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ORIGINAL

Lung ultrasonography for assessment of oxygenation response to prone position ventilation in ARDS

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Abstract

Purpose: Prone position (PP) improves oxygenation and outcome of acute respiratory distress syndrome (ARDS) patients with a PaO_2/FiO_2 ratio <150 mmHg. Regional changes in lung aeration can be assessed by lung ultrasound (LUS). Our aim was to predict the magnitude of oxygenation response after PP using bedside LUS.

Methods: We conducted a prospective multicenter study that included adult patients with severe and moderate ARDS. LUS data were collected at four time points: 1 h before (baseline) and 1 h after turning the patient to PP, 1 h before and 1 h after turning the patient back to the supine position. Regional lung aeration changes and ultrasound reaeration scores were assessed at each time. Overdistension was not assessed.

Results: Fifty-one patients were included. Oxygenation response after PP was not correlated with a specific LUS pattern. The patients with focal and non-focal ARDS showed no difference in global reaeration score. With regard to the entire PP session, the patients with non-focal ARDS had an improved aeration gain in the anterior areas. Oxygenation response was not associated with aeration changes. No difference in $PaCO_2$ change was found according to oxygenation response or lung morphology.

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Take-home message: Bedside LUS cannot predict oxygenation response after the first Prone positioning (PP) session performed in ARDS patients with a PaO_2/FiO_2 ratio ≤150 mmHg. Oxygenation response was not associated with aeration changes. PP is required for ARDS patients if the PaO_2/FiO_2 ratio remains below 150 mmHg.

Conclusions: In ARDS patients with a PaO_2/FiO_2 ratio ≤150 mmHg, bedside LUS cannot predict oxygenation response after the first PP session. At the bedside, LUS enables monitoring of aeration changes during PP.

Keywords: Acute respiratory distress syndrome, Prone position, Lung ultrasound, Oxygenation, Recruitment

Introduction

The severity of acute respiratory distress syndrome (ARDS) is correlated to the level of oxygenation of the patient defined by the ratio of partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (PaO_2/FiO_2 ratio) [1]. Prone positioning (PP) improves the outcome of ARDS patients with a PaO_2/FiO_2 ratio of less than 150 mmHg and is therefore recommended [2, 3]. Randomized controlled trials have reported that PP improves the oxygenation of patients with ARDS [4, 5].

Ultrasound is increasing in use in the intensive care unit (ICU) [6]. It is a non-invasive technology, performed at the bedside, easily repeatable, and reproducible. Lung ultrasound (LUS) provides accurate information on lung status [7], lung aeration [8], lung recruitment [9], lung perfusion [10], and lung morphology [11]. Guidelines recommend its use in ICU patients [12]. As compared with chest radiograph or computed tomography, LUS reduces the risks associated with intrahospital transfer and irradiation [13, 14]. The learning curve for acquiring the skills to perform LUS is steep [15].

We hypothesized that LUS could predict the intensity of oxygenation response resulting from PP. The primary objective of our study [16] was to evaluate the performance of LUS to predict the intensity of oxygenation benefit following PP, 1 h after turning the patient back to the supine position. Our secondary objectives were to evaluate the performance of LUS to predict the intensity of oxygenation benefit at the end of the PP session and to assess the impact of lung morphology on oxygenation benefit, carbon dioxide (CO_2) elimination, and regional lung recruitment during PP. The original aspect of this study was to assess the persistent response over the PP session.

Methods

Study design, patients

The study was approved by our institutional review board (no. 00008526) and the Commission Nationale de l'Informatique et des Libertés (no. 26130008100484). The institutional review board waived the need for patient (or relative) consent since this was a non-interventional, observational, prospective, and multicenter study. The study was conducted in six ICUs in the AzuRea and CAR'Echo Networks from March 2014 to January 2015 and from December 2015 to January 2016.

According to the criteria of a recent study [2], ARDS patients with severe hypoxemia persisting from 12 to 24 h were included according to the following criteria: PaO_2/FiO_2 ratio less than 150 mmHg with FiO_2 at least 0.6, positive end-expiratory pressure (PEEP) at least 5 cmH_2O, and tidal volume close to 6 ml/kg of predicted body weight (PBW) under a heated humidifier [1, 17]. Each patient was included during the first session of PP after ruling out contraindications to PP [2] (exclusion criteria are listed in the Electronic Supplementary Material, ESM).

Prone positioning, protocol, measurements, and classification of response

In each participating ICU, PP sessions were performed according to local written protocols. The procedure is described in the ESM. LUS was performed according to international guidelines [12]. We used 1–5 MHz convex probes. All intercostal spaces of the upper and lower parts of the anterior, lateral, and posterior areas of the left and right chest wall were examined [7] (Fig. 1). Four LUS exams were performed for each patient 1 h before and after each reversal. Data were collected 1 h before PP (LUS 1), 1 h after PP (LUS 2), 1 h before the patient was turned back to the supine position (LUS 3), and 1 h after the patient was returned to the supine position (LUS 4) (Fig. 2).

A second person lifted the shoulder of the patient to examine the posterior areas in the supine position. In the prone position, the second person lifted the shoulder of the patient to examine the anterior areas. LUS exams were performed in the center of each area by an intensivist who was not in charge of the patient and who had prior experience of at least 30 supervised LUS. Double reading was conducted to reduce inter- and intraobserver variability. In case of inadequacy between the readers, a consensual decision was made after discussion. LUS exams each took from 5–10 min. All areas were labeled the same whatever the position. We reported only the first prone session for each patient included.

Arterial blood gas analysis, hemodynamic and ventilator variables were recorded at each time point. Four LUS patterns were defined for each area allowing the calculation of a regional aeration score characterizing anterior, lateral, and posterior lung areas (Table 1a). Points were allocated according to the worst ultrasound pattern observed. The LUS score corresponds to the sum of each

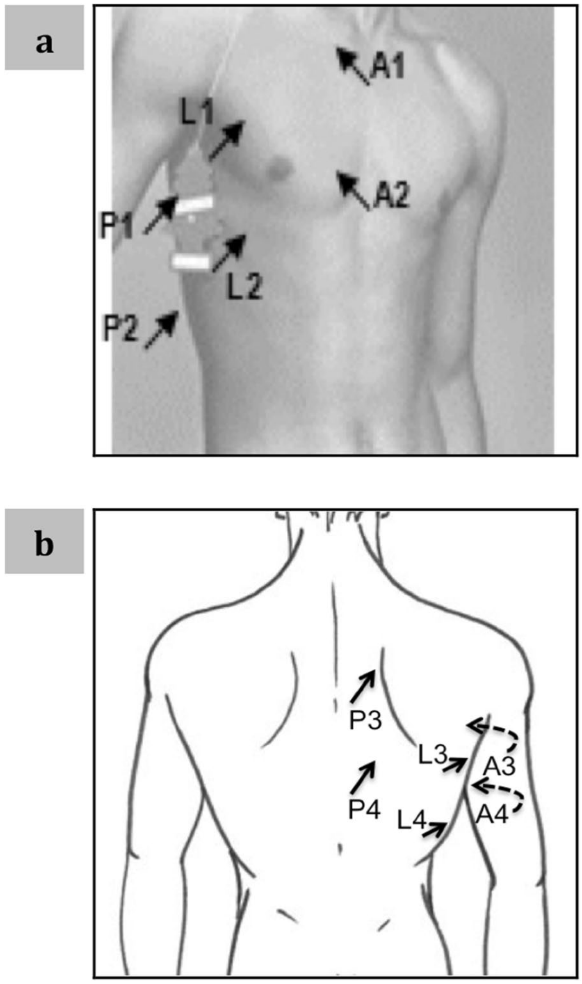


Fig. 1 Areas of chest wall where LUS was performed in supine (**a**) and prone (**b**) position: *A1/A3* anterosuperior, *A2/A4* anteroinferior, *L1/L3* laterosuperior, *L2/L4* lateroinferior, *P1/P3* posterosuperior, *P2/P4* posteroinferior

examined area score (maximum score = 36) [7, 8]. At every step, each regional score (anterior, lateral, and posterior) was calculated by the sum of four quadrants (left and right, superior and inferior) allocated to it (maximum score = 12).

An ultrasound reaeration score was calculated as previously described [9, 18] from changes in the ultrasound pattern of each area examined between each ultrasound. The method of calculation is summarized at the bottom of Table 1. A positive reaeration score means an aeration gain; a negative reaeration score corresponds to an aeration loss.

Patients were classified as having focal ARDS if they had at least four normally aerated lung areas (scored 0 by the lung ultrasound score) [9]. Referring to previous studies [19–21], we decided to define lung morphology of ARDS patients by analogy to CT scan. Finally, the duration of the PP session and events resulting from the protocol were recorded. Survival at 28 days was reported.

Patients with high oxygenation response after PP were classified as "high oxygenation response" if the PaO_2/FiO_2 ratio increased more than the median value observed in the entire group between the first and the last ultrasound scan [$\Delta PaO_2 : FiO_2 = \left(PaO_2 : FiO_2^{LUS\,4} - PaO_2 : FiO_2^{LUS\,1}\right) / \left(PaO_2 : FiO_2^{LUS\,1}\right) \times 100$]. Other patients with low to moderate oxygenation response were classified as "low to moderate oxygenation response". Patients with high CO_2 elimination response after PP were defined as "high CO_2 elimination response" if $PaCO_2$ decreased more than the median value of $PaCO_2$ variation between the first and the last LUS scan ($\Delta PaCO_2$) [22].

Statistical analysis

Statistical analysis was performed with R-Project 3.1 for GNU Linux Ubuntu (Vienna, Austria) [23]. Quantitative data were expressed as mean ± standard deviation. Respiratory variables at the different times of measurement were compared between the patients with high oxygenation response and those with moderate to low oxygenation response, and between the patients with focal and non-focal ARDS. Means were compared using the Mann–Whitney *U* test. The Bonferroni correction was applied for repeated measures.

Qualitative data were expressed in absolute values with their percentage. Comparisons of proportions were made with Fisher's exact test. All comparisons were two-tailed. $P < 0.05$ was required to exclude the null hypothesis.

Results

Patient characteristics on inclusion

During the study period, 426 patients admitted to the six ICUs developed ARDS. Ninety-eight (23 %) of them underwent at least one session of PP and 51 (12 %) were included (ESM, Fig. 1). Patient characteristics are summarized in Table 2. The duration of the first session of PP was 17 ± 3 h. Thirteen (25 %) patients received treatment with nitric oxide and no patient received almitrine bismesylate. No notable events occurring during the protocol were recorded.

Oxygenation response to prone position

One hour after return to the supine position, 42 patients showed an increase in their PaO_2/FiO_2 ratio ranging from 2 to 292 %. After PP, a 20 % increase in the PaO_2/FiO_2 ratio was reported in 71 % of the patients. According to median values, 26 (51 %) patients had a high oxygenation response characterized by a $\Delta PaO_2/FiO_2$ greater than

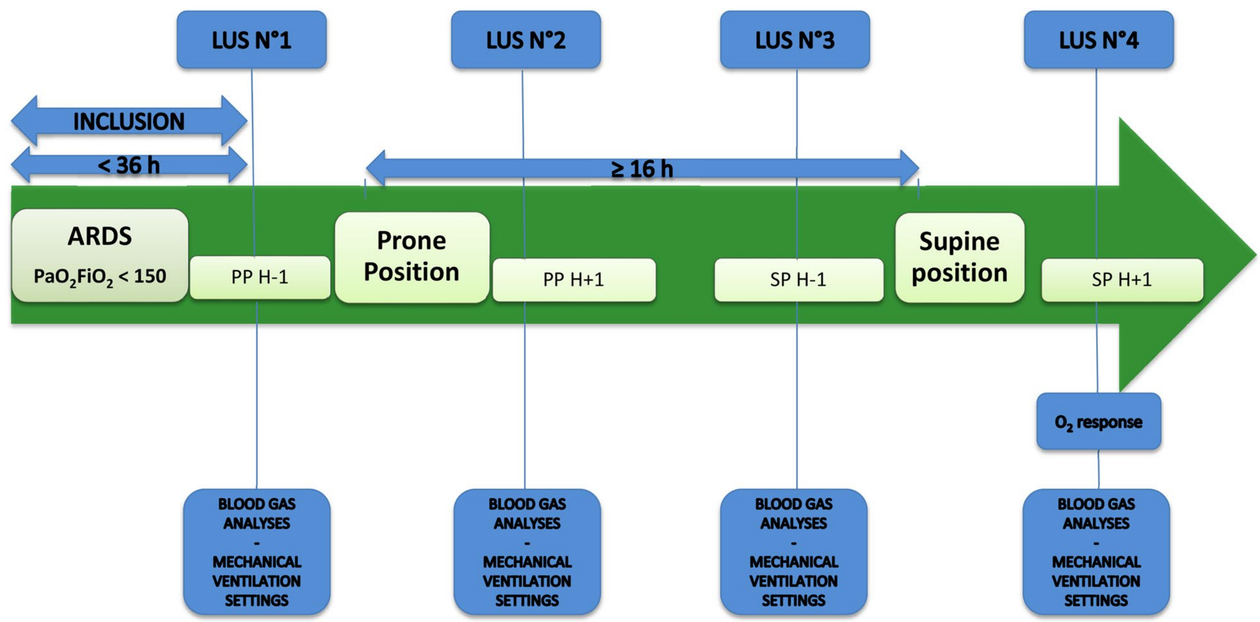


Fig. 2 Time point analysis. Four LUS exams were performed for each patient 1 h before and after each reversal. *ARDS* acute respiratory distress syndrome, *LUS* lung ultrasound, *PP* prone position, *SP* supine position

60 % after PP. At baseline, the PaO_2/FiO_2 ratio was lower in the patients with high oxygenation response than in the patients with low to moderate oxygenation response (86 ± 26 vs. 105 ± 25 mmHg, $P = 0.01$) (Table 2).

No significant correlation was found between the different LUS scores before PP (LUS 1) and the PaO_2 response 1 h after return to the supine position (3 ± 2 vs. 4 ± 3, $P = 0.2$ for the anterior LUS score; 5 ± 3 vs. 6 ± 3, $P = 0.7$ for the lateral LUS score; 10 ± 3 vs. 9 ± 2, $P = 0.9$ for the posterior LUS score; 18 ± 5 vs. 19 ± 6, $P = 0.6$ for the global LUS score) (Table 2). Similarly, at the onset of PP session, bedside LUS (LUS 2) was not correlated to oxygenation response (6 ± 2 vs. 7 ± 3, $p = 0.3$ for anterior LUS score; 5 ± 3 vs. 6 ± 3, $p = 0.4$ for lateral LUS score; 5 ± 3 vs. 5 ± 3, $p = 0.7$ for posterior LUS score; 16 ± 6 vs. 18 ± 7, $p = 0.4$ for global LUS score).

Secondary outcomes

Concerning oxygenation response 1 h before return the patient back to the supine position, 26 (51 %) patients increased their PaO_2/FiO_2 ratio above the median value of PaO_2/FiO_2 ratios. No significant correlation was found with LUS scores (LUS 1) (3 ± 3 vs. 4 ± 3, $P = 0.3$ for the anterior LUS score; 5 ± 3 vs. 5 ± 3, $P = 0.9$ for the lateral LUS score; 9 ± 2 vs. 10 ± 2, $P = 0.6$ for the posterior LUS score; 18 ± 5 vs. 19 ± 6, $P = 0.5$ for the global LUS score).

One hour after return to the supine position, the median value of $\Delta PaCO_2$ was 4 ± 11 mmHg. Twenty-nine (57 %) patients were considered as having a high CO_2 elimination response. After the entire PP session, $PaCO_2$ levels were lower in high oxygenation responders (42 ± 9 vs. 53 ± 14 mmHg, $P = 0.003$) and in patients with focal ARDS (42 ± 8 vs. 50 ± 14 mmHg, $P = 0.05$). No association was found between LUS scores prior to PP or lung morphology and $PaCO_2$ response.

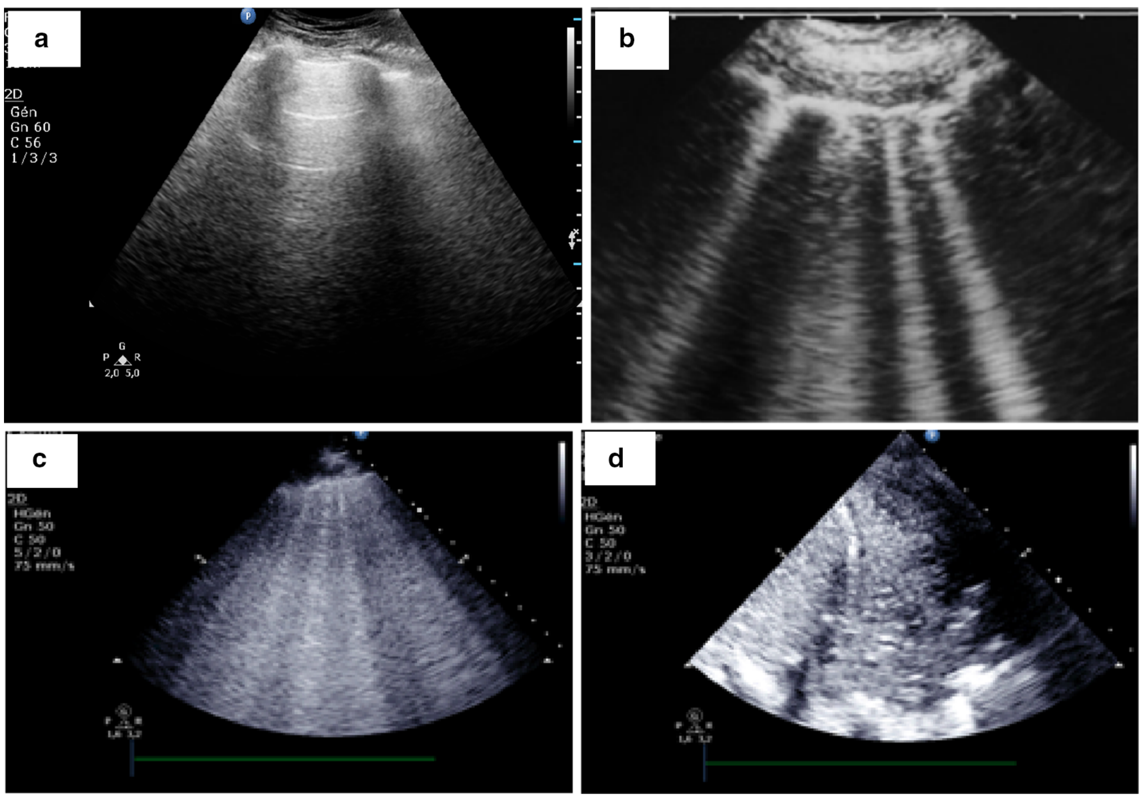
Ultrasound analysis of lung reaeration according to ARDS morphology and oxygenation response group

The evolution of arterial blood gas analyses and ventilator settings at the various PP sessions according to ARDS morphology and oxygenation response is summarized in the ESM (Table 1). Thirty-five (69 %) patients had a positive LUS score of reaeration after PP. The global reaeration score after PP was 2 ± 7. There was no significant association between the reaeration score and the magnitude of oxygenation response ($P = 0.5$). The changes of respiratory mechanics (driving pressure and compliance) were not correlated with reaeration score at each step of the PP session (LUS 1–2, LUS 2–3, LUS 3–4, and LUS 1–4) ($P > 0.05$). In the supine position after PP (LUS 1–4), the decrease in driving pressure was more pronounced in the high oxygenation responders than in the low-to-moderate responders ($P = 0.03$). In parallel, the increase in respiratory system compliance was higher in the high oxygenation responders ($P = 0.04$) (ESM, Table 1).

Seventeen (33 %) patients had a focal ultrasound pattern of ARDS. The global reaeration score did

Table 1 Description of four LUS patterns and ultrasound reaeration scores

	LUS score	LUS pattern
a	0	Normal aeration corresponding to presence of lung sliding with A lines or fewer than two isolated B lines
b	1	Moderate loss of lung aeration corresponding to multiple well-defined B lines or spaced ultrasound lung called "comet-tail artifact"
c	2	Severe loss of lung aeration corresponding to multiple coalescent B lines or multiple abutting ultrasound lung comet-tails issued from the pleural line
d	3	Lung consolidation corresponding to presence of a tissue pattern containing hyperechoic punctiform images representative of air bronchograms Presence or absence of regional pulmonary blood flow and/or dynamic bronchograms



Quantification of reaeration*			Quantification of loss of aeration		
1 point	3 points	5 points	5 points	3 points	1 point
1 → 0	2 → 0	3 → 0	0 → 3	0 → 2	0 → 1
2 → 1	3 → 1			1 → 3	1 → 2
3 → 2					2 → 3

* The ultrasound reaeration score was calculated as follows: in the first step, ultrasound lung aeration (0, 1, 2, and 3) was assessed in each of the 12 lung areas examined before and after prone position. In the second step, ultrasound lung reaeration score was calculated as the sum of each score characterizing each lung area examined according to the scale shown at the bottom of the table

not differ according to ARDS morphology (Fig. 3). At the onset of PP sessions (LUS 2), the patients with focal ARDS had an improved reaeration in the posterior area ($P = 0.009$), while the loss of aeration was increased in the anterior areas ($P = 0.0001$) (Fig. 3). These changes in aeration were associated with a transient better response in PaO_2/FiO_2 at the onset of PP (LUS 2) ($P = 0.03$) (ESM, Table 1). As for the entire PP session, the patients with non-focal ARDS had a higher aeration gain in the anterior areas ($P = 0.005$) (Fig. 3). There was no difference in global and regional aeration during PP sessions according to the magnitude of oxygenation response (Fig. 4). Overdistension was not assessed. No difference in survival was found between

Table 2 Patient characteristics

	Total ($n = 51$)	HO_2R ($n = 26$)	LMO_2R ($n = 25$)	*P*
Age (years)	58 ± 15	59 ± 18	58 ± 12	0.92
Male sex, *n* (%)	35 (69)	19 (54)	16 (46)	0.69
Weight at day 0 (kg)	78 ± 17	79 ± 18	76 ± 17	0.55
Height (cm)	169 ± 9	169 ± 11	168 ± 8	0.57
PaO_2/FiO_2 (mmHg)	95 ± 27	86 ± 26	105 ± 25	0.01
$PaCO_2$ (mmHg)	52 ± 13	48 ± 13	55 ± 11	0.06
PEEP (cmH_2O)	11 ± 3	11 ± 2	11 ± 3	0.39
Plateau pressure (cmH_2O)	26 ± 5	26 ± 5	26 ± 5	0.98
Calculated compliance (ml/cmH_2O)	29 ± 11	28 ± 10	31 ± 12	0.35
Driving pressure (cmH_2O)	15 ± 5	15 ± 4	14 ± 5	0.59
Tidal volume (ml/kg of PBW)	6 ± 1	6 ± 1	6 ± 1	0.95
Primary lung disease, *n* (%)	38 (75)	19 (50)	19 (50)	1
Medical admission, *n* (%)	26 (51)	12 (46)	14 (54)	0.7
Days from diagnosis of ARDS to study inclusion	4 ± 7	5 ± 8	4 ± 6	0.49
SAPSII at inclusion	55 ± 18	58 ± 18	51 ± 17	0.29
28-day survival, *n* (%)	25 (49)	14 (56)	11 (44)	0.37
Global LUS	18 ± 5	18 ± 5	19 ± 6	0.58
Anterior LUS	3 ± 3	3 ± 2	4 ± 3	0.19
Lateral LUS	5 ± 3	5 ± 3	6 ± 3	0.74
Posterior LUS	9 ± 2	10 ± 3	9 ± 2	0.87

HO_2R high oxygenation response, *LMO_2R* low to moderate oxygenation response, *PBW* predicted body weight, *SAPSII* simplified acute physiology score II, *LUS* lung ultrasound, *PEEP* positive end-expiratory pressure

high responder and low to moderate responder patients ($P = 0.4$) (Table 2).

Discussion

Oxygenation response to PP

The major finding of our study is that LUS does not predict oxygenation response after the first PP session in ARDS patients with a PaO_2/FiO_2 ratio no greater than 150 mmHg. At variance with previous studies [20, 24, 25], our findings were confirmed over the PP session, corresponding to a persistent response. Improving oxygenation by PP is supported by several mechanisms, as previously described [4, 26, 27]. The dorsal region tends to re-expand while the ventral zone tends to increase in density. Global lung inflation is more homogeneous in PP from dorsal to ventral than in the supine position. The stress and strain are more equally distributed. Since the blood flow distribution is almost unchanged in both postures [28, 29], the recruitment of perfused lung in the dorsal regions exceeds ventral derecruitment and explains oxygenation improvement. Another explanation is the decrease of intrapulmonary shunt by an improved ventilation of perfused lung areas [24].

Our study confirmed that the dorsal zones were reaerated. The ventral zones showed an aeration loss at the onset of PP in focal ARDS patients. According to oxygenation response, PP did not affect global and regional aerations. This finding suggests that oxygenation response during PP is related to complex and multifactorial mechanisms [30]. This point is also suggested by the fact that high oxygenation responders had lower $PaCO_2$ during and after PP. In addition, they increased their respiratory system [31] and decreased their driving pressure [32]. Alveolar recruitment and/or decreased hyperinflation happened and participated in gas exchange improvement.

In a previous study, the response to recruitment was correlated with lung morphology [19]. The predominance of aeration loss in dependent and dorsal lung areas measured by CT scan did not influence the response to PP [20]. Our study confirms that lung morphology does not predict response to PP in terms of oxygenation. Other mechanisms such as facilitated secretion drainage, decreased ventilator-induced lung injury, or heart-induced dorsal compression could explain the benefits of PP [4].

Before initiating PP, bedside LUS did not differentiate the two groups in contrast with a previous study [33]. In the supine position, a normal pattern of anterobasal regions was associated with the oxygenation response. This pattern concerned only few patients and was not validated in our cohort. Oxygenation improvement was

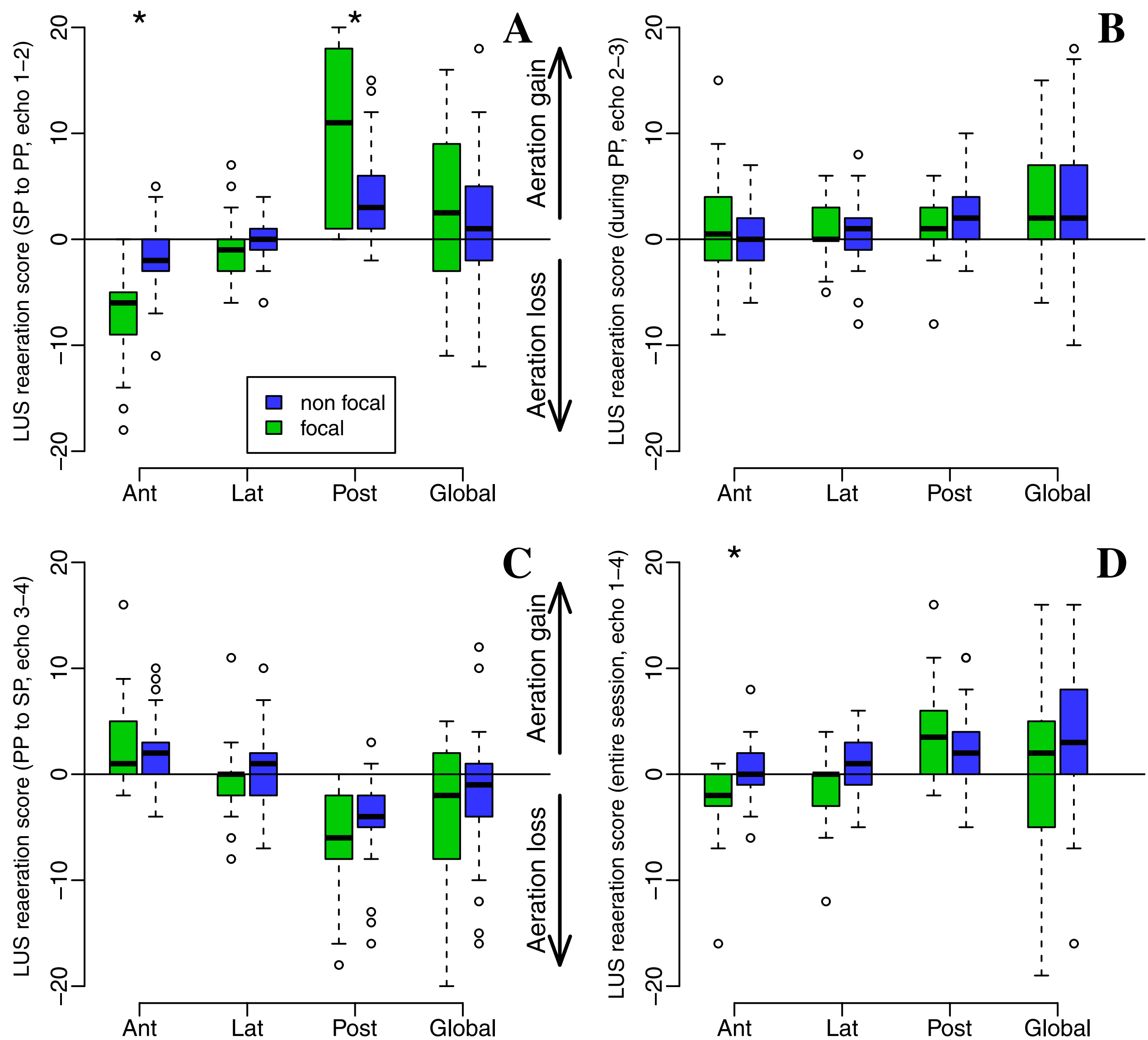


Fig. 3 Ultrasound analysis of pulmonary aeration changes at four predefined time points of PP session according to ARDS morphology. **a** Beginning of PP session (echo 1–2), **b** during PP session (echo 2–3), **c** after PP session (echo 3–4), **d** entire PP session (echo 1–4). The box plots represent the evolution of pulmonary reaeration at each time of PP session for predefined pulmonary areas (anterior, lateral, posterior, superior, inferior, and global). Patients with focal ARDS are represented by *green bars*. Patients with non-focal ARDS are represented by *blue bars*. LUS reaeration score was calculated from changes in the ultrasound pattern of each of 12 lung areas examined before and after PP. Focal and non-focal ARDS patients showed no difference in global reaeration score after the entire PP session. Focal and non-focal ARDS patients showed different changes in regional aeration especially during the early stage of PP. Focal ARDS patients showed a significantly higher reaeration in the posterior areas and a higher aeration loss in the anterior areas. Over the entire session, non-focal ARDS had greater aeration of the anterior areas

assessed by the SpO_2/FiO_2 ratio, which is probably less accurate than the PaO_2 levels in ARDS patients [34]. The sample is monocentric and only 19 patients were included, limiting the interpretation of these results.

As suggested elsewhere [25], $PaCO_2$ changes should be more relevant than PaO_2/FiO_2 ratio changes. In our study, $PaCO_2$ changes did not differ according to oxygenation response or pulmonary morphology. The response

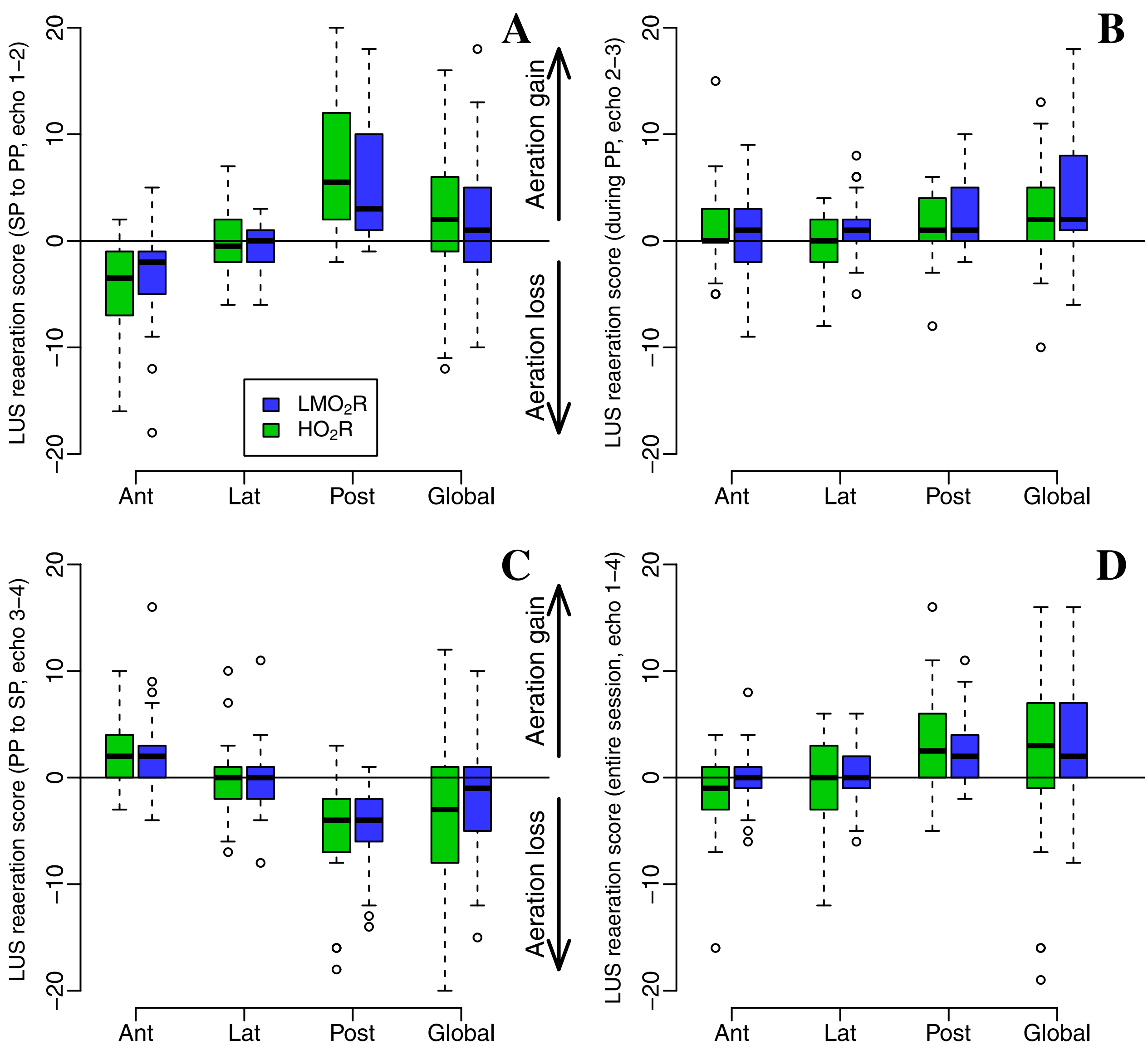


Fig. 4 Ultrasound analysis of pulmonary aeration changes at four predefined time points of PP session according to magnitude of oxygenation response. **a** Beginning of PP session (echo 1–2), **b** during PP session (echo 2–3), **c** after PP session (echo 3–4), **d** entire PP session (echo 1–4). *HO_2R* high oxygenation response, *LMO_2R* low to moderate oxygenation response

to recruitment has been previously correlated with lung morphology [19]. Since PP enhances lung recruitment and decreases hyperinflation, especially in ventral regions, the patients with normal anterior lobes probably optimize their ventilation–perfusion ratio [24, 35]. In other patients, in line with a previous study, recruitment maneuvers and high PEEP should probably be recommended in the first line [19]. In our study, the causes of the lack of improvement in CO_2 clearance are unclear. One could suppose insufficient dorsal recruitment or excessive ventral derecruitment after an entire PP session [35, 36]. In addition, the overdistention that was not assessed could have resulted in increased alveolar dead space, explaining the lack of difference in terms of recruitment.

The use of LUS provides additional knowledge towards the PP mechanism. At the onset of PP sessions (LUS 2), the patients with focal ARDS improved their reaeration in the posterior areas, while the loss of aeration increased in the anterior areas [35, 36]. Patients with non-focal ARDS had a higher aeration gain in the anterior areas after PP. They probably responded to PP by decreasing the non-aerated areas [36]. However, after entire PP sessions, the focal and non-focal ARDS patients showed no difference in global reaeration score.

Limitations

Our study has several limitations. Firstly, one could wonder if PaO_2 response is a relevant end-point to opt for PP. One may argue that the goal of this study was not to predict the oxygenation response but an attempt to explain why some patients increase oxygenation whereas others do not. In previous work, early or late PaO_2 response during the PP session was not associated with survival [37]. However, a seminal study found a trend to lower the PaO_2/FiO_2 ratio in a group of patients with increased survival on day 28 [38]. Moreover, the PaO_2/FiO_2 ratio also defines the severity of ARDS [1]. Since PP was associated with a reduction in the mortality rate of patients with low PaO_2/FiO_2 ratios, one could suppose that this end-point is critical [2, 30]. Most previous studies have used early measurements of arterial blood gas, i.e., 1–6 h after prone installation [20, 24, 25]. In our study, we looked for further longitudinal information over the PP session. Thus, we analyzed the PaO_2/FiO_2 ratio 1 h after turning back to the PP.

All of the patients included were turned prone early after the onset of moderate to severe ARDS for a period of at least 16 h. These subgroups of patients are the most likely to have better survival outcome [39]. Other factors such as tidal volume, PEEP, and driving pressure have been associated with outcome. As for oxygenation response or lung morphology, these factors were similar in both groups and consistent with the results of previous studies [17, 32, 38]. PP could also positively impact hemodynamics [2, 40]. However, we did not focus on this point in the present study.

Moreover, we did not define PaO_2 responders by $\Delta PaO_2/FiO_2$ greater than 20 %. This definition would have resulted in a heterogeneous distribution of patients. Indeed, after PP, a 20 % increase in the PaO_2/FiO_2 ratio was reported in 71 % of the patients. We therefore used a cutoff based on the median response in our cohort, as Gattinoni et al. previously published [22]. In order to assess lung recruitment, we did not use CT. Previous studies compared LUS and CT to assess changes in aeration [9, 18]. Compared with chest radiograph or CT, LUS reduces the risks associated with intrahospital transfer and irradiation [13, 14]. However, normal LUS corresponds to either a normal pulmonary pattern or overdistension [9, 18, 21]. Thus, the detection of hyperinflation is a limitation.

During the performance of LUS, the change in patient position could generate some recruitment and derecruitment. This can be considered as a confounding factor, although limited owing to the short examination time. Another point is the non-inclusion of patients because a trained operator was not available at the time of inclusion. This limitation underlines the need to educate all the clinicians to perform LUS [6]. Finally, there were no technical problems with bedside LUS during the study. Our study confirms that LUS is a rapid, non-invasive, non-radiating bedside technique that is routinely feasible [41].

Conclusion

In ARDS patients with a PaO_2/FiO_2 ratio no greater than 150 mmHg, LUS does not predict oxygenation response after the first PP session. The originality of our study was to confirm those findings over the PP session. Prone positioning is required for ARDS patients if the PaO_2/FiO_2 ratio remains below 150 mmHg. We did not confirm that lung morphology predicts response to PP. At the bedside, LUS provides comprehensive monitoring of regional lung aeration changes associated with PP. Future studies should define the use of this interesting tool in PP assessment.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4411-7) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

The authors report no conflicts of interests in relation to this manuscript.

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