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Assessment of Lung Aeration and Recruitment by CT Scan and Ultrasound in Acute Respiratory Distress Syndrome Patients

Chiumello, Davide ; Mongodi, Silvia ; Algieri, Ilaria ; Vergani, Giordano Luca ; Orlando, Anita ; Via, Gabriele ; Crimella, Francesco ; Cressoni, Massimo ; Mojoli, Francesco

Abstract: OBJECTIVES: Lung ultrasound is commonly used to evaluate lung morphology in patients with acute respiratory distress syndrome. Aim of this study was to determine lung ultrasound reliability in assessing lung aeration and positive end-expiratory pressure-induced recruitment compared with CT. DESIGN: Randomized crossover study. SETTING: University hospital ICU. PATIENTS: Twenty sedated paralyzed acute respiratory distress syndrome patients: age 56 years (43-72 yr), body mass index 25 kg/m (22-27 kg/m), and PaO2/FIO2 160 (113-218). INTERVENTIONS: Lung CT and lung ultrasound examination were performed at positive end-expiratory pressure 5 and 15 cm H2O. MEASUREMENTS AND MAIN RESULTS: Global and regional Lung Ultrasound scores were compared with CT quantitative analysis. Lung recruitment (i.e., decrease in not aerated tissue as assessed with CT) was compared with global Lung Ultrasound score variations. Global Lung Ultrasound score was strongly associated with average lung tissue density at positive end-expiratory pressure 5 ($R = 0.78$; $p < 0.0001$) and positive end-expiratory pressure 15 ($R = 0.62$; $p < 0.0001$). Regional Lung Ultrasound score strongly correlated with tissue density at positive end-expiratory pressure 5 ($rs = 0.79$; $p < 0.0001$) and positive end-expiratory pressure 15 ($rs = 0.79$; $p < 0.0001$). Each step increase of regional Lung Ultrasound score was associated with significant increase of tissue density ($p < 0.005$). A substantial agreement was found between regional Lung Ultrasound score and CT classification at positive end-expiratory pressure 5 ($k = 0.69$ [0.63-0.75]) and at positive end-expiratory pressure 15 ($k = 0.70$ [0.64-0.75]). At positive end-expiratory pressure 15, both global Lung Ultrasound score (22 [16-27] vs 26 [21-29]; $p < 0.0001$) and not aerated tissue (42% [25-57%] vs 52% [39-67%]; $p < 0.0001$) decreased. However, Lung Ultrasound score variations were not associated with lung recruitment ($R = 0.01$; $p = 0.67$). CONCLUSIONS: Lung Ultrasound score is a valid tool to assess regional and global lung aeration. Global Lung Ultrasound score variations should not be used for bedside assessment of positive end-expiratory pressure-induced recruitment.

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Assessment of Lung Aeration and Recruitment by CT Scan and Ultrasound in Acute Respiratory Distress Syndrome Patients*

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Objectives: Lung ultrasound is commonly used to evaluate lung morphology in patients with acute respiratory distress syndrome. Aim of this study was to determine lung ultrasound reliability in assessing lung aeration and positive end-expiratory pressure–induced recruitment compared with CT.

Design: Randomized crossover study.

Setting: University hospital ICU.

Patients: Twenty sedated paralyzed acute respiratory distress syndrome patients: age 56 years (43–72 yr), body mass index 25 kg/m^2 (22–27 kg/m^2), and Pa_{O_2}/F_{IO_2} 160 (113–218).

Interventions: Lung CT and lung ultrasound examination were performed at positive end-expiratory pressure 5 and 15 cm H_2O.

Measurements and Main Results: Global and regional Lung Ultrasound scores were compared with CT quantitative analysis. Lung recruitment (i.e., decrease in not aerated tissue as assessed with CT) was compared with global Lung Ultrasound score variations. Global Lung Ultrasound score was strongly associated with average lung tissue density at positive end-expiratory pressure 5 ($R^2 = 0.78$; $p < 0.0001$) and positive end-expiratory pressure 15 ($R^2 = 0.62$; $p < 0.0001$). Regional Lung Ultrasound score strongly correlated with tissue density at positive end-expiratory pressure 5 ($r_s = 0.79$; $p < 0.0001$) and positive end-expiratory pressure 15 ($r_s = 0.79$; $p < 0.0001$). Each step increase of regional Lung Ultrasound score was associated with significant increase of tissue density ($p < 0.005$). A substantial agreement was found between regional Lung Ultrasound score and CT classification at positive end-expiratory pressure 5 (k = 0.69 [0.63–0.75]) and at positive end-expiratory pressure 15 (k = 0.70 [0.64–0.75]). At positive end-expiratory pressure 15, both global Lung Ultrasound score (22 [16–27] vs 26 [21–29]; $p < 0.0001$) and not aerated tissue (42% [25–57%] vs 52% [39–67%]; $p < 0.0001$) decreased. However, Lung Ultrasound score variations were not associated with lung recruitment ($R^2 = 0.01$; $p = 0.67$).

Conclusions: Lung Ultrasound score is a valid tool to assess regional and global lung aeration. Global Lung Ultrasound score variations should not be used for bedside assessment of positive end-expiratory pressure–induced recruitment. (*Crit Care Med* 2018; 46:1761–1768)

Key Words: acute respiratory distress syndrome; computed tomography; lung imaging; lung recruitment; lung ultrasound

The acute respiratory distress syndrome (ARDS) is defined as a noncardiogenic pulmonary edema with alveolar shunt and arterial hypoxemia (1). Through the years, the use of mechanical ventilation moved to reduce the ventilation-induced lung injury with high positive end-expiratory pressure (PEEP) levels, low tidal volumes, recruitment maneuvers, and prone position (2–5).

However, the response to PEEP, prone position, and recruitment maneuver is highly variable and poorly predictable, being affected by severity of the disease, type of injury, amount

***See also p. 1873.**

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of lung edema, timing of onset, and alteration of chest wall compliance (6, 7).

Lung CT is the gold standard chest imaging technique to evaluate lung morphology and to perform a quantitative analysis of lung tissue aeration and recruitment (8). However, CT requires intrahospital patient transfer from ICU to radiology department and the use of ionizing radiation, precluding a widespread clinical use. The possibility to have a repeatable and noninvasive imaging technique to assess lung aeration could significantly improve the management of ARDS patients (9–11). Lung ultrasound (LUS) has been proposed as an alternative bedside imaging technique (12–16). Ex vivo, LUS artifacts changed with the progressive increase in lung density (17). In a controlled human model of lung air content variation, LUS reliably recorded the changes in lung aeration (18). A LUS scoring system was proposed and successfully applied to assess reaeration in ventilator-associated pneumonia (VAP) (19), predict weaning failure from mechanical ventilation (20), and monitor aeration in extracorporeal membrane oxygenation patients (21). PEEP-induced recruitment was also studied but compared with pressure-volume curve (22), which in contrast to CT mainly computes the inflation of both newly and already open alveolar units (3, 23, 24).

We hypothesized that LUS score can provide a reliable bedside assessment of both regional and global lung aeration and that changes in LUS score are associated with PEEP-induced recruitment.

The aims of the present study were 1) to compare LUS score to quantitative CT in the assessment of regional and global lung aeration and 2) to analyze the relationship between LUS score variations and PEEP-induced lung recruitment in ARDS patients.

METHODS

Further details are mentioned in the **supplemental material** (Supplemental Digital Content 1, http://links.lww.com/CCM/D837).

Population

Twenty consecutive ARDS patients were prospectively enrolled at the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Italy. The study was approved by the institutional review board of the hospital; written consent was obtained according to Italian regulation. This study was not registered in a registry of clinical trials, according to the definition of the International Committee of Medical Journal Editors (25).

Protocol

The study protocol is summarized in supplement (**Fig. E1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D837). In radiology department, a recruitment maneuver was performed in pressure control ventilation at PEEP 5 cm H_2O, with a plateau pressure of 45 cm H_2O, inspiratory:expiratory ratio 1:1, respiratory rate of 10 breaths for 2 minutes. After the recruitment maneuver, 5 and 15 cm H_2O of PEEP were randomly applied with a similar ventilator settings; the order of PEEP for the second examination (LUS or CT) was kept the same. Subsequently, patients returned to intensive care where a new recruitment maneuver was applied, and LUS at two levels of PEEP was applied. The whole trial was performed within 2 hours.

LUS Acquisition

Transversal scans were performed with linear (12 MHz) or phased-array probe (2.5 MHz) for visualization of pleural line or tissue-like pattern, respectively (19, 22, 26). Six regions per hemithorax (upper and lower parts of anterior, lateral, and posterior chest wall) were identified (19–22). To evaluate interobserver reproducibility, six patients were examined by two blinded investigators (D.C., I.A.).

LUS Analysis

LUS videos were analyzed offline by four expert physicians (S.M., A.O., G.V., F.M.); each clip was analyzed by two operators, discordant clips by a third. Analyzers were blinded relatively to patients' identity, PEEP level, lung region, and CT findings.

According to the ultrasound pattern, the LUS score was computed as presence of A line alone or less than three B lines (0 point); at least three well-spaced B lines (1 point), coalescent B lines (2 points), and lung consolidation (3 points) (20). The LUS score of each region (regional LUS score) corresponded to the rounded average score of all pertaining intercostal spaces and ranged from 0 to 3. Global LUS score was computed as the sum of the 12 regions' score, therefore ranging from 0 to 36.

CT Scan Acquisition

Lung CT scan variables were 110 mAs, tube voltage 120 kV, rotation time 0.5 s, collimation 128 × 0.6 mm, pitch 0.85, and reconstruction matrix 512 × 512.

CT Scan Analysis

In each CT slice, lung profiles were manually delineated and analyzed with a dedicated software package (Soft-E-Film, Centro di Ricerca Coordinata di Insufficienza respiratorioa - Università degli Studi di Milano; http://www.softefilm.eu).

Lung tissue was classified according to gas/tissue content as not aerated (CT number between +100 and –100 Hounsfield unit [HU]), poorly aerated (CT number between –101 and –500 HU), normally aerated (–501 and –900 HU), and hyperinflated (–901 and –1,000 HU) (23).

Each lung was divided in six areas to mirror as much as possible the regions explored by ultrasound: two of equal height along the apex-base axis and three of equal height along the sternum-vertebral axis.

Lung Recruitment and Respiratory Mechanics

Recruitment was estimated as the amount of not aerated tissue that gained inflation moving from 5 to 15 cm H_2O of PEEP (6). Respiratory system elastance was computed as the difference in airway plateau pressure and PEEP divided by the tidal volume (24).

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Statistical Analysis

Power calculation was performed: with 20 subjects, it was possible to demonstrate an effect size of about 0.65 and a correlation of at least 0.60, with significance of 0.05 and power of 0.80. Data are presented as median (interquartile range) for quantitative variables or as absolute number (%) for qualitative variables. Differences were assessed with Fisher exact test, Wilcoxon rank-sum test for paired samples, Mann-Whitney *U* test for unpaired samples, Kruskal-Wallis test, or factorial analysis of variance with repeated measurements as an exploratory analysis; association was tested by simple linear regression model (reported with the coefficient of determination: R^2) or by Spearman rank correlation (r_s) as appropriate. The agreement between regional LUS score and CT classification was assessed with Cohen's kappa (27). *p* value of less than or equal to 0.05 was considered significant (two sided).

RESULTS

Main characteristics of the whole population are reported in **Table 1**. The interobserver agreement for LUS score was kappa equals to 0.84 (95% CI, 0.79–0.90). Carryover effect was not statistically significant at a Mann-Whitney *U* test for independent samples.

Global Lung Aeration

Global LUS score was strongly associated with average lung tissue density at PEEP 5 ($R^2 = 0.78$; $p < 0.0001$) and PEEP 15 ($R^2 = 0.62$; $p < 0.0001$); a weaker relationship was observed between LUS score and not aerated tissue at PEEP 5 ($R^2 = 0.30$; $p = 0.01$) and PEEP 15 ($R^2 = 0.23$; $p = 0.03$). Regression analysis is displayed in **Figure 1**. Global LUS score was inversely associated with lung gas/volume ratio and well-aerated tissue at both

TABLE 1. Baseline Clinical and Ventilatory Characteristics of the Population

Baseline Characteristics	Total, *n* = 20	Mild ARDS, *n* = 3	Moderate ARDS, *n* = 10	Severe ARDS, *n* = 7	*p*
Age (yr), median (IQR)	56 (43–72)	58 (39–71)	53 (46–68)	59 (43–72)	0.94
Female sex, *n* (%)	7 (35)	1 (33)	4 (40)	2 (29)	
Body mass index (kg/m^2), median (IQR)	25 (22–27)	22 (21–23)	24 (22–27)	25 (25–29)	0.18
Intensive care mortality, number of patients (*n*) (%)	9 (45)	1 (33)	3 (30)	5 (71)	0.28
Cause of lung injury, *n* (%)					
Pneumonia	9 (45)	1 (33)	4 (40)	4 (57)	
Sepsis	4 (20)	1 (33)	2 (20)	1 (14)	
Aspiration	2 (10)	0	1 (10)	1 (14)	
Trauma	1 (5)	0	1 (10)	0 (0)	
Other	4 (20)	1 (33)	2 (20)	1 (14)	
Pao_2/Fio_2 (mm Hg), median (IQR)	160 (113–218)	224 (170–253)	180 (159–225)[a]	106 (91–118)[a,b]	0.01
$Paco_2$ (mm Hg), median (IQR)	43 (40–56)	44 (42–50)	41 (37–48)	43 (43–56)	0.34
pH, median (IQR)	7.40 (7.37–7.42)	7.40 (7.38–7.41)	7.41 (7.37–7.42)	7.37 (7.37–7.42)	0.73
Respiratory rate (breaths/min), median (IQR)	16 (14–20)	15 (13–16)	16 (14–20)	18 (14–23)	0.55
Minute ventilation (L/min), median (IQR)	9.3 (6.9–9.9)	7.2 (4.7–7.4)	9.3 (8.4–9.8)	9.8 (7.8–10.3)	0.15
Tidal volume (mL/kg ideal body weight), median (IQR)	8 (5–8)	8 (6–8)	8 (6–9)	6 (5–8)	0.42
Clinical positive end-expiratory pressure (cm H_2O), median (IQR)	11 (10–15)	10 (10–15)	10 (10–12)	15 (14–15)	0.21
Fio_2, median (IQR)	0.5 (0.5–0.6)	0.5 (0.5–0.5)	0.5 (0.5–0.5)	0.7 (0.5–0.8)[b]	0.05
Respiratory system elastance (cm H_2O/L), median (IQR)	35 (27–41)	28 (23–32)	35 (29–40)	36 (27–68)	0.46
Study days from intubation, median (IQR)	5 (2–8)	6 (4–9)	5 (2–10)	4 (2–6)	0.61

ARDS = acute respiratory distress syndrome, IQR = interquartile range.

[a]$p < 0.05$ vs mild.

[b]$p < 0.05$ vs moderate.

Summary of the main baseline characteristics of the ARDS study population divided according to the Berlin definition: mild if Pao_2/Fio_2 between 201 and 300 mm Hg, moderate if Pao_2/Fio_2 between 101 and 200 mm Hg, severe if Pao_2/Fio_2 equal or below 100 mm Hg, or undertaking extracorporeal membrane oxygenation. Data are presented as median (interquartile range) or numerosity (%), as appropriate and a Kruskal-Wallis test and Fisher exact test were applied, respectively. Statistical analysis of the cause of ARDS and sex has not be done owing to the too scanty numbers. Respiratory system elastance is computed as the ratio between the plateau pressure minus positive end-expiratory pressure (PEEP) and the tidal volume. The gas exchange variables and the elastance considered are those measured at PEEP 5.

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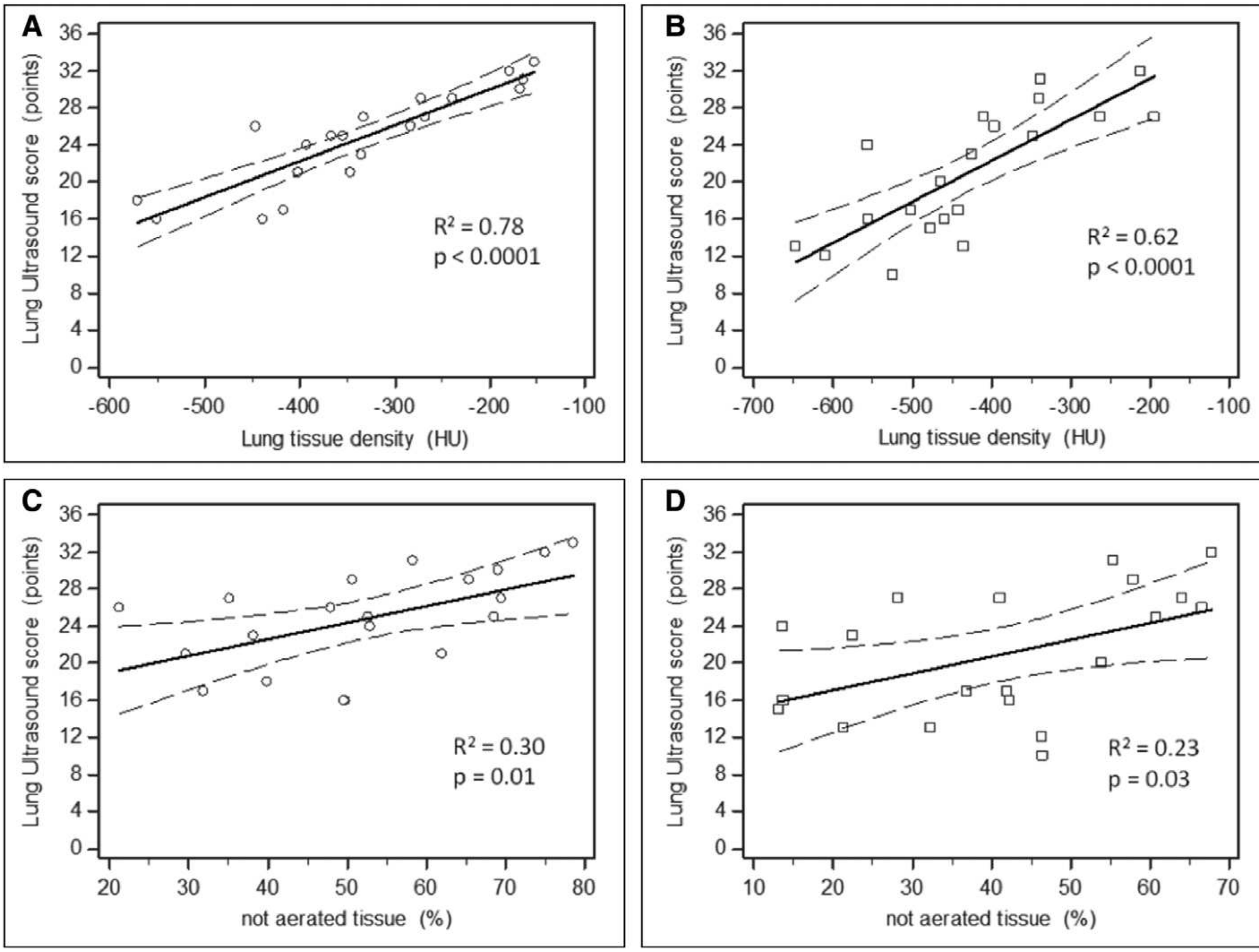

Figure 1. Global Lung Ultrasound (LUS) score, lung tissue density, and not aerated lung tissue. **A**, Global LUS score—lung tissue density relationship at positive end-expiratory pressure (PEEP) 5 ($p < 0.0001$). Regression equation: $y = 37.73 + 0.04\ x$. Coefficient of determination R^2 equals to 0.78. **B**, Global LUS score—lung tissue density relationship at PEEP 15 ($p < 0.0001$). Regression equation: $y = 39.92 + 0.04\ x$. Coefficient of determination R^2 equals to 0.62. **C**, Global LUS score—not aerated tissue relationship ($p = 0.01$). Regression equation: $y = 15.48 + 0.18\ x$. Coefficient of determination R^2 equals to 0.30. **D**, Global LUS score—not aerated tissue relationship ($p = 0.03$). Regression equation: $y = 13.51 + 0.18\ x$. Coefficient of determination R^2 equals to 0.23. *Circles* and *squares* refer to PEEP 5 and 15, respectively. *Black dashed lines* mark 95% CIs of regression lines. HU = Hounsfield unit.

PEEP levels (**Figs. E2** and **E3**, Supplemental Digital Content 1, http://links.lww.com/CCM/D837).

Regional Lung Aeration

Regional LUS score strongly correlated with tissue density at PEEP 5 ($r_s = 0.79$ [0.74–0.83]; $p < 0.0001$) and PEEP 15 ($r_s = 0.79$ [0.74–0.83]; $p < 0.0001$). At both PEEP levels, lung regions with different LUS scores had also different lung density as assessed by CT ($p < 0.000001$) (**Fig. 2**); each step increase of LUS score was associated with a statistically significant increase of density ($p < 0.005$).

At both PEEP levels, lung regions with different LUS scores, similarly to regions with different CT classification, had also statistically different proportions of hyperinflated, well, poorly, and not aerated tissue as assessed by CT ($p < 0.000001$) (**Fig. 3**). Well, poorly, and not aerated tissues were the most represented ($p < 0.005$) in LUS scores 0–1, 2, and 3, respectively. Well-aerated tissue was statistically more ($p < 0.002$) and not aerated tissue less represented ($p < 0.002$) in LUS 2 regions compared with poorly aerated regions. Well and poorly aerated tissues were statistically more ($p < 0.0001$) and not aerated tissue less represented ($p < 0.0001$) in LUS 3 regions compared with not aerated regions.

There was a substantial agreement between regional LUS score and CT classification (**Table E1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D837), at PEEP 5 (k = 0.69 [0.63–0.75]) and PEEP 15 (k = 0.70 [0.64–0.75]). Overall, LUS overestimated regional aeration in 25 observations (5%) and underestimated it in 150 observations (31%). The most frequent error was LUS score 3 in 106 regions assessed by CT as poorly aerated. In these regions, not aerated tissue was well represented (51% [32–64%] of total tissue). Furthermore, in 44 well-aerated regions, LUS score was 2. Agreement was assessed separately for different lung regions (**Table E2**, Supplemental Digital Content 1, http://links.lww.com/CCM/D837).

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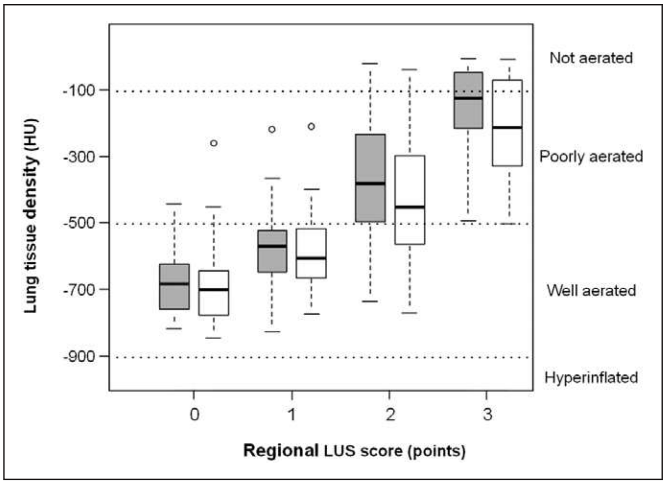

Figure 2. CT tissue density in lung regions with different Lung Ultrasound (LUS) score. *Box* and *whiskers* plots are displayed separately for positive end-expiratory pressure (PEEP) 5 (*gray boxes*) and PEEP 15 (*white boxes*). *Dotted lines* mark intervals of lung density corresponding to hyperinflated, well aerated, poorly aerated, and not aerated tissue. Regional LUS score correlated with tissue density at PEEP 5 ($r_s = 0.79$ [0.74–0.83]; $p < 0.0001$) and PEEP 15 ($r_s = 0.79$ [0.74–0.83]; $p < 0.0001$). Lung density was different in regions with different LUS score ($p < 0.000001$). Each step increase of LUS score was associated with significant increase of density ($p < 0.005$). HU = Hounsfield unit.

Lung Recruitment

PEEP-induced changes of lung aeration variables are reported in **Table 2**.

At PEEP 15, compared with PEEP 5, lung density decreased (–439 HU [–513 to –344 HU] vs –341 HU [–409 to 254 HU]; $p < 0.0001$), gas/volume ratio increased (0.43 [0.35–0.50] vs 0.32 [0.23–0.39]; $p < 0.0001$), not aerated tissue decreased (42% [25–57%] vs 52% [39–67%]; $p < 0.0001$), well-aerated tissue increased (24% [16–35%] vs 13% [9–23%]; $p < 0.0001$), whereas poorly aerated tissue did not statistically change (28% [24–47%] vs 27% [20–42%]; $p = 0.19$).

At PEEP 15, compared with PEEP 5, global LUS score decreased (22 [16–27] vs 26 [21–29]; $p < 0.0001$), LUS 3 regions decreased (3.5 [1.0–6.5] vs 4.0 [3.0–8.0]; $p = 0.0001$), LUS 0–1 regions increased (5.0 [2.0–7.0] vs 3.0 [0.0–4.5]; $p < 0.002$), whereas LUS 2 regions did not statistically change (4.0 [2.0–6.0] vs 3.5 [2.0–6.0]; $p = 0.9$).

Changes of global LUS score were not statistically associated with lung recruitment defined as decrease of not aerated tissue ($R^2 = 0.01$; $p = 0.67$) (**Fig. E4**, Supplemental Digital Content 1, http://links.lww.com/CCM/D837). **Figure E5** (Supplemental Digital Content 1, http://links.lww.com/CCM/D837) shows examples of LUS variations not consistent with lung recruitment. Median value of lung recruitment was 9.5%: patients were defined as high and low recruiters if presenting more or less than the median. Change of global LUS score did not statistically differ between high and low recruiters (–4 [–8 to –1] vs –2 [–5 to –1]; $p = 0.32$).

DISCUSSION

The major findings of this study are as follows: 1) global and regional LUS scores were strongly associated with lung tissue density as assessed by CT, 2) a substantial agreement between

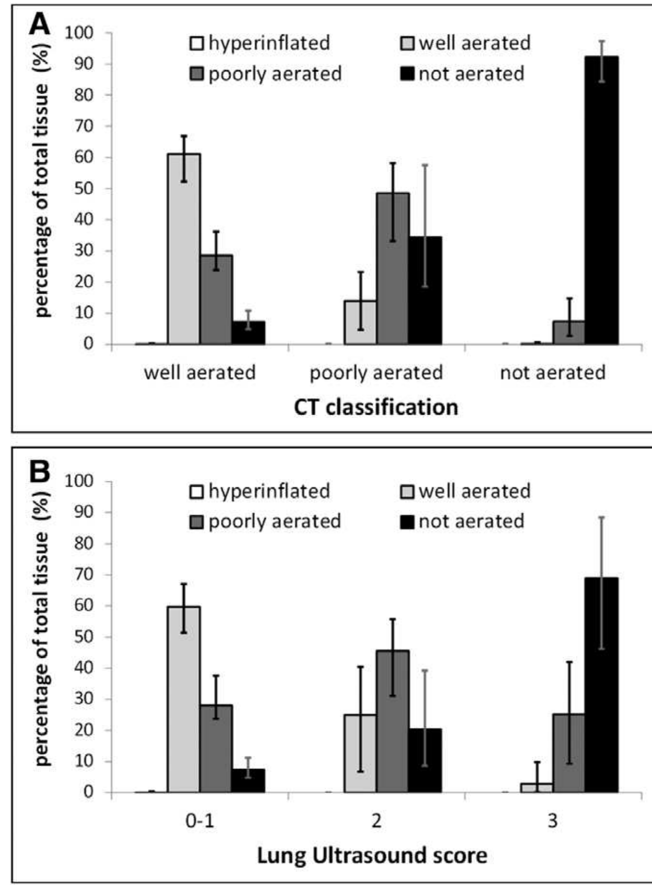

Figure 3. Lung tissue aeration according to regional Lung Ultrasound (LUS) score and CT classification. Median values and interquartile ranges of hyperinflated, well, poorly, and not aerated tissue in lung regions with different CT classification and regional LUS score are displayed. In order to have the same number of classes, regions with LUS scores 0 and 1 were grouped. **A**, Hyperinflated tissue was more represented in well-aerated regions than in poorly and not aerated regions ($p < 0.005$), well-inflated tissue progressively decreased moving from well to poorly and to not aerated regions ($p < 0.005$), poorly inflated tissue was more represented in poorly aerated than in well and not aerated regions ($p < 0.005$), and not aerated tissue progressively increased moving from well to poorly and to not aerated regions ($p < 0.005$). Same results were observed when positive end-expiratory pressure (PEEP) 5 and PEEP 15 were analyzed separately. **B**, Hyperinflated tissue was more represented in LUS 0–1 regions than in LUS 2 and LUS 3 regions ($p < 0.005$), well-inflated tissue progressively decreased moving from LUS 0–1 to LUS 2 and to LUS 3 regions ($p < 0.005$), poorly inflated tissue was more represented in LUS 2 than in LUS 0–1 and LUS 3 regions ($p < 0.005$), and not aerated tissue progressively increased moving from LUS 0–1 to LUS 2 and to LUS 3 regions ($p < 0.005$). Same results when PEEP 5 and PEEP 15 were analyzed separately. Proportions of hyperinflated, well, poorly, and not aerated tissue were similar in regions with LUS scores 0–1 and in regions assessed by CT as well aerated. Well-aerated tissue was higher ($p < 0.002$) and not aerated tissue was lower ($p < 0.002$) in LUS 2 regions compared with poorly aerated regions. Well and poorly aerated tissues were higher ($p < 0.0001$) and not aerated tissue was lower ($p < 0.0001$) in LUS 3 regions compared with not aerated regions. Same results when PEEP 5 and PEEP 15 were analyzed separately.

LUS and CT classification of regional lung aeration was found, and 3) global LUS score variations were not statistically related to PEEP-induced recruitment.

Lung Aeration Assessment

In ARDS, CT scan shows the simultaneous presence of normal aeration and ground glass, with or without consolidations.

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TABLE 2. Gas Exchange, Lung CT, and Lung Ultrasound Variables Response to Different Positive End-Expiratory Pressure

Gas Exchange, Lung CT, and LUS Variables	PEEP 5 cm H_2O, Median (IQR)	PEEP 15 cm H_2O, Median (IQR)	*p*
Pa_{O_2} (mm Hg)	77 (63–88)	105 (80–133)	< 0.01
Pa_{CO_2} (mm Hg)	43 (40–52)	42 (38–54)	0.30
Respiratory system elastance (cm H_2O/L)	29 (25–34)	29 (26–37)	0.33
Total lung volume (mL)	2,394 (1,871–3,201)	2,987 (2,370–3,526)	< 0.0001
Total gas (mL)	730 (445–987)	1,251 (812–1,561)	< 0.0001
Lung weight (*g*)	1,431 (1,330–1,836)	1,452 (1,372–1,860)	< 0.01
Lung CT density (Hounsfield unit)	−341 (−409 to −254)	−439 (−513 to −344)	< 0.0001
Gas/volume ratio	0.32 (0.23–0.39)	0.43 (0.35–0.50)	< 0.0001
Not aerated tissue (%)	52 (39–67)	42 (25–57)	< 0.0001
Poorly aerated tissue (%)	27 (20–42)	28 (24–47)	0.19
Well-aerated tissue (%)	13 (9–23)	24 (16–35)	< 0.0001
Global LUS score	26 (21–29)	22 (16–27)	< 0.001

IQR = interquartile range, LUS = lung ultrasound, PEEP = positive end-expiratory pressure.

The table shows the differences in CT scan whole lung variables and gas exchange between the two levels of PEEP. Respiratory system elastance is computed as the ratio between the plateau pressure minus PEEP and the tidal volume. Lung tissues are classified according to the mean CT density. Not aerated tissue if −100 Hounsfield unit (HU) or above, poorly aerated between −101 and −500 HU, well aerated between −501 and −900 HU, hyperinflated if lower than −901 HU. All compartments are expressed as fraction on the total lung weight. The *p* values refer to the comparisons within the same subject. Hyperinflation was not analyzed since ranging from 0% to 2% at PEEP 5 and from 0% to 4% at PEEP 15.

This corresponds in LUS to multiple (eventually coalescent) B lines juxtaposed to normal A pattern areas (spared areas), with or without small subpleural and lobar consolidations (11, 14). Quantitative CT is the gold standard technique to assess lung aeration in ARDS patients; lung tissue density is quantified, and four levels of aeration are classically identified: hyperinflated, well, poorly, and not aerated tissues (23). A quantitative LUS score has been proposed for lung aeration assessment, based on the identification of four patterns in function of number and type of visualized artifacts: normal aeration, moderate, severe, and complete loss of aeration (19–22). Baldi et al (28) reported a relationship between the number of B lines and lung density in mechanically ventilated patients. In patients with VAP, changes in LUS score before and after antibiotics predicted the improvement in lung aeration (19). These findings are consistent with the fact that CT scan computes the lung density, which is also the main determinant of appearance, number, and coalescence of LUS artifacts (17). In our study, global LUS score showed a statistically significant association with lung density and a significant inverse relationship with gas/volume ratio as assessed by CT. A weaker association was found between LUS score and not aerated tissue; this is explained by the fact that regions with moderate and severe loss of aeration also contribute to LUS score computation. One of the main endpoints of this study was to determine whether LUS score parallels CT classification. Regions with different LUS score had also different lung tissue density, and each step of LUS score increase corresponded to a significant gain in tissue density. When analyzing CT classification, we remarked that all types of tissue were represented in well, poorly, and not aerated regions, but in different proportions. A similar distribution was observed in LUS scoring. In particular, score 0–1 regions showed almost identical proportions of tissue compared with well-aerated regions. Scores 2 and 3 regions had similar—but not identical—tissue composition compared with poorly and not aerated regions, respectively, the main difference being a lower amount of not aerated tissue. Thus, LUS slightly overestimated regional loss of aeration.

Accordingly, there was a substantial agreement in regional aeration assessment between LUS and CT at both PEEP levels, but in around 30% of observations, LUS underestimated regional lung aeration. Two types of disagreement were observed. First, score 2 (severe loss of aeration) was assigned to well-aerated regions in 9% of observations. Current LUS scoring system identifies score 2 on the basis of coalescence of B lines; a recent study suggested this may lead to overestimation of loss of aeration because of focal coalescence, a frequent finding in ARDS (26). Our results seem to confirm this problem and the need for a different definition of score 2, for instance based on the amount of pleura showing artifacts (26).

Second, score 3 (complete loss of aeration) was assigned to poorly aerated regions in 22% of observations. A LUS limitation consists in fact in attributing a score 3 whenever a tissue-like pattern is observed, independent of its dimension. To note, when a score 3 was wrongly attributed to a lung region in the present study, not aerated tissue was well represented (median value: 50% of total tissue) and thus easily detected by LUS. To further improve agreement with CT, our findings suggest that

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LUS 3 score should be attributed only to regions where tissue-like pattern is largely predominant.

Despite these (correctable) flaws of current LUS score, our findings are consistent with and provide an objective explanation of previous studies supporting LUS score as reliable bedside tool to assess and monitor lung disease severity (10, 19, 21) and to predict outcome (16, 20).

Lung Recruitment Assessment

ARDS patients are typically characterized by the presence of consolidated/atelectatic areas mainly located in the dependent lung regions, which can be recruited by applying a transient increase in transpulmonary pressure and adequate PEEP level to prevent its closure (3, 6, 7). A previous study in ARDS patients observed a good correlation between pressure-volume curve and LUS assessment of PEEP-induced recruitment (22). However, this recruitment does not correspond to the reinflation of previously collapsed lung units, as most of the gas enters already inflated lung regions (24). Therefore, we investigated the relationship between the change of LUS score and the variation of not aerated tissue measured by CT, to test the hypothesis that LUS can assess lung recruitment and thus the amount of lung tissue that is at risk of cyclic opening and closing at the low PEEP level.

In the present study, both CT and LUS showed a significant increase in lung aeration at PEEP 15 versus PEEP 5 cm H_2O with a similar pattern: CT showed increase of well aerated, decrease of not aerated, and unchanged poorly aerated tissue; LUS similarly showed increase of score 0–1, decrease of score 3, and unchanged score 2. However, LUS score variations were not associated with PEEP-induced recruitment.

Thus, LUS score mirrors lung tissue aeration, but not PEEP-induced recruitment. These apparently contradictory findings are explained by the fact that LUS has a gradation of scores (normal aeration, moderate, severe, and complete loss of aeration) according to the presence of A lines, B lines, and consolidation and is not dedicated to consolidation assessment only. Thus, LUS score changes in function of any aeration modification, even when consolidated regions are not involved. On the contrary, lung recruitment in ARDS is defined as not aerated tissue turning into aerated tissue at CT assessment, that is, opening up of closed atelectatic lung. Therefore, a patient with severe (but not complete) loss of aeration may respond to PEEP with substantial improvement of lung tissue aeration (and significant decrease of LUS score) but, by definition, cannot be a recruiter because potentially recruitable not aerated tissue is missing (see the example in Fig. E5, right panel, Supplemental Digital Content 1, http://links.lww.com/CCM/D837). This also explains why LUS changes correlated with pressure-volume curve recruitment in the study of Bouhemad et al (22), but not with CT recruitment in the present study. Furthermore, a weakness of current definition of LUS score 3 is that it does not change if a tissue-like pattern is still detected, although significantly reduced in size (see the example in Fig. E5, left panel, Supplemental Digital Content 1, http://links.lww.com/CCM/D837). This means that a substantial PEEP-induced decrease of not aerated tissue (i.e., recruitment) will not be associated with a change in LUS score, unless tissue-like pattern completely disappears at ultrasound examination. For these reasons, variations of LUS score should not be used as a bedside alternative to CT assessment of lung recruitment.

Our results may have been influenced by several methodological limitations. LUS and CT were not performed simultaneously; transportation to/from the ICU was always needed in between. LUS examination lasts minutes and is performed during tidal ventilation whereas CT lasts seconds and is performed during an expiratory pause. Correspondence between the division of lung areas in LUS and in CT is acceptable, but not still definite. Standard LUS is performed in semirecumbent position whereas CT in supine. Furthermore, LUS analysis performed by expert operators blind to clinical conditions, PEEP setting, and examined lung region, certainly represents a strength of the study; anyway, offline interpretation of images acquired by other physicians represents a potential source of misinterpretation. Despite this limitation, LUS score interobserver agreement was clinically acceptable and similar to previous data (19, 26). Finally, a general limitation of LUS is the detection of lung overinflation, which may be induced by high PEEP.

CONCLUSIONS

LUS is a reliable bedside tool to evaluate global and regional lung aeration, accounting for its acknowledged role in assessing and monitoring lung disease severity. LUS score variations are not associated with PEEP-induced recruitment as assessed by CT and should not be used as an alternative bedside tool for this purpose.

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