Lung Ultrasound Targeted Recruitment (Lustr): a Novel Protocol to Optimize Open Lung Ventilation in Critically Ill Neonates

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Research Article

Keywords: Respiratory insufficiency, Ventilator-Induced Lung Injury, Intensive Care, Neonatal, Respiratory Distress Syn-drome, Mechanical Ventilation, Point-Of-Care Diagnostics

Posted Date: May 18th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1362301/v2>

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Abstract

Purpose

The objective of this study was to investigate the effectiveness of an original Lung UltraSound Targeted Recruitment (LUSTR) protocol to improve the success of lung recruitment maneuvers (LRMs), performed as a rescue approach in critically ill neonates, as compared to the standard oxygenation-guided LRM.

Methods

All the LUSTR maneuvers, performed in infants with oxygen saturation/fraction of inspired oxygen (S/F) ratio below 200, were included in this case-control study (LUSTR-group). The LUSTR-group was matched by the initial S/F ratio (which is inversely proportional to the severity of the respiratory insufficiency) and underlying respiratory disease with a control group of lung recruitments performed following the standard oxygenation-guided procedure (Ox-group). The primary outcome was the improvement of the S/F ratio (Delta S/F) throughout the LRM. Secondary outcomes included the variation of the Oxygen Saturation Index (OSI) and the rate of air-leaks.

Results

Each group was constituted of fourteen LRMs. As compared to the standard approach, the LUSTR protocol was associated with a higher success of the procedure in terms of delta S/F (110 ± 47.3 vs 64.1 ± 54.6 , $p = 0.02$), and delta OSI (8.2 ± 6.8 vs 2.8 ± 2.2 , $p = 0.01$). These results remained significant after adjusting for confounding variables through multiple linear regressions. All the LRMs in the LUSTR group obtained the sonographic resolution of the lung derecruitment. Patient position before and during LRM was modified more frequently in the LUSTR group. The incidence of pneumothorax was lower, although not reaching statistical significance, in the LUSTR-group (0 vs 14.3%, $p = 0.15$).

Conclusion

The LUSTR protocol may be a more effective and potentially safer option than the oxygenation-based procedure to guide open lung ventilation in neonates.

What Is Known

- Ventilator induced lung injury (VILI) is one of the major causes of mortality in the neonatal intensive care units
- VILI may be reduced by open lung ventilation through lung recruitment maneuvers (LRM), although their failure and complications are not infrequent
- Lung Ultrasound (LUS) may enhance open lung ventilation strategies

What Is New

- The study might suggest that a novel Lung UltraSound Targeted Recruitment (LUSTR) protocol may be superior to the standard oxygenation guided method, for LRMs in critically ill neonates
- The possibility of early detect lung recruitability and adjusting of patient's positioning are likely the keys to the success of the LUSTR protocol

Introduction

Lung Ultrasound (LUS) has been used in adult and pediatric patients to improve the safety and the efficacy of open lung ventilation [1, 2]. Open lung ventilation represents a well-known approach to evenly distribute the tidal volume throughout the mechanically ventilated lungs, through lung recruitment maneuvers (LRMs) [3-5], with the aim to minimize VILI and improve the overall outcome. In a recent randomized trial [6], elective LUS-guided recruitment, performed in premature infants suffering from respiratory distress syndrome (RDS), was proved to be more effective than the standard oxygenation-based procedure, in terms of duration of invasive ventilation, length of stay, and intra-alveolar concentration of interleukin-6 [6]. However, the role of ultrasound-guided LRMs as a rescue approach in critically ill infants has not been evaluated yet. The lungs of these patients, who are highly unstable, may not always be "recruitable" and the risk of failure and clinical deterioration after LRMs is increased. Therefore, it is crucial to select the cases that would benefit the most from the procedure, minimizing the risk of pulmonary and hemodynamic side effects. In a recent case series [7], our group described a novel sonographic pattern, the Sunray(S)-pattern, that develops early during rescue LRMs, as a sign of lung recruitability [7-9]. This study aimed to compare the effectiveness of rescue LUS-guided LRMs showing signs of lung recruitability, to the traditional oxygenation-guided maneuvers in critically ill ventilated neonates.

Material And Methods

Patients, equipment, and study groups

All the LUS-guided recruitments, starting from a consolidation pattern (C-pattern) and showing signs of lung recruitability performed between January 2019 and August 2021 were included in this case-control study and constituted the **Lung UltraSound Targeted Recruitment (LUSTR)** group. The recruitable lung was determined by the development of the S-pattern during pressure augmentation and was based on our previous report [7]. The S-pattern is characterized by the presence of vertical hyperechoic artifacts starting from the reopening bronchi, representing a sonographic sign of lung recruitability. As these linear artifacts resemble the sun rays crossing the clouds, they were named Sunray(S)-lines. The pattern is characterized by the appearance of at least one S-line per field [7]. LRMs were excluded from the study if no S-pattern was detected during the procedure.

The LRM was performed in the case of severe respiratory deterioration, expressed as S/F ratio below 200 [10-12]. LUS evaluation was executed by an expert neonatologist, trained in LUS and with expertise in the LUS-guided recruitment maneuver, using a high-frequency linear probe (9-16 MHz) with General Electric Medical System LOGIQ S8 or with Mindray DC8-EXP ultrasound machines.

The control group (Ox-group) was constituted by rescue LRMs conducted with the oxygenation-guided procedure, as the personnel trained in LUS and with the expertise in the LUS-guided LRM was not available. The oxygenation-guided LRMs were performed during the same period and selected to match those of the LUSTR-group, in terms of type of pulmonary disease and severity of the disease (initial S/F ratio).

As established by local clinical guidelines, the placement of the saturation probes was pre-ductal. Echocardiography was part of the evaluation, in accordance with current international guidelines [13]. Left ventricular dysfunction, pulmonary hypertension, or hypovolemia were evaluated and eventually treated before LRMs in both groups. All the infants were well-sedated during the maneuver. No muscle relaxant was given.

Infants enrolled were mechanically ventilated either with VN500 (Draeger, Lubecca, Germany) or with Sensor medics 3100A (Carefusion, San Diego, USA).

This study was approved by the local ethics committee (CEROM, n. 4510 Prot. 8317/2021 I.5/16), and conducted in accordance with the declaration of Helsinki.

Lung Recruitment Protocols

In the intervention group, LUS was systematically performed on all lung fields: anterior superior, lateral superior, posterior superior, anterior inferior, lateral inferior, and posterior inferior for the right and left sides [14].

If signs of lung consolidation or derecruitment were detected, after the exclusion of any modifiable causes of lung collapse (e.g., endotracheal tube misplacement), LUS-guided recruitment was initiated [7].

In accordance with previous reports in adults and children [1, 15], the patient was positioned to maintain the most severely affected lung fields on the upper side, with constant ultrasound monitoring to visualize the progressive parenchymal reopening throughout the procedure in the most derecruited lung area. LRM was performed through the stepwise increase of airway pressure, either positive end-expiratory pressure (PEEP) during conventional mechanical ventilation (CMV) with volume guarantee or continuous distending pressure (CDP) during high-frequency oscillatory ventilation (HFOV).

Airway pressure was augmented by 1 cmH₂O every 1-2 minutes. The pressure was increased stepwise until the consolidation disappeared and converted into a B2 or B1 pattern, and the corresponding level of airway pressure was defined as opening PEEP/CDP (figure 1). The procedure was planned to be interrupted in the case of clinical deterioration (i.e., increasing oxygen need, hemodynamic instability).

PEEP/CDP was reduced stepwise until LUS began to show signs of lung consolidation or aeration loss in the lung field previously monitored. The corresponding airway pressure was defined as closing PEEP/CDP (figure 1). The optimal PEEP/CDP was set right above the closing pressure. In the case of atelectasis development/persistence in other lung fields, the infant's position was modified again to maintain the atelectatic lung field on the upper side and another LRM was repeated, again monitoring the collapsed area with ultrasound throughout the procedure. A comprehensive LUS follow-up was performed 1 hour, 6 hours, and 12 hours after the end of the maneuver.

In the control group, the procedure in HFOV was performed as described in previous reports on neonates [6, 16]. LRMs on conventional ventilation in neonates follow very different protocols [17]. Our internal protocol for LRM while on conventional ventilation is derived from the one described in precedent reports in children and adults [18, 19] and PEEP is increased by 1 cmH₂O every 1-2 minutes. This protocol results in a similar pressure increase over time in both HFOV and CMV.

Data collection

The following clinical data were retrospectively retrieved from medical records: birth weight (BW); gestational age (GA); CRIB-II score; sex; 5-minutes Apgar score; prenatal steroids administration; mode of delivery; chorioamnionitis; underlying lung disease, defined as (i) respiratory distress syndrome (RDS) [20], resistant to surfactant administration, (ii) neonatal acute respiratory distress syndrome (NARDS), following neonatal sepsis [21], (iii) lung derecruitment during mechanical ventilation detected at chest X-ray or LUS; days of life at recruitment; incidence of bronchopulmonary dysplasia (BPD), defined in accordance with current consensus [22]; length of stay; duration of mechanical ventilation; survival.

The following data were collected about LRMs: mode of ventilation; type of ventilator; Fraction of inspired oxygen (FiO₂), CDP/PEEP, oxygen saturation (SpO₂), heart rate, and mean blood pressure at each time point (start, opening, and optimal pressure); duration of clinical/sonographic benefit, defined as hours without respiratory deterioration and/or echographic evidence of atelectasis; air leaks within 12 hours from LRM; the need for chest drain for air leaks within 12 hours from LRM. The presence of air-leak was suggested by clinical deterioration which prompted the X-ray execution in the Ox-group. While in the LUS group, this was excluded by the follow-up LUS examinations. To assess the severity of the lung disease we used the following parameters: the S/F ratio [10] and oxygen saturation index (OSI = CDP x FiO₂/SpO₂) [23].

In the LUSTR-group was collected the number of steps of pressure needed to obtain the S-pattern. Furthermore, in accordance with the literature [24], a LUS aeration score was carried out before and after the LRM, using the extended newborn specific score described by Loi et al [25]. Ultrasound images and videos were retrospectively analyzed by two independent operators.

Study bias

Selection bias was avoided including all the infants undergoing the rescue procedure (S/F) ratio below 200.

Patients undergoing LUS guided recruitment starting from a C-pattern and not showing signs of lung reopening (S-pattern development) were excluded from the study. To reduce the selection bias, the exclusion of the LUS guided recruitment that did not develop the S-pattern was done in parallel by two authors (RC, EC) that were blinded to the outcome of the LRM. The authors had a 100% agreement in the selection process.

The Ox-group was obtained by automatically matching for 2 relevant different variables. There was no follow-up, therefore no loss was experienced in this study. The multiple linear regressions were performed to correct for the most important confounding variables.

Primary and secondary outcomes

The primary outcome was the difference between the final and the initial S/F ratio (delta S/F ratio). A secondary efficacy outcome in patients undergoing HFOV ventilation was the difference between the final and the initial oxygen saturation index (delta OSI). A secondary safety outcome was the development of pneumothorax with and without the need for chest drain within 12 hours from the LRM.

Statistical analysis

To compare the characteristics across the groups, Chi-square test of independence and an F-test were performed for categorical and continuous variables, respectively. A one-way nested ANOVA was conducted for each comparison group to determine whether the differences between the group means were statistically significant and to take into account the nested structure of the data as multiple observations are associated with the same patient. To this end, the response variable (Delta S/F) was log-transformed to normalize its distribution.

A multiple linear regression model was used to estimate the association between the S/F ratio and relevant explanatory variables. Initially, a model was built by including all the variables considered relevant to the impact of the procedure based on the theory (study groups, GA, CRIB-II score, starting S/F, starting CDP/PEEP, day of life, underlying lung disease, mode of ventilation, sex, change of position before LRM, opening CDP/PEEP). Successively, we performed a stepwise selection process to obtain a reduced final model. The mean with the SD (standard deviation) and the median with the IQR (interquartile range) were reported for the characteristics related to the observations and to the patients, respectively. All model assumptions were checked, and evaluated for multicollinearity, without detecting any relevant effect. As a result of the multiple linear regression, we reported the unstandardized regression coefficient (B) which describes how much the dependent variable is expected to increase when the related independent variable increases by one, holding all the other independent variables constant. We then reported the standard error for the unstandardized beta (SE B), in order to describe the variation around the estimates of the regression coefficient; the t-test statistic (t), and the p-value.

All the recruitments included in the LUSTR-group were matched through the software matching system with one control, based on the severity of the disease (initial S/F) and the type of lung disease. No

missing data regarding the variable of interest (delta S/F) were found. Missing data regarding the independent variables were replaced with the median whereas variables with a significant number of missing data were excluded from the analysis.

A two-way repeated measures ANOVA was used to assess the difference in the oxygenation parameters and vital signs within the two groups across the timepoints. The off-line inter-operator reliability was evaluated using the intra-class correlation coefficient (ICC).

All statistical analyses were performed by a statistician (LA), using the statistical software R (Version 4.1.2, R Development Core Team, Vienna, Austria).

Results

Fourteen LUS-guided recruitments showing signs of lung recruitability were included in the LUSTR-group. Four LUS-guided recruitments performed during the study period and starting from a C-pattern were excluded, as they did not show the S-pattern (details are described in the online supplement). No disagreements were reported in the off-line assessment of the S-pattern (ICC = 1). The S-pattern developed within a median of 2 steps of pressure increase (IQR 1-3, range 1-4). None of the included LRMs was interrupted because of clinical deterioration. Eighteen recruitments performed with the oxygenation-guided approach during the study period and meeting the inclusion criteria were found. Out of these, fourteen were best matched as described in the methods section. Five patients enrolled in the study received both LUS-guided and oxygenation-guided LRM. The main clinical characteristics of the patients enrolled (n = 13) are summarized in Table 1, while the procedural and clinical characteristics regarding the LRMs are reported in Table 2. LRMs were more frequently carried out in patients undergoing HFOV (n = 26, 92.9 %). The two LRMs (7.1 %) during CMV were both performed using patient-triggered Pressure-Control Assist-Control ventilation mode with volume guarantee; synchronization was provided by flow sensor. No signs of shunt fraction potentially impacting on oxygenation deficit on the vascular side were detected in any of the cases at the time of the LRM.

The univariate analysis (Table 2) and the multiple linear regression (Table 3) showed significantly improved respiratory outcomes in the LUSTR-group as compared to the Ox-group in terms of improvement of the S/F ratio (Delta S/F 110 +/- 47.3 vs 64.1 +/- 52.6, crude p 0.02, adjusted p 0.009) and OSI (Delta OSI 8.2 +/- 6.8 vs 2.8 +/- 2.2, p 0.01). The scatterplot graphs of the two outcomes are outlined in Figures 2a and 2b, respectively. No correlation was found between the underlying pulmonary condition and the initial respiratory picture (data not shown).

The patient position was modified more frequently before the procedure in the LUSTR-group (64.3% vs 7.1%, p 0.02). The supine position was more common during the LRM in the Ox-group (35.7% vs 92.9%, p=0.001), while the lateral position was significantly more frequent in the LUSTR-group (35.7% vs 0 %, p=0.04). Prone position was more frequent in the LUSTR group, although this difference was not statistically significant (21.4% vs 7.1%, p=0.22) (Table 2).

The incidence of pneumothorax within 12 hours from the end of the procedure was lower in the LUSTR-group (0 vs 14.2%, p 0.15), as well as the need for chest drain (0 vs 7.1%, p 0.31) (Table 2). These differences were not statistically significant. The outlier LRM in the Ox-group, showing a much higher delta S/F than the other ones (figure 2a), was one of the two that led to the development of the pneumothorax in the subsequent 12 hours. Interestingly, the opening pressure in the LUSTR-group was significantly higher than in the Ox-group (27.1 ± 2.7 cmH₂O vs 19.6 ± 4.9 cmH₂O) (Table 2). The sonographic resolution of lung derecruitment was obtained in all the cases. Neither group presented respiratory or hemodynamic deterioration throughout the procedure. Further details about the progression of vital signs and oxygenation parameters can be consulted in the online supplement.

Discussion

Our study suggests that the LUS-guided recruitment displaying the S-pattern is associated with a higher success of the LUS-guided pulmonary recruitment in critically ill neonates suffering from severe respiratory insufficiency as compared to the standard oxygenation-guided procedure. The recruitments included in the LUSTR group obtained delta S/F ratios with an average of 50-point higher than the LRM in the Ox-group (Table 3). Interestingly, the S-pattern appeared during the early phase of the procedure (with a maximum of 4 pressure steps, mostly after 2 pressure steps), making it a promising sonographic sign to guide the LRM.

A recent randomized controlled trial demonstrated the beneficial impact of LUS in guiding elective LRMs as opposed to the oxygenation-guided method, on a population of preterm infants before the first surfactant administration [6]. Infants enrolled in this trial were all suffering from RDS, a homogenous lung disease, known to respond well to lung recruitment, including oxygenation-guided maneuvers [16, 26]. In fact, despite LUS-guided recruitment better mitigated lung inflammation and reduced the duration of mechanical ventilation, both groups showed a striking improvement in oxygen saturation and FiO₂ after the LRM. In our study, LRMs were attempted as a rescue approach in the case of severe respiratory failure, demonstrated by the critically low starting S/F ratio as compared to the previous report [6]. The Ox-group did not show a very significant improvement in the S/F ratio and experienced a higher rate of air leaks. Patients with heterogeneous respiratory diseases, in terms of physiopathology and spatial distribution, may present a poor response to LRMs. According to our results, in this clinical setting LUS can consistently enhance the open lung ventilation strategy.

The incidence of air-leak and need for chest drain, although not significantly ($p = 0.15$ and 0.31 , respectively), were lower in the LUSTR-group, despite reaching higher opening pressures. Interestingly, also the starting CDP and the derived OSI were higher in the LUSTR-group, suggesting a worse clinical condition and more aggressive initial ventilation settings. This result is consistent with previous reports comparing LUS guided recruitment and oxygenation guided recruitment in the animal model, in children, [1, 2, 16] and adults [1, 15, 27, 28]. It could be arguable that the higher opening PEEP/CDP may have been itself the cause of the respiratory amelioration in the LUSTR-group. In order to address this issue, we included the opening PEEP/CDP in the stepwise process of the linear regression, which ruled it out as a

predictor of the success of the procedure. Moreover, updating the oxygenation-guided protocol to obtain higher opening pressures, would not be feasible as no monitoring tools currently exist and may be detrimental in terms of safety of the procedure [16, 26].

The LRM in the Ox-group that showed a much higher delta S/F than the other ones (figure 2b), was one of the two that developed the pneumothorax. This observation suggests a particularly severe lung disease, responding well to the LRM, although consequently being at higher risk for pneumothorax.

The safety and the efficacy correlated with the LUS-guided recruitment may be due in part to the spatial detection of the collapsed parenchyma, allowing for LUS guided postural recruitment. Indeed, the change of patient position before or during the procedure, to maintain the derecruited lung fields on the upper side, constituted a key feature of LUS-guided LRMs and was performed in almost 80% of the cases, while it was episodic in the oxygenation-guided group (7%). In accordance with the gravity-dependent lung physiology [4, 29], patient position guided by LUS allowed the opening pressure to be targeted towards the most derecruited parenchyma, improving the lung reopening of the collapsed areas and reducing the risk of over-distension of the aerated segments. Although no evidence is available to suggest that a particular body position during mechanical ventilation of the neonate is effective in producing a sustained and clinically relevant improvement [30], it has been described in adult patients that lung recruitment performed in prone position may obtain better results than the supine position [31, 32]. In our population the prone position was more frequent in the LUSTR group, although this difference was not significant, while substantial was the difference between the lateral and the supine position in the two groups, suggesting that the prone position itself could not justify the better results obtained in the LUSTR group, while the LUS-guided postural recruitment is likely a key feature of the LUSTR protocol.

Performing lung ultrasound to guide recruitment is an act of integrated POCUS, as hemodynamics must be taken into account. In our study some patients needed inotropic support of inhaled nitric oxide therapy (supplemental material). As suggested in previous reports [2], the hemodynamics derangements were corrected before starting the LRM[1, 2]. Our results should be seen in connection with the ESPNIC guidelines that describe lung ultrasound as a point of care integrated technique and particularly recommend using it to guide ventilation [13].

The present study has limitations, including the retrospective design and the small sample size. Thoracic X-ray was not systematically performed before and after the recruitment, and overdistension could not be ruled out. In the LUSTR-group, the development of air leaks was excluded by LUS. In the Ox-group the presence of air leaks was suggested by the clinical deterioration which prompted the X-ray execution. Less clinically relevant air leaks may have been not detected in the Ox-group. Another limitation is the inclusion of different underlying diseases in a small population. Two LRMs (one per group) were performed in conventional ventilation. Therefore, the generalizability of the findings is limited in the least represented groups.

Including neonates with a starting S/F ratio below 200 was somehow arbitrary, even if previously reported in the literature as a threshold for high-risk respiratory conditions [10-12]. Furthermore, it was not possible

to correct the SpO₂ value for the fetal hemoglobin content.

Patients undergoing LUS guided recruitment and not showing signs of lung reopening were excluded from the study. On the contrary, no criteria are available to our knowledge to early interrupt the oxygen-guided recruitment protocols or to early detect the not-recruitable lung during oxygenation-guided recruitment. This is a limitation of our study as we could not infer how many patients have non-recruitable lungs in the Ox-group. Despite the increase in the selection bias, one of the strengths of the LUSTR protocol is to target the intervention to the population showing signs of lung reopening. We believe that this is an important step toward the optimization of the procedure.

The primary outcome is focused on the respiratory improvement given by the specific LRM. Other clinically relevant outcomes could not be compared as five patients had both kinds of LRMs. Although the different interventions were not conducted in two separate periods, the choice of the approach was based on the availability of operators trained in LUS and with the expertise in the LUS-guided LRM. Hence, this constituted a source of significant bias.

Conclusions

Based on the present study, the LUSTR protocol may be superior to the oxygenated-guided procedure to optimize open lung ventilation in critically-ill neonates. The possibility to early detect lung recruitability and perform postural recruitment are the cornerstones of this novel lung recruitment protocol. Further large prospective trials are needed to confirm our results and verify if more clinically relevant outcomes are affected by the LUSTR protocol in this patient population.

List Of Abbreviations

CDP: Continuous Distending Pressure

D-Pattern: Dead space-Pattern

HFOV: High-frequency oscillatory ventilation

IQR: Interquartile range

LUS: Lung Ultrasound

LUSTR: Lung Ultrasound Targeted Recruitment

LRM: Lung Recruitment Maneuver

NICU: Neonatal Intensive Care Unit

OSI: Oxygen Saturation Index

Ox-group: Oxygenation based lung recruitment group

S/F: Oxygen Saturation/ Fraction of Inspired Oxygen ratio

S-Pattern: Sunray-Pattern

Statements And Declarations

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript

Conflicts of interest/Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material

The data that support the findings of this study are available on request from the corresponding author, Maria Pierro

Code Availability

Non applicable.

Authors' Contribution

All authors contributed to the study conception and design. Maria Pierro took the lead on the project, conceived the idea and guided the writing process. Enrico Storti, Piergiorgio Villani and Roberto Copetti provided their expertise on lung ultrasound thought the study design and article writing. Giovanni Vento provided is expertise on oxygenation guided recruitment and critically revised the manuscript. Material preparation, data collection and analysis were performed by Roberto Chioma, Lorenzo Amabili, Maria Pierro, Elena Ciarmoli and Miria Natile. The first draft of the manuscript was written by Roberto Chioma, Lorenzo Amabili and Maria Pierro and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. The protocol was reviewed and approved by the local Ethical Committee [Comitato Etico della Romagna, CEROM], approval number [4510 Prot. 8317/2021 I.5/16].

Consent to participate

Written consent was obtained from the parents/legal guardian of the participants of the study.

Consent to publish

The authors affirm that human research participants provided informed consent for publication of the images in Figure 1.

Acknowledgment

The authors would like to thank Gina Ancora and Marcello Stella, as chiefs of the centres involved in the study, and Cole Reynolds for language editing.

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Tables

Table 1. Clinical characteristics of the patients enrolled. Abbreviations: IQR (interquartile range), GA (gestational age), BW (birth weight), CRIB-II (Clinical Risk Index for Babies), BPD (bronchopulmonary dysplasia). The prenatal steroids administration refers to patients with GA below 37 (n= 12). The BPD rate refers to patients with GA below 32 weeks only (n= 8).

Characteristics	Study population n = 13
Weeks of gestation, median [IQR]	26.5 [23.25 – 28]
BW in grams, median [IQR]	715 [552.5 – 1175]
Sex, n (%)	7 (53.8)
Prenatal steroids, n (%)	9 (75)
Vaginal delivery, n (%)	2 (15.4)
5-minutes Apgar score, median [IQR]	7 [6.5 – 8]
CRIB-II, median [IQR]	13 [11 – 15]
Chorioamnionitis, n (%)	5 (38.5)
Days of invasive ventilation, median [IQR]	18 [9 – 39.75]
Days of non-invasive ventilation, median [IQR]	63.5 [56.25 – 98]
BPD incidence, n (%)	7 (87.5)
Survival, n (%)	9 (69.3)
Days of hospital stay, median [IQR]	109.5 [99 – 181]
Day of life at recruitment, mean (SD)	14.4 (1.7)
SpO2 at recruitment, mean (SD)	85.1 (11)
FiO2 at recruitment, mean (SD)	0.83 (0.18)

Table 2. Characteristics of the S-group and Ox group. Abbreviations: Gestational age (GA), Birth weight (BW), Neonatal Acute Respiratory Distress Syndrome (NARDS), Lung recruitment maneuver (LRM), Oxygen Saturation (SpO2), Fraction of Inspired Oxygen (FiO2), SpO2/FiO2 (S/F), Oxygen saturation index (OSI), Extended Lung Ultrasound Score (eLUS), High frequency oscillatory ventilation (HFOV), Continuous distending pressure (CDP), Conventional mechanical ventilation (CMV), Positive end expiratory pressure (PEEP), Pneumothorax (PNX).

*If the position was changed during the procedure from lateral to prone or vice versa.

Characteristics	Ox-group (n= 14)	LUSTR-group (n = 14)	<i>p</i>
Day of life, mean (SD)	14.1 (10.5)	14.8 (7.9)	0.84
Lung condition, n (%)			1
Derecruitment during MV	5 (35.7)	5 (35.7)	
NARDS	5 (35.7)	5 (35.7)	
RDS	4 (28.6)	4 (28.6)	
Change of position, n (%)			
Before LRM	1 (7.1)	9 (64.3)	0.02
During LRM	0	2 (14.3)	0.46
Position during LRM, n (%)			
Supine	13 (92.9)	5 (35.7)	0.001
Prone	1 (7.1)	3 (21.4)	0.22
Lateral	0	5 (35.7)	0.04
Prone and lateral*	0	1 (7.1)	0.31
SpO2, mean (SD)			
Starting	88 (9)	82 (12.5)	0.13
Final	92 (1.5)	95 (3)	0.002
FiO2, mean (SD)			
Starting	0.83 (0.18)	0.82 (0.19)	0.92
Final	0.6 (0.21)	0.45 (0.08)	0.02
S/F ratio, mean (SD)			
Starting	113.6 (36.5)	107.5 (38.1)	0.67
Final	177.7 (77.3)	217.5 (43.4)	0.1
Delta	64.1 (52.6)	110 (47.3)	0.02
OSI, mean (SD)			
Starting	11.6 (4)	16.9 (8.1)	0.04
Final	8.9 (3.1)	8.8 (6.8)	0.96
Delta	2.8 (2.2)	8.2 (6.8)	0.01
eLUS score, median [IQR]	NA		NA

Starting		22.5 [21 – 24]	
Final		19 [18 – 20]	
HFOV, n (%)	13 (92.9)	13 (92.9)	1
CDP (cmH2O), mean (SD)			
Starting	12.5 (3)	15.9 (4.5)	0.03
Opening	19.6 (4.9)	27.1 (2.7)	< 0.001
Optimal	14.3 (2.5)	18.4 (4.2)	0.007
CMV, n (%)	1 (7.1)	1 (7.1)	NA
PEEP (cmH2O), mean (SD)			
Starting	7	5	NA
Opening	9	10	NA
Optimal	6	7	NA
Duration of the procedure (min), median [IQR]	20 [15 – 31.2]	35 [30 – 40]	0.002
PNX, n (%)	2 (14.3)	0	0.15
Chest drain, n (%)	1 (7.1)	0	0.31

Table 3. Final model of the multiple linear regression for the log-transformed (delta) between the final and the initial Oxygen Saturation/Fraction of Inspired Oxygen (SCR/F) ratio. Abbreviations: the unstandardized beta (B); the standard error for the unstandardized beta (SE B); the *t* test statistic (*t*); the probability value (*p*); Gestational age (GA), neonatal Acute Respiratory Distress Syndrome (NARDS), CRIB-II (Clinical Risk Index for Babies).

Variables	B	SE B	<i>t</i>	<i>p</i>
LUSTR	0.68	0.23	2.82	0.009
Underlying lung disease,				
NARDS	0.62	0.24	2.56	0.017
RDS	0.38	0.34	1.13	0.27
Male sex	0.46	0.30	1.53	0.14
CRIB-II	0.09	0.06	1.168	0.10

Figures

Figure 1

Lung UltraSound Targeted Recruited (LUSTR) protocol.

Figure 2

a: difference between initial and final Oxygen saturation/Fraction of inspired oxygen ratio (Delta S/F) in the LUSTR-group and Ox-group. b: difference between initial and final Oxygen Saturation Index (Delta OSI) in the LUSTR-group and Ox-group.

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