

Accuracy of ultrasound B-lines score and E/Ea ratio to estimate extravascular lung water and its variations in patients with acute respiratory distress syndrome

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Abstract Extravascular lung water (EVLW) could increase by permeability pulmonary oedema, cardiogenic oedema, or both. Transthoracic echocardiography examination of a patient allows quantifying B-lines, originating from water-thickened interlobular septa, and the E/Ea ratio, related to pulmonary capillary wedge pressure. The aim of our study was to assess the correlation and the trending ability between EVLW measured by transpulmonary thermodilution and the B-lines score or the E/Ea ratio in patients with ARDS. Twenty-six intensive care unit patients were prospectively included. B-lines score was obtained from four ultrasound zones (anterior and lateral chest on left and right hemithorax). E/Ea was measured from the apical four-chamber view. EVLW was compared with the B-lines score and the E/Ea ratio. A linear mixed effect model was used to take account the repeated measurements. A p value <0.05 was considered significant. A total of 73 measurements were collected. The correlation coefficient between EVLW and B-lines score was 0.66 ($\text{EVLW} = 0.71 \text{ B-lines} + 7.64$, $R^2 = 0.44$, $p = 0.001$), versus 0.31 for E/Ea ($p = 0.06$). The correlation between EVLW changes and B-lines variations was significant

($R^2 = 0.26$, $p < 0.01$), with a concordance rate of 74 %. A B-lines score ≥ 6 had a sensitivity of 82 % and a specificity of 77 % to predict $\text{EVLW} > 10 \text{ ml/kg}$, with an AUC equal to 0.86 (0.76–0.93). The gray zone approach identified a range of B-lines between four and seven for which $\text{EVLW} > 10 \text{ ml/kg}$ could not be predicted reliably. The correlation between ultrasound B-lines and EVLW was significant, but the B-lines score was not able to track EVLW changes reliably.

Keywords Measurement techniques—thermodilution · Measurement techniques—Doppler echocardiography · Lung—adult respiratory distress syndrome · Heart—myocardial function

1 Introduction

Acute respiratory distress syndrome (ARDS) might be associated with an increase of extravascular lung water (EVLW), which is the amount of water contained in the lungs outside the pulmonary vasculature. That is the sum of interstitial, alveolar, intracellular, and lymphatic fluids, except pleural effusion. EVLW is an independent risk-factor of 28 day mortality in patients with ARDS [1]. Moreover, there was some evidence that the EVLW guided treatment reduced mortality rate in patients with permeability pulmonary oedema [2], therefore methods to accurately quantify the amount of EVLW may be of value to clinicians who treat patient with ARDS [3]. EVLW can be measured by devices using transpulmonary thermo-dilution. The estimation of EVLW by a single (cold) indicator has been shown closely correlated with the double indicator dilution technique (thermo-dye): the coefficient

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correlation was 0.96 and the mean bias (SD) was -0.5 (1.9) ml/kg [4].

Echographic examination of the lung surface may reveal B-lines artifact originated from water-thickened interlobular septa. The inter-rater reliability of quantifying pleural B-lines is acceptable with an intraclass coefficient correlation equal to 0.89 (0.87–0.91) [5]. The number of B-lines has been shown to correlate with EVLW and pulmonary capillary wedge pressure [6]. However, there are few studies evaluating the correlation between B-lines and EVLW in critically ill patients with ARDS [7]. Moreover, there is no validated model to estimate EVLW based on an ultrasound score in this setting, therefore the ability of B-lines score to predict EVLW and its changes in clinical practice is unknown.

In addition, a septic shock associated with ARDS could impair left ventricular relaxation and induce a diastolic dysfunction, which could lead to heart failure and pulmonary oedema [8]. Volume expansion, performed at the early phase of sepsis to improve organ perfusion, could increase EVLW by permeability pulmonary oedema, cardiogenic oedema, or both. The peak velocity of the mitral annulus early wave during diastole (Ea), measured by tissue Doppler imaging, was reduced in patient with impaired relaxation [9]. The ratio between the peak velocity of the mitral annulus early wave (E wave measured by pulse-Doppler) and Ea related well to pulmonary capillary wedge pressure [9, 10], which has been shown to correlate with the number of B lines [6, 11, 12] and therefore might be correlated with EVLW changes.

The primary aim of our study was to assess the correlation between B-lines score, E/Ea ratio and EVLW measured by transpulmonary thermodilution (TPTD) in patients with ARDS, and evaluate the accuracy of this model to predict an increase of EVLW. The secondary aim was to evaluate the ability of B-lines score and E/Ea ratio to detect a variation of EVLW.

2 Materials and methods

2.1 Population

This single centre prospective observational study was conducted in the intensive care of Narbonne Hospital (France). After institutional approval, 26 patients admitted in intensive care were included (Fig. 1). No additional invasive procedure or blood samples were necessary for this study, therefore the need for informed consent was waived by the Institutional Review Board of Narbonne Hospital [13]. The inclusion criteria were: ARDS defined in accordance with the Berlin definition [14] and septic shock (hypotension persisting after initial fluid challenge or

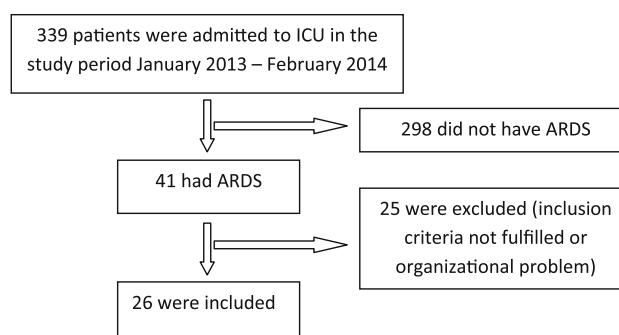


Fig. 1 Enrollment of the study participants

blood lactate concentration ≥ 4 mmol/l) requiring an advanced hemodynamic monitoring by TPTD [15]. The etiology of ARDS included in our study was pneumonia. Patients were excluded if they were <18 years old, or if they had severe cardiac valvulopathy, femoral artery stenosis or major pleural effusion.

2.2 Measured variables

Patients characteristics (age, sex, height, and weight), Simplified Acute Physiology Score (SAPS2), use of vasoactive agents, hemodynamic data, i.e. cardiac output, EVLW, heart rate, mean arterial pressure were collected. All patients were ventilated with a tidal volume ranged between 6 and 8 ml/kg. A calibration of EV1000 system was made before each measurement. During the study, the investigators were blinded to each's other results.

2.3 EVLW measurements

A central venous catheter was inserted into the left or right jugular vein and used for cold indicator injections. A VolumeViewTM catheter (Edwards Lifesciences) was inserted through the left or right femoral artery and connected to the EV1000TM monitoring system (software version 1.4). Thermodilution measurements were performed in sets of at least three consecutive injections of 20 ml cold saline, randomly distributed over the respiratory cycle. Bolus sets that contained a bolus that differed by more than 15 % from the mean within the set were considered faulty and excluded from the analysis. The previous study of Bendjelid and coll. showed a good reproducibility with a coefficient of variation equal to 5.7 ± 4.2 % [16]. The exact algorithm to calculate the cardiac output and EVLW has been described elsewhere [16–18]. We used EVLW indexed to predicted body weight (PBW) because this value had been shown to correlate better with $\text{PaO}_2/\text{FiO}_2$ ratio than EVLW indexed to real body weight [19, 20]. PBW (kg) was calculated as $50 + 0.91 * (\text{height in cm} -$

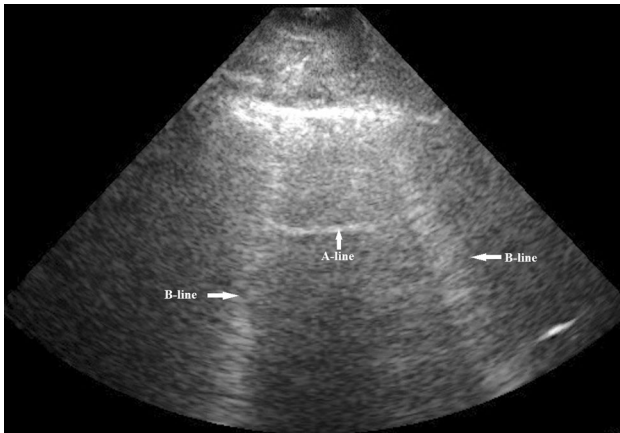


Fig. 2 Ultrasound B-lines. The B-lines arise from the pleural line, move with lung sliding and erase A-lines

152.4) for males and $45.5 + 0.91 \cdot (\text{height in cm} - 152.4)$ for females. Normally, EVLW is inferior to 10 ml/kg [19, 21].

2.4 Ultrasound B-lines Lung Score

The ultrasound scanning of the anterior and lateral chest was obtained on left and right hemithorax, on the second intercostal space at the midclavicular line, and on the fourth intercostal space at the middle axillary line. The inclination of the probe was chosen to obtain a maximum number of B-lines on a frozen image. B-lines at lateral bases were not studied because they were observed in 27 % of healthy subjects [22]. Only four ultrasound zones for each patient were used in our study and the sum of the B-lines of each zone determined the B-lines score. The B-lines were counted in a single rib space at the moment when the most number of B-lines were seen on a frozen image [5]. The B-lines were defined as hyper-echoic, arising strictly from the pleural line, moving with lung sliding, spreading to the edge of the screen without fading, and erasing A lines (Fig. 2) [23]. At the pleural line, the distance between B-lines is roughly 7 mm. The number of B-lines observed in a single rib space was ranged between 0 and 5, therefore the total B-lines score of the four zones was ranged between 0 and 20. The examination was performed using an ultrasound system (“Sonosite™ Micro-Maxx”) with a probe of 2–4 MHz.

2.5 Transthoracic echocardiographic measurements

From the apical four-chamber view, transmitral flow velocities were recorded with the pulse wave Doppler sample volume placed at the mitral tips. Peak early (E) and late (A) velocities were recorded, as well as E wave

deceleration time (EDT). From the same view, mitral annulus velocities were obtained using tissue Doppler settings, with the Doppler sample volume placed at the lateral side of the mitral annulus. Myocardial systolic velocity (Sa) and early (Ea) velocities were measured, and the E/Ea ratio was calculated. The ejection fraction was measured using the Simpson method.

2.6 Statistical analysis

The normality of the quantitative data was verified using a Shapiro–Wilk test, and expressed as mean \pm standard deviation (SD) or median [range]. Based on the previous study of Agricola and coll. [6], at least 26 measurements were needed to test a correlation coefficient of 0.5, with an α -risk of 0.05 and a power of 80 % (logiciel G*Power 3.1.5). Twenty-six patients were included in the study with one to four measures by patient, with a period of 1 day between each measurement. If a patient was weaned from mechanical ventilation, died or was transferred to another department for ExtraCorporeal Membrane Oxygenation, the inclusion of patient data was stopped, therefore a variable number of measurements was realized for each patient. To take account repeated measurements, a linear mixed effect model was used to assess the correlation between EVLW, B-lines score, E/Ea ratio and $\text{PaO}_2/\text{FiO}_2$ ratio [24]. A multivariate linear mixed effect model was used to test the correlation of EVLW with B-lines score and E/Ea ratio. The Akaike information criterion (AIC) was used to choose the optimal model. The normality of the data was verified and a bootstrap procedure (1000 permutations) was used to estimate coefficients if the distribution was not Gaussian. When three experimented operators were simultaneously available (B.B., P-E.M., P.C.), the intraclass correlation coefficients (ICC) of B-lines score and E/Ea ratio were evaluated on a random sample of 10 patients to assess the inter-observer reproducibility of the echographic measurements. Interobserver variability was calculated as the ratio (expressed as percentage) of the difference between the values obtained by each observer (expressed as absolute value) divided by the mean of the two values. Intraobserver variability was calculated by a similar approach.

A ROC curve, corrected for repeated measurements by a generalized linear mixed effect model [25], was used to determine the optimal B-lines threshold predicting EVLW >10 ml/kg and EVLW >15 ml/kg [21, 26]. The highest sum of sensitivity and specificity was considered as being the optimal threshold. The accuracy was defined as $(\text{true positive} + \text{true negative}) / (\text{positive} + \text{negative})$. The “gray zone” was determined using a 2-step procedure [27, 28]. The first step consisted of the determination of the optimal threshold for the B-lines score. The second step was

Table 1 Main characteristics of the patients

Demographic data	Patients (n = 26)
Age (years)	61 ± 13 [35–79]
Weight (kg)	76 ± 17 [50–120]
Height (cm)	169 ± 9 [149–185]
Female/male	9 (35)/17 (65)
Simplified Acute Physiology Score (SAPS2)	60 ± 24 [23–99]
ARDS severity	
Mild (PaO ₂ /FiO ₂ > 200 and < 300)	6 (23)
Moderate (PaO ₂ /FiO ₂ > 100 and < 200)	9 (35)
Severe (PaO ₂ /FiO ₂ < 100)	11 (42)
Positive end-expiratory pressure (cm H ₂ O)	7 ± 3 [3–15]
Peak airway pressure (cm H ₂ O)	25 ± 6 [15–34]
Use of catecholamine	22 (85)
Atrial fibrillation	8 (31)
Heart rate (beats/min)	89 ± 21 [54–126]
Mean arterial pressure (mmHg)	82 ± 14 [45–118]
Cardiac output (l/min)	6.4 ± 2 [2.6–11.4]
EVLW (ml/kg)	12 [6–28]
Left ventricular ejection fraction (%)	48 ± 13 [15–75]
Sa wave (cm/s)	12 ± 3 [6–18]
E wave (cm/s)	90 ± 24 [38–150]
E wave deceleration time (ms)	197 ± 45 [105–300]
A wave (cm/s) (no atrial fibrillation)	60 ± 17 [28–100]
E/A ratio (no atrial fibrillation)	1.6 ± 0.6 [0.6–3]
Ea wave (cm/s)	13 ± 3 [6–21]
E/Ea ratio	7 ± 2 [4–13]
B-lines score	8 [1–20]

EVLW and B-lines score are expressed as median [range]. The others values are expressed as mean ± SD [range] or number (percentage)

conducted to determine the values for which the B-lines score did not provide conclusive information. We defined inconclusive responses for values presenting with either sensitivity <90 % or specificity <90 %. The gray zone was then defined as the values of the B-lines score that did not allow having 10 % of diagnosis tolerance. However, if the 95 % confidence interval of the optimal threshold was larger than the inconclusive zone, the values obtained during the first step were retained as gray zone.

A four quadrant plot was used to test the trending ability of the B-lines score [29]. The concordance rate was defined as the percentage of the total number of data point changing in the same direction (i.e. data points located in the upper right and lower left corners of Fig. 5). When a central exclusion zone of 15 % was used, a concordance rate superior to 90 % was considered acceptable [29].

A Jonckheere–Terpstra test was performed to test a relationship among EVLW, B-lines score, E/Ea ratio, and ARDS severity (determined based on the lowest PaO₂/FiO₂ ratio during the study period) [30]. For this analysis, only

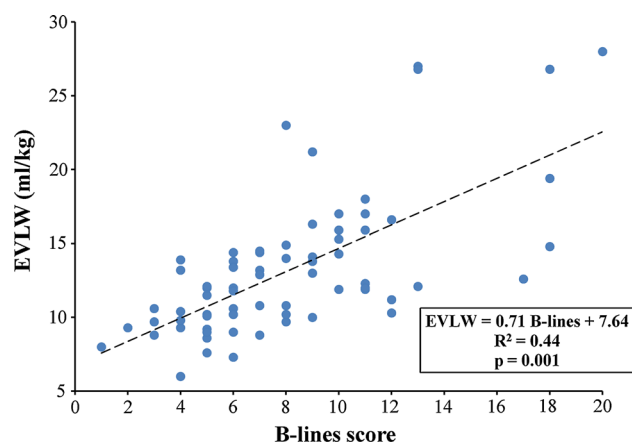


Fig. 3 Correlation between EVLW and B-lines. There was a significant correlation between the B-lines score and EVLW ($R^2 = 0.44$, $p = 0.001$). The equation was corrected for repeated measurements

the data corresponding to the lowest value of PaO₂/FiO₂ for each patient were retained.

A p value <0.05 was considered significant. The statistical analysis was performed using R software (R Foundation, Vienna, Austria), Tanagra 1.4.45 (Rakotomalala, Lyon University, France) and SPSS 20 (Armonk, NY: IBM Corp).

3 Results

From January 2013 through February 2014, twenty-six patients with ARDS were included in this study (Fig. 1). No patient was excluded for an insufficient echogenicity. A total number of 73 measurements were analyzed. The demographic data were described in Table 1. The ICC, performed on a sample of 10 patients, was 0.93 (95 % CI 0.75–0.98) for the B-lines score and 0.94 (95 % CI 0.80–0.99) for the E/Ea ratio. For B-lines score, the interobserver variability was 11.3 ± 7.9 % (which represents a median [range] variation of 1 [0–3] B lines between 2 observers) and intraobserver variability was 8.8 ± 6.3 %. For E/Ea ratio, the interobserver variability was 6.1 ± 4.7 % and intraobserver variability was 4.2 ± 3.6 %.

3.1 Correlations with EVLW

Analysis of the overall relationship between EVLW and B-lines score (Fig. 3) showed a significant correlation between EVLW and B-lines score ($R^2 = 0.44$, AIC = 354, $p = 0.001$). There was no significant correlation between EVLW and E/Ea ($R^2 = 0.10$, AIC = 387, $p = 0.055$). A multivariate linear mixed effect model, including B-lines

Table 2 Results of linear mixed effect model between EVLW, PaO₂/FiO₂, B-lines and E/Ea

R ²	Variables	Coef. β [CI ₉₅ %]	Intercept α [CI ₉₅ %]	p value
EVLW ⁽¹⁾				
0.44	B-lines	0.71 [0.46 +0.96]	7.64 [5.68 +9.79]	0.001
0.10	E/Ea	0.55 [−0.08 +0.97]	9.42 [6.20 +14.09]	0.055
EVLW ⁽²⁾				
0.47	B-lines	0.68 [0.45 +0.89]	5.58 [3.14 +9.31]	0.001
	E/Ea	0.33 [−0.11 +0.63]		0.09
PaO ₂ /FiO ₂				
0.32	EVLW	−11.1 [−16.5 −8.2]	330 [284 +401]	0.001
0.18	B-lines	−9.1 [−14.5 −3.6]	255 [211 +300]	0.002
0.02	E/Ea	−5.8 [−16.2 +4.6]	224 [148 +299]	0.32

The 95 % confidence intervals were determined by a bootstrap procedure (1,000 permutations). The coefficients for EVLW⁽¹⁾ are univariate. The coefficients for EVLW⁽²⁾ are multivariate, including B-lines and E/Ea ratio. Bold values are significant

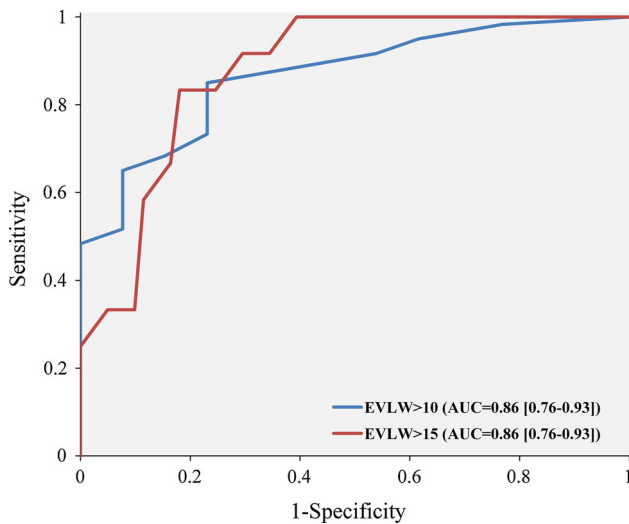


Fig. 4 ROC curves. A B-lines score ≥ 6 had a sensitivity of 82 % and a specificity of 77 % to predict EVLW >10 ml/kg. A B-lines score ≥ 10 had a sensitivity of 83 % and a specificity of 79 % to predict EVLW >15 ml/kg. The analysis was corrected for repeated measurements

score and E/Ea, did not improve the correlation with EVLW ($R^2 = 0.47$, AIC = 354). The PaO₂/FiO₂ ratio appeared correlated with EVLW ($R^2 = 0.32$, $p = 0.001$) and B-lines score ($R^2 = 0.18$, $p = 0.002$), but not with E/Ea ($R^2 = 0.02$, $p = 0.32$) (Table 2). No significant correlation was found between EVLW and the other parameters such as left ventricular ejection fraction, Sa, EDT or E/A ratio.

3.2 Receiver operating characteristic (ROC) analysis

A B-lines score ≥ 6 had a sensitivity of 82 % and a specificity of 77 % to predict EVLW >10 ml/kg (Fig. 4), with an accuracy of 81 % and an Area Under the Curve (AUC) equal to 0.86 (95 % CI 0.76–0.93, $p < 0.001$). The positive predictive value (PPV) was 94 % and the negative

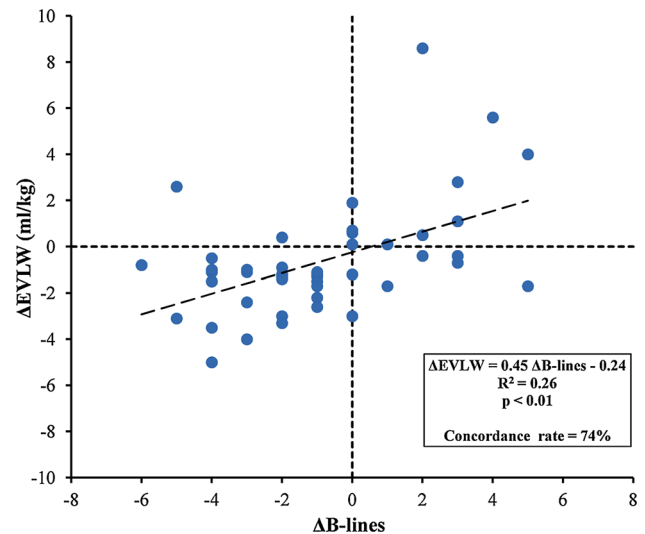


Fig. 5 Four quadrant plot representing the correlation and concordance between Δ EVLW and Δ B-lines. The coefficient of determination R^2 was 0.26 ($p < 0.01$) and the concordance rate was 74 %. The equation was corrected for repeated measurements

predictive value (NPV) was 48 %. The gray zone approach identified a range of B-lines between 4 and 7 for which EVLW >10 ml/kg could not be predicted reliably. A B-lines score ≥ 10 had a sensitivity of 83 % and a specificity of 79 % to predict EVLW >15 ml/kg, with an accuracy of 79 % and an AUC equal to 0.86 (95 % CI 0.76–0.93, $p < 0.001$). The PPV was 44 % and the NPV was 96 %. The gray zone predicting EVLW >15 ml/kg was ranged between 9 and 12 B-lines.

3.3 Trending ability

The linear mixed effect model showed a significant correlation between Δ EVLW and Δ B-lines ($R^2 = 0.26$, $p < 0.01$). The concordance rate without data exclusion was 74 % (95 % CI 60–85 %) ($n = 35/47$): 26 % of

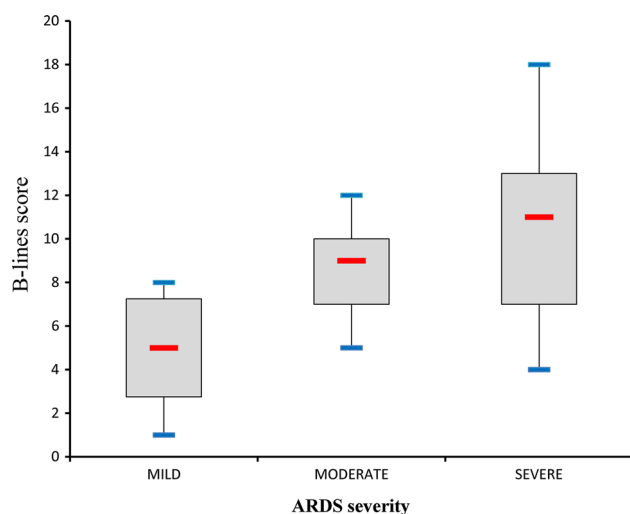


Fig. 6 Box plot representing the values of B-lines score among the three categories of ARDS. Increasing ARDS severity was associated with higher B-lines score (Jonckheere–Terpstra test $p = 0.005$)

variations in EVLW yielded opposite changes, i.e. negative variation with one technique and positive with the other. These data points are located in the upper left and lower right corners of Fig. 5. When a central exclusion zone of 15 % was used (i.e. $\Delta\text{EVLW} < 2$ ml/kg and $\Delta\text{B lines} < 2$), the concordance rate was 76 % (95 % CI 62–86 %) ($n = 22/29$). There was no significant correlation between ΔEVLW and $\Delta\text{E}/\Delta\text{Ea}$ ($R^2 = 0.04$, $p = 0.21$).

3.4 Relationship among EVLW, B-lines score, E/Ea ratio, and ARDS severity

ARDS severity was determined based on the lowest $\text{PaO}_2/\text{FiO}_2$ ratio measured during the study period. The median [range] values of EVLW (ml/kg) for mild, moderate and severe ARDS were 10 [8–12], 13 [7.6–16.3] and 16.6 [10.4–27], respectively ($p = 0.001$). ARDS severity was associated with an increase of B-lines score (mild, 5 [1–8]; moderate, 9 [5–12]; severe, 11 [4–18]; $p = 0.005$; Fig. 6). There was no significant correlation between E/Ea ratio and ARDS severity ($p = 0.97$).

4 Discussion

To our knowledge, this is the first prospective observational study, conducted in critically ill patients with ARDS, assessing the accuracy of an echographic model to predict EVLW and its variations. We showed a significant correlation between the ultrasound B-lines score and EVLW ($\text{EVLW} = 0.71 \text{ B-lines} + 7.64$, $R^2 = 0.44$). A B-lines score ≥ 6 had a sensitivity of 82 % and a specificity of

77 % to detect a pathologic value of EVLW > 10 ml/kg, with a gray zone between 4 and 7 B-lines.

In cardiac surgery setting, Agricola and coll. [6] had found a significant correlation between EVLW determined by the PICCO™ system and B-lines ($R = 0.42$). We have also observed a significant correlation between EVLW and B-lines ($R = 0.66$), even if our methodology was different: in the study of Agricola and coll. the patients with lung diseases were excluded, only 4 chest zones were included in our study to calculate the simplified B-lines score and the algorithm to determinate EVLW used by the EV1000™ system was slightly different of the PICCO™ algorithm [17]. The PICCO™ algorithm to calculate EVLW is based on the time of the temperature decay between two set points in the thermodilution curve, while the EV1000™ algorithm relies on maximum up-slope and maximum down-slope of the thermodilution curve.

The correlation between EVLW and E/Ea ratio was not significant in our study. The number of B-lines had been previously shown to correlate with wedge pressures ($R = 0.48$) [6] and the degree of diastolic dysfunction [31]. However, in patients with ARDS, the permeability pulmonary oedema is the *primum movens* of the increased EVLW and could explain the poor relationship between EVLW and E/Ea ratio. In addition, E/Ea variations, reflecting changes in wedge pressures, were not clinically relevant to track EVLW alterations, at least in ARDS setting.

The correlation between ΔEVLW and $\Delta\text{B-lines}$ was significant. This is coherent with the study of Noble and coll. [32]: the authors had shown that during dialysis every 500 ml volume removed induced a decrease of 2.7 B-lines. However, in our study, the concordance rate of 74 % was poor, therefore an invasive monitoring by TPTD seems necessary for an accurate evaluation of EVLW changes.

Our study had some limitations. The most significant was the use of an imprecise reference method. The measurement of EVLW is actually based on gravimetry [33, 34], pulmonary imaging [7] or transpulmonary dilution marker methods [4]. The gold standard for in vivo EVLW assessment is represented by quantitative computed tomography scan, which is often not feasible, requiring the transfer of a critical patient to the radiology department. Moreover the computed tomography scan employs ionizing radiations that do not allow repeating it to study EVLW changes. We have not compared EVLW measured with EV1000 with a chest radiographic score: the study of Brown and coll. [26] has clearly showed that the change in daily chest radiograph scores was not predictive of time to death, by contrast with $\text{PaO}_2/\text{FiO}_2$ ratio or EVLW changes measured by TPTD that predicted mortality. Likewise, the correlation between EVLW and the chest radiograph score was moderate ($R = 0.35$). Furthermore, the $\text{PaO}_2/\text{FiO}_2$

ratio, the level of PEEP and the value of EVLW might have slightly increased the bias of EVLW measurements [4]. Even if our model may be useful to estimate EVLW at the admission of a patient with acute respiratory failure, it is imperfect and an invasive monitor is necessary if an accurate EVLW measurement is needed. This was confirmed by the fact that the correlation between $\text{PaO}_2/\text{FiO}_2$ ratio and EVLW ($R = -0.57$) was better than the correlation between $\text{PaO}_2/\text{FiO}_2$ ratio and B-Lines score ($R = -0.43$) or E/Ea ratio ($R = -0.16$).

Moreover, the pulmonary capillary wedge pressure was not measured [35], and could be abnormally elevated and interfere with the diagnosis of ARDS. However, the E/Ea ratio was relatively low (7 ± 2) with a range between 4 and 13. An E/Ea threshold >15 has been previously shown predictive of a wedge pressure >15 mmHg [36, 37]. None of our patient had an E/Ea ratio >13 , therefore a pure cardiogenic oedema was unlikely [12].

The results could have been operator-dependent or echograph-dependent. The ICC of B-lines score (ICC = 0.93) and E/Ea ratio (ICC = 0.94) were acceptable, therefore the influence of the operator was irrelevant. However, the model could have been different with another type of echograph: the B-lines are artifacts that depend of echographic parameters. In our study, only one echograph was used, with a probe of 2–4 MHz. The results were also limited by the range of EVLW between 6 and 28 ml/kg, therefore we cannot extrapolate to higher values.

In conclusion, in patients with ARDS, the correlation between ultrasound B-lines score and EVLW was significant and might be useful to detect a pathologic value of EVLW at ICU admission. However, the poor trending ability justifies an invasive monitoring by TPTD to track EVLW changes accurately.

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