Lung ultrasound to monitor respiratory function in extremely preterm neonates (LUSTRE study)

Presented to the SRLF Ethical Commettee under the n° SRLF16-58 and approved on March 10, 2017- Original French title: [Étude de précision diagnostique de l'échographie pulmonaire chez les nouveau-nés (d'âge gestationnel ≤ 30 semaines ou de > 34 semaines)]

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Last protocol English version n.2/may 2020

BACKGROUND

Lung ultrasound is a bedside technique that has an increasingly important role in neonatal intensive care units (NICU) for its simplicity of use and learn.[1] Furthermore, as recently shown, lung ultrasound allows reducing radiation exposure in preterm neonates.[2] Lung ultrasound can be used to diagnose several acute neonatal respiratory disorders such as respiratory distress syndrome (RDS), transient tachypnoea of the neonate (TTN), meconium aspiration syndrome (MAS) and pneumothorax, amongst the others.[3–7] In particular, the use of a "semi-quantitative" lung ultrasound through the application of a score (LUS) is reliable to predict CPAP failure in preterm newborns with RDS and guide respiratory support both in neonates and adults.[8–12]

To the best of our knowledge there are no data about the use of lung ultrasound in the monitoring of preterm infants at risk of bronchopulmonary dysplasia (BPD) and for the diagnosis of BPD. BPD is the most important long-term respiratory outcome of prematurity and it is still lacking of a clear diagnostic tool.[13] This lack has been identified as a major clinical unmet need by the International Neonatal Consortium working on drug development to improve respiratory outcomes of preterm infants.[13] BPD is classically diagnosed at 36 weeks' post-menstrual age,[14] although preterm infants may be affected by chronic pulmonary insufficiency of prematurity (CPIP) on a continuum overtime starting after the first days of life.[13]

STUDY PURPOSES

The objectives of this study are to verify the hypotheses that: 1) LUS is useful to monitor neonates with CPIP, and 2) LUS is accurate to predict BPD occurrence.

STUDY DESIGN

This study is a part of a larger research initiative aiming to investigate the diagnostic accuracy and clinical usefulness of lung ultrasound both in extremely preterm neonates at risk of BPD, and in those closer to the term who may be affected by other respiratory disorders.

This study is a multicenter, pragmatic, international, prospective, observational, non-invasive, diagnostic accuracy study conducted in five academic tertiary referral neonatal intensive care units (NICU) in France and Italy. The NICU at Paris Saclay University Hospital served as coordinating center. Other recruiting centers are represented by the NICUs in the following hospitals:

- Ospedale Materno-Infantile "*G.Salesi*"- Università Politecnica delle Marche (Ancona, Italy)
- Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico (Clinica "*Mangiagalli*"), Università degli Studi di Milano (Milano, Italy)
- Secondo Policlinico – Università "*Federico II*" (Napoli, Italy)
- Policlinico Universitario – Università degli Studi di Padova (Padova, Italy)

Participating NICU teams are proficient in lung ultrasound and routinely use the technique in their clinical care, according to clinicians' evaluation. NICU have been chosen by contacts between peers, for their proficiency in lung ultrasound, expertise in respiratory critical care and previous research track.

POPULATION

All extremely preterm inborn neonates with gestational age ≤30^{+6} weeks, whose parents will accept to participate, will be considered eligible for the study, if they do not have any of the following *a priori* exclusion criteria: 1) complex congenital malformations; 2) chromosomal abnormalities; 3) pulmonary hypoplasia; 4) congenital anomalies of surfactant proteins or any other suspected congenital lung disorders. At the end of recruitment, all data will be sent to the coordinating centre, merged and reviewed to check for completeness and accuracy. Local investigators will be contacted if clarification or more data are needed and infants will be excluded *post hoc* in case of: 1) death or transfer to other hospitals before 36 weeks post-menstrual age; 2) missing data needed for the BPD diagnosis.

LUNG ULTRASOUND PROTOCOL

All patients will serially undergo five lung ultrasounds: at NICU admission (and anyway before any surfactant administration), at 7-14-28 days of life and at 36 weeks of post-menstrual age. The lung ultrasound will be pragmatically realised with a micro-linear, high frequency (15-18 MHz), “golf cub”-shaped, probe or a broadband linear (8-10 MHz) probem, according to the local availability. Lung ultrasound will be performed by investigators who are not the attending physician in charge of the patient on that day. All investigators are expert ultrasonographers and have at least 1 year of experience in neonatal lung ultrasound and have followed a specific training course on the subject.[15] Scans will be performed by automatically adjusting the gain; depth and focus were set according to patients’ size and the sign of interest. Lung ultrasound will be performed in incubators, when neonates are quiet and lying supine

or slightly tilted to scan the posterior zones, during routine clinical care to minimize discomfort.

Lung ultrasound findings will be used to calculate LUS, as previously published.[8] Basically, the lung is divided into three areas (anterior, posterior and lateral) and for each lung area, a 0- to 3-point score is given: 0 for a normal A-pattern; 1 for B-pattern (not aerated lung); 2 for coalescent B pattern and 3 for presence of consolidations. Additionally, investigators using a micro-linear probe will also calculate an extended score (eLUS) over 10 chest areas (5 per each side, ranging from 0 to 30) including the scan of the upper posterior and lower posterior chest areas, using the same lung ultrasound semiology. We will also perform a qualitative description of lung ultrasound findings along the whole chest and images will be anonymously recorded.

DATA COLLECTION

Data will be prospectively collected into customized, secured, electronic spreadsheets by local investigators in each recruiting center. Data will be completely anonymous in accordance with local and European privacy regulations, with only local investigators maintaining an identification log, separate from the spreadsheet used for data collection.

The following data will be collected:

- basic demographics at the NICU admission (such as, for instance: recruiting centre, sex, gestational age, birth weight, type of delivery, antenatal steroid treatment, intrauterine growth and appropriateness for gestational age according to Fenton's curve).[16]

- Lung ultrasound data at first, seventh, fourteenth and twenty-eighth day of life, and at 36 weeks' post-menstrual age. Lung ultrasound will be performed within these time-points in conjunction with routine clinical care to minimize discomfort. Lung ultrasound score (LUS), as described by Brat, will be calculated based on classical lung ultrasound findings.[8] Moreover, an extended lung ultrasound score (eLUS) will be calculated, based on the same lung ultrasound semiology, by scanning also the posterior lung zones. High resolution, anonymous images (still frame) will electronically be saved.
- Vital and respiratory parameters at first, seventh, fourteenth and twenty-eighth day of life, and at 36 weeks post-menstrual age. These will be real time recorded as they appear on the patients' monitoring system within one hour from lung ultrasound and include, for instance, mean airway pressure, mean arterial pressure, inspired oxygen fraction and peripheral oxygen saturation. At the same time, Silverman's score will also be calculated by patients' observation and recorded.
- Gas exchange data at first, seventh, fourteenth and twenty-eighth day of life, and at 36 weeks post-menstrual age. These will be recorded by using transcutaneous monitoring devices within one hour from lung ultrasound. These devices will be adequately calibrated at 44°C to increase accuracy and used according to the American Association for Respiratory Care guidelines[17] and manufacturer's recommendations. Probes will be applied until the achievement of a stable measurement and anyway for a maximum of fifteen minutes.[18] During transcutaneous measurements, ventilatory parameters will not be changed and, for neonates receiving non-invasive respiratory support, pressure leaks will be minimized, by using appropriately

sized interfaces and closing the mouth with gentle pressure on the jaw or chinstraps, according to local policy.

- BPD diagnosis at 36 weeks of post-menstrual age will be provided, and its severity will be described according to classical Jobe's and Bancalari's definition.[14]
- Any relevant comment from local investigators.

These variables were chosen in order to keep a pragmatic design: in fact, they shall be available in all recruiting centres as we wanted to test semi-quantitative lung ultrasound with no change in the clinical practice provided in modern, third level, academic referral NICUs.

OUTCOMES

The primary outcomes will be: (1) to efficaciously monitor lung aeration in neonates with CPIP by calculating LUS and describing its relationship with gas exchange at different time points; 2) to demonstrate accuracy of LUS to predict BPD at 36 weeks' post-menstrual age. The secondary outcome will be to compare the performance of the classical and extended LUS to monitor lung aeration and predict BPD. BPD was diagnosed according to Jobe and Bancalari's criteria[14] by a clinician blinded to LUS data.

STATISTICS AND CALCULATIONS

Oxygenation index and other metrics will be calculated as previously described.[8] Sample size was calculated for the two primary outcomes as follows. To monitor lung aeration and function we targeted a correlation coefficient between LUS and OI of at least 0.6, based on previous data obtained in a similar population of extremely

preterm neonates.[9] To predict BPD occurrence, we targeted an area under curve (AUC) of at least 0.7, based on available preliminary data[19] and considering as null hypothesis the prediction by chance (AUC=0.5) and a positive/negative (i.e.: BPD/no BPD) case ratio of 1. For both calculations α and β were set at 0.05 and sample size resulted 98 and 100 for the two outcomes respectively. An *interim* analysis will be performed at approximately 50% of the recruitment, to analyze if there is any problem with patients' enrolment and if the protocol needs any amendments.

Data distribution will be tested and data will be described and compared accordingly. Lung ultrasound scores calculated at the various timepoints will be compared by repeated measures-ANOVA, using the BPD diagnosis as between subjects' factor and followed by Bonferroni *post hoc* test. Correlation analyses with lung ultrasound scores will be performed using Spearman coefficients, followed by multivariate linear regressions with backward-stepwise method, adjusting for gestational age and the diagnosis of BPD. Covariates will be removed from the model if *p*-value was >0.10. Gestational age will be chosen as covariate because of its association with BPD; birth weight will not be included because it is correlated with gestational age and creates significant multicollinearity. Results will be graphically shown in scatter plots with trendline generated by local regression smoothing procedure (Epanechnikov's kernel with at least 85% of span).

Receiver operator characteristics (ROC) procedure will be used to analyze the diagnostic accuracy of lung ultrasound scores to predict BPD: curves will be compared with DeLong's method and results reported as area under the curve (AUC and 95% confidence interval) and derived statistics. Since BPD is associated with

gestational age, lung ultrasound scores with highest AUC will be chosen and entered in multivariate, logistic, backward-stepwise models together with gestational age. Covariate treatment will be as above; goodness-of-fit will be evaluated with Hosmer-Lemeshow test. If lung ultrasound scores and gestational age will remain significant on logistic models, they will be combined according to their odds ratio and finally tested with ROC analysis. Post-test probability will be estimated according to the Fagan nomogram.[20] Analyses will be performed with SPSS 25.0 (SPSS Inc, Chicago, IL - USA), MedCalc 13.3 (MedCalc bvba, Ostend, Belgium), and GPower 3.1 (HHU, Dusseldorf, Germany). *p*-values<0.05 was considered significant.

WHY THE PROJECT IS IMPORTANT AND JUSTIFIED

Conventional radiology is known to be unreliable to predict respiratory outcomes in preterm neonates.[13] Lung ultrasound may be more useful because it is easily repeatable, quick and radiation free, notwithstanding its higher accuracy to detect loss of lung aeration.[21,22] Thus, it seems logical to use LUS to monitor the evolution of respiratory function and predict respiratory outcomes in preterm neonates. This is strengthened even more as international evidence-based guidelines for the use of lung ultrasound in NICU have been recently issued.[1] Our results will have a place within the increasing drive towards a reduced invasiveness of neonatal care worldwide.

Last but not least, as BPD has no clearly validated diagnostic tool,[13] and there are some potential drugs being investigated,[23–25] it is extremely important to have a

reliable and validated tool for the early identification of BPD-developing infants. This will allow an earlier treatment which seems necessary to improve outcomes. [13]

ETHICAL CONSIDERATIONS

This is a multicenter, pragmatic, international, noninvasive, observational, prospective, diagnostic accuracy study and it was approved by the Ethical Committee of the French Society for Critical Care (n.SRLF16-58). The study was also (or will be) approved by local ethical boards of participating centres, if required by local regulations. Parental/guardian consent will also be obtained following local regulations. The study will be registered in the ISRCTN Registry and protocol details will be available there. Although this is not considered necessary for an observational study, authors feel that this is increasing the quality of data as it reduces the chance of publication bias and selective data reporting.

The study is pragmatic as the participation did not change the clinical management, which will be provided according to local NICU protocols, essentially based on optimal prenatal care and international guidelines for neonatal resuscitation and respiratory management of preterm neonates.[20,26] The study does not modify the routine care in anyway as lung ultrasound is already routinely used as point of care tool in participating NICUs. Collected data are those already registered in the clinical care and no others are recorded. All data will be totally anonymous with only local investigators maintaining a separated log to identify patients. Data will be collected in secured computers dedicated only to research purpose and transmitted using secured files. Local and European privacy regulations will be respected.

The project does not carry any risk for the patients, since lung ultrasound is a totally non-invasive technique and will be performed in conjunction with routine clinical care in order to minimize infants' discomfort. Conversely, the participation to the study may even increase the knowledge about the respiratory conditions of recruited infants and will be helpful for other patients, once its usefulness will be definitively ascertained.

The study has no sponsor of any type and no honorarium is previewed for the participation to the study. Authors are performing the study for free during their worktime and they do not have any conflict of interest to disclose in relation to the project.

DATA DEFINITION USED IN THE STUDY

The following definitions will be used for study purposes:

- Airleaks are considered as pneumothorax or pneumomediastinum diagnosed by lung ultrasound or chest X-rays. If this will be found during a lung ultrasound scan for the study purposes, the attending clinician will be immediately informed and he will decide the diagnostic and therapeutic management independently.
- Bronchopulmonary dysplasia (BPD) will be diagnosed and graded according to classical Jobe's and Bancalari's definition,[14] by attending physicians not involved in the study and blinded to lung ultrasound data.
- Chronic pulmonary insufficiency of prematurity (CPIP) is defined as respiratory morbidity needing any type of respiratory support (from continuous positive airway pressure to various forms of non-invasive ventilation, to invasive and

high frequency oscillatory ventilation) after preterm birth (and resolution of RDS) during the birth hospitalization.[13]

- Congenital heart defect (other than patent *ductus arteriosus*) will be considered as diagnosed by echocardiography performed by certified paediatric cardiologists and indicated clinically by the attending neonatologist and the clinical history.
- Gestational age is based on the postmenstrual date and early gestation ultrasound findings.
- Haemodynamically significant patent *ductus arteriosus* will be diagnosed according to local protocol for each centre, based on common echocardiographic and clinical criteria.[27]
- Lung ultrasound signs were divided in 4 patterns as previously described[8] and the lung ultrasound scores will be calculated as follows: 0 indicates A-pattern (defined by the presence of the only A-lines); 1, B-pattern (defined as the presence of ≥3 well-spaced B-lines); 2, severe B pattern (defined as the presence of crowded and coalescent B-lines with or without consolidations with a size of ≤1 cm); and 3, extended consolidations (i.e.: subpleural echo-poor area or one with tissue-like echotexture with size >1 cm and irregular borders, which may also have mixed hypo- and hyper-echogenic zones representing bronchogram).

  These represent classical definitions of lung ultrasound semiology and are very easy to learn and be applied in clinical practice.

- PPHN will be diagnosed according to classical echocardiographic signs.[28]

- Perinatal Asphyxia, will be defined according to the American College of Obstetricians and Gynaecologists and the American Academy of Paediatrics definition.[29]
- Pulmonary hypoplasia was defined as previously described.[30]
- Respiratory distress syndrome (RDS, i.e.: hyaline membrane disease or primary surfactant deficiency), as defined in the Montreux definition as exclusion criterion.[18]

COMMUNICATION AND PUBLICATION PLAN

Several videoconferences and in-person meetings are planned between the study investigators to update on the project. These will be done in conjunction with main congress or meetings in the field in order to reduce expenses or through video-communication common tools. Collaborating NICU and local investigators are already in contact since longtime and have participated together in several other research and training project so communication will not face any particular problem.

Results will be shared by email and videoconference with all authors and a group authorship will be crated. Order of authors will be decided by consensus guided by the international Committee of Medical Journals Editors guidelines.[31]

Results will be partially presented in main pediatric or critical care congresses such as those of Pediatric Academic Societies in North America or of European Society for Pediatric and Neonatal Intensive Care (ESPNIC) and European Academy of Pediatric Societies in Europe. Final results will be published in one or more articles in top international journals in the field of pediatrics or critical care.

Data presentation and curation will follow the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) Statement.[32]

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