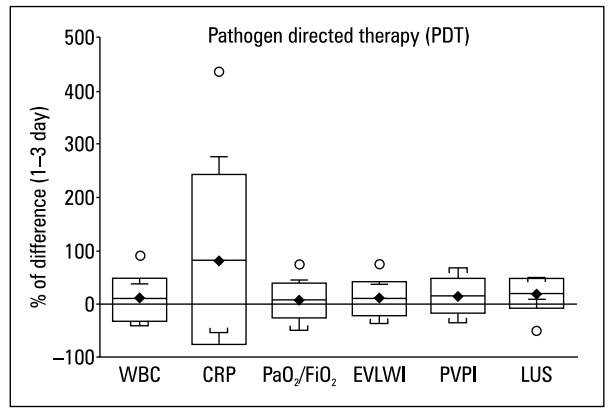

Figure 5. Differences in variables between first and third day of pathogen directed therapy

the following: *A. baumani* (35%), co-infection of *A. baumani* and *P. aeruginosa* (5%), *E. cloace* (5%), *K. pneumoniae* (40%), *S. epiredmidis* (5%). Two results were negative (10%). The patients were administered either broad spectrum antibiotics or pathogen directed therapy such as: ertapenem, meropenem, imipenem/cilastin, colistin, linezolid, ciprofloxacin, ceftriaxon, sultamicillin. The mean lung ultrasound score (LUS) was 9.3 (SD 4.2; 95%CI 7.8–10.8), mean vascular permeability index value (PVPI) 1.7 (SD 0.4; 95%CI 1.5–1.8), median of index of extravascular lung water (EVLWI) was 9.6 ml/kg (IQR 4.8; 8.3–13.1 ml/kg). We did not find any correlation between LUS and PVPI or LUS and EVLWI ($p > 0.05$). We found a weak correlation between the values of EVLWI and PVPI (Rho = 0.3; 95%CI –0.02–0.59; $p = 0.03$) as well as between the trends of EVLWI and PVPI (Rho = 0.6; 95%CI 0.2–0.8; $p = 0.005$). There was no statistically significant difference between variables in pathogen directed and inappropriate empirical therapy ($p > 0.05$). A summary is presented in Table 1 and Figures 1, 2.

Discussion

The need for accurate and reliable monitoring of the pneumonia therapy in ICU patients inclines physicians to seek new diagnostic methods. The main issue to be faced may be the coexistence of a complex pathology in a patient, which makes it much more difficult to determine the primary cause of a disease. In case of pneumonia, an increase in pulmonary vascular permeability leads to fluid exudation, without the increase in hydrostatic pressure inside the vessels [9]. Different pathophysiology is seen in cardiogenic pulmonary edema (CPE), which develops during acute heart failure and involves the increase in hydrostatic pressure and Starling filtration forces in undamaged pulmonary vessels [10]. The same may concern neurogenic pulmonary edema (NPE), the pathogenesis of which has not been established completely, but still a significant role in developing NPE is attributed to the activation of the sympathetic nervous system [11]. Another example is pulmonary edema during upper airway obstruction resulting from the generation of high negative intrathoracic pressure during inhaling (negative pressure pulmonary edema [NPPE]) [12]. All of these clinical conditions lead to lung edema in different mechanisms and, therefore, pose a challenge in terms of objective diagnosis, treatment and monitoring. Laboratory tests like WBC count monitoring, CRP, PCT, galactomannan antigen and beta-d-glucan values can be useful. However, attention should be paid to the fact that basing on the above-mentioned parameters, we cannot definitely say whether high values result from pulmonary pathology or there is another cause, including a new focus of infection or systemic inflammatory response syndrome (SIRS). The correlation between laboratory tests, diagnostic imaging and clinical symptoms in ICU patients also tends to be ambiguous. Body temperature measurements in a patient under renal replacement therapy may not be reliable, and the assessment of bronchial tree secretion appears to be very subjective. Auscultation has low sensitivity and specificity for the assessment of pulmonary pathology. When applying broad-spectrum antibiotics, microbiologic tests may yield false negative results, and positive results only sometimes correlate with the clinical state of a patient.

Diagnostic tests such as CXR and chest CT may be very helpful to assess pulmonary disorders, although, as has been mentioned earlier, they come with numerous limitations. Lung ultra-

sound has become very popular within the last couple of years. Not only is it repeatable, bedside and quick, but most of all it is characterized by significantly higher sensitivity and specificity as compared to common diagnostic methods.

The usefulness of PiCCO in monitoring therapy in ICU patients has been confirmed by many studies. For clinical practice, PiCCO is a source of invaluable hemodynamic and volumetric data such as stroke volume (SV) and cardiac output (CO), maximum left ventricular contractility (dPmax), systemic vascular resistance (SVR), global end-diastolic volume (GEDV), extravascular lung water (EVLW), or finally pulmonary vascular permeability index (PVPI). Extravascular lung water assessed using thermodilution is comparable to the lung weight measured posthumously and with the use of gravimetry; however, there is no correlation between EVLW and PaO_2/FiO_2 in patients with ALI/ARDS [5, 13, 14]. The large volume of extravascular lung water is closely associated with the increase in mortality (65-85%), while a strict control of fluid therapy and EVLW leads to a considerable reduction of mechanical ventilation time and patient's hospitalization [15–17]. Kushimoto *et al.* [18] pointed out that there is a high correlation between PVPI and EVLWI ($r = 0.729$, $p < 0.01$) and a poor association between EVLWI and ITBV ($r = 0.236$, $p < 0.01$) among patients with ALI/ARDS. Among patients without ALI/ARDS, the correlation between EVLWI and PVPI, and EVLW and ITBV was moderate ($r = 0.464$, $r = 0.493$, $p < 0.01$ respectively), whereas there was no association between EVLWI and PVPI ($r = –0.176$, $p = 0.39$) in patients with cardiogenic pulmonary edema [18].

The aim of this study was to answer whether volumetric parameters obtained with PiCCO correlate with lung ultrasound in ICU patients treated for pneumonia. Clinical implications of such correlation may be significant, giving physicians a new bedside diagnostic tool for monitoring antimicrobial therapy.

We did not find any current study comparing lungs ultrasound to transpulmonary thermodilution in ICU patients treated for pneumonia. To perform the statistical analysis on a group as homogeneous as possible, we designed a retrospective research, knowing the limitations of statistical inference.

In our study, the values of EVLWI and PVPI obtained during the PiCCO monitoring do not correlate with the lung assessment using ultrasound. In a *post hoc* analysis we also did not find any differences in LUS score with EVLWI cut-off 10 ml/kg: for EVLWI > 10 ml/kg, the mean of LUS was 9.6 and for ≤ 10 ml/kg, the mean of LUS was 8.9 (95%Ci for difference between the means –3.8 to 2.1, two-sided $p = 0.56$). Despite a very low cohort size, we decided to perform logistic regression to check if LUS can identify EVLWI > 10 ml/kg. Calculated odds ratio (OR) = 1.05 (95%CI 0.9–1.2; $p = 0.54$).

Inconsistent results from correlative studies show the magnitude of the problem of adequate lungs assessment. ICU patients are a heterogenous population, therefore unbiased study is difficult to perform and time- consuming. Davids *et al.* [19] did not find a correlation between EVLW and lung ultrasound in the critically ill. Contrary, Anile *et al.* [20] showed a good correlation between lung ultrasound and EVLW in nineteen adult patients requiring mechanical ventilation due to several clinical conditions, but only six of them were diagnosed with acute respiratory failure. Volpicelli *et al.* [21] investigated a correlation between LUS, EVLW and wedge pressure in seventy-three patients, but only five with pneumonia. They showed that assessment of B-lines can be a useful bedside tool for evaluating hemodynamic status of the ICU patient but these conclusions cannot be easily extrapolated on a subgroup of subjects treated for pneumonia. The prospective study by Bataile *et al.* [22] revealed a good correlation of EVLW and LUS in individuals with acute respiratory distress syndrome. In ARDS, changes in the lungs are diffused and clinically well-defined, therefore, ultrasound examination and PICCO values are sensitive for this clinical syndrome. By analogy, in our study we searched for correlation between LUS and EVLWI in pneumonia, the condition more heterogenous in terms of affected lung volume than ARDS.

Our primary results indicate low usefulness of monitoring extravascular lung water and pulmonary vascular permeability index during pneumonia. It seems the reason behind this is the fact that parameters such as EVLWI and PVPI assess the entire pulmonary tissue, which — if inflamed — is heterogenous, while atelectasis and edema areas often coexist with uncongested ones. This applies to the both lungs and segments of the same lung. The value of EVLWI and PVPI may be within the limit in case of a severe inflammation that affects a limited area of the pulmonary tissue. Incorrect evaluation of patient's body weight may pose another problem during the interpretation of the PiCCO results. The EVLW values obtained with the use of the thermodilution technique should be indexed only for height and ideal body weight because a positive fluid balances, and, thus, a considerable increase in body weight, may reduce the EVLWI values [23].

In ultrasound, single parts of the lung are evaluated and therefore monitoring may be more adequate. The example is the lung aeration score described by Bouhemad *et al.* [7], which was verified by computed tomography. The authors have not found any publication that would evaluate the values of the EVLWI and PVPI in comparison with CT during pneumonia. Ultrasound limitations may stem from the fact that due to the necessity to change the patient's position, paraspinal segments are not conventionally evaluated. The differences in projection interpretation by sonographers may also pose a great problem, especially in terms of differentiation between N and B1 levels. One reasonable way to investigate accuracy of transpulmonary thermodilution and lung ultrasound during pneumonia is to compare them both with computed tomography, and it should be designed as prospective blinded clinical trial.

Conclusions

The results of the study indicate that volumetric values measured with the PiCCO method as well as lung ultrasound should be interpreted with care and related to the clinical state of a patient, keeping in mind that no correlation between the obtained results and the actual state of inflammatory changes in the lungs may be possible.

Conflict of interest

The authors declare no conflict of interest.

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