[Critical Care Original Research]

CHEST

Inspiratory Effort and Dynamic Transpulmonary Driving Pressure in Extremely Preterm Infants

Daniele De Luca, MD, PhD; Sofia De La Rubia, MD; Francesca Miselli, MD, PhD; Guillaume Emeriaud, MD, PhD; Barbara Loi, MD; Marco Piastra, MD; Giorgio Conti, MD; Massimo Antonelli, MD; and Domenico Luca Grieco, MD

BACKGROUND: In preterm infants receiving noninvasive ventilation, data about inspiratory effort (ΔP_{es}) and transpulmonary driving pressure (ΔP_L) are scarce. Electrical activity of the diaphragm (EAdi) can estimate ΔP_{es} and ΔP_L when patient size precludes more accurate measurements. This estimation may reveal new insights into respiratory pathophysiology and potential risk of self-inflicted lung injury in neonates receiving noninvasive support.

RESEARCH QUESTION: What are the characteristics of ΔP_{es} and ΔP_L in extremely preterm infants undergoing noninvasive ventilation?

STUDY DESIGN AND METHODS: Prospective, observational pilot cohort study, in which EAdi was recorded in neonates receiving noninvasive ventilation during recovery from respiratory distress syndrome (RDS), in those with evolving bronchopulmonary dysplasia (BPD), and in term controls. EAdi was used to estimate ΔP_{es} and ΔP_L. In a subset of patients with RDS and BPD, diaphragmatic thickening fraction (TF) and oxygen saturation (Spo_2)/Fio_2 were recorded.

RESULTS: Ten patients with RDS, 25 patients with evolving BPD, and 5 control term neonates were studied. Average EAdi, ΔP_{es}, ΔP_L, and TF were similar between control infants and those with RDS and BPD. Inter-patient variability of ΔP_{es} (RDS, 24 [9]%; BPD, 28 [9]%; controls, 10 [6]%; $P < .001$) and ΔP_L (RDS, 25 [7]%; BPD, 27 [9]%; controls, 17 (7)%; $P = .05$) was higher in patients than in controls. Breaths with $\Delta P_{es} > 10$ cm H_2O occurred more often in BPD than in RDS patients ($P = .035$) and control infants ($P = .006$). Breaths with $\Delta P_L > 20$ cm H_2O occurred similarly in patients with BPD or RDS and more frequently than in control infants ($P < .001$). EAdi-based estimations correlated with TF, and ΔP_L had an inverse correlation with Spo_2/Fio_2 ($\rho = -0.64$; $P = .018$).

INTERPRETATION: ΔP_{es} and ΔP_L show relevant variability in preterm infants. High ΔP_{es} is more common in patients with BPD than in those with RDS or control infants. High ΔP_L was observed in patients with BPD and RDS, occurred more often than in control infants, and correlated with the degree of oxygenation impairment. CHEST 2025; ■(■):■-■

KEY WORDS: diaphragm; lung; neonate; patient self-inflicted lung injury; stress

ABBREVIATIONS: ΔP_{es} = esophageal pressure swing; ΔP_L = dynamic transpulmonary driving pressure; BPD = bronchopulmonary dysplasia; CV = coefficient of variance; EAdi = electrical activity of the diaphragm; NAVA = neurally adjusted ventilatory assistance; NICU = neonatal intensive care unit; P_{peak} = maximal inspiratory pressure; P-SILI = patient self-inflicted lung injury; RDS = respiratory distress syndrome; STROBE = Strengthening the Reporting of Observational Studies in Epidemiology; TF = thickening fraction

AFFILIATIONS: From the Division of Pediatric and Neonatal Critical Care (D. D. L., S. D. L. R., F. M., and B. L.), "A.Béclère" Medical Center, APHP/Paris Saclay University; the Physiopathology and Therapeutic Innovation Unit—INSERM U999 (D. D. L., S. D. L. R., and B. L.), Paris Saclay University, Paris, France; the Pediatric Intensive Care Unit (G. E.), CHU Sainte Justine, Université de Montréal, Montreal, ON, Canada; the Pediatric Intensive Care Unit

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Take-Home Points

Study Question: What are the characteristics of the determinants of self-inflicted lung injury (ie, inspiratory effort and transpulmonary driving pressure) in extremely preterm infants undergoing noninvasive respiratory support?

Results: In this prospective study involving neonates receiving noninvasive ventilation during recovery from respiratory distress syndrome (RDS), in those with evolving bronchopulmonary dysplasia (BPD), and in term control infants, high effort was more common in BPD, whereas elevated transpulmonary driving pressure occurred in both RDS and BPD more frequently than in control infantss, with higher transpulmonary driving pressure associated with the extent of oxygenation impairment.

Interpretation: Determinants of self-inflicted lung injury show wide variability in preterm infants receiving noninvasive support: patients with BPD are more prone to show increased inspiratory effort, and high transpulmonary driving pressure is linked to worse oxygenation.

In invasively ventilated preterm infants with respiratory failure, ventilator-induced lung injury contributes to the development of bronchopulmonary dysplasia (BPD).[1] To mitigate the risk of ventilator-induced lung injury and prevent progression to BPD and long-term negative respiratory outcomes, preterm infants are increasingly supported with noninvasive respiratory techniques.[2]

However, lung injury progression, in the form of patient self-inflicted lung injury (P-SILI), might occur during spontaneous breathing as well. In spontaneously breathing adults with acute hypoxemic respiratory failure or ARDS, P-SILI occurs by means of increased stress and strain, regional aeration heterogeneity, transvascular pressure with consequent hydrostatic edema, and diaphragmatic injury.[3,4] The mechanistic determinant of P-SILI is the intensity of spontaneous inspiratory effort.[4-6] No data are available, however, about the occurrence of P-SILI in neonates.

This lack of knowledge is mainly attributable to the challenges in measuring inspiratory effort and transpulmonary driving pressure in neonates, particularly in extremely preterm infants, because of their small size and the resulting lack of adequate instrumentation.

Electrical activity of the diaphragm (EAdi) monitoring is available, even for extremely preterm infants, within the noninvasive neurally adjusted ventilatory assistance (NAVA) that can be deployed to support these patients.[7] EAdi can be used to estimate inspiratory effort and transpulmonary driving pressure at the bedside.[8] This might offer insights into their respiratory pathophysiology and the optimal ventilatory strategies.

We conducted a study to describe the magnitude of inspiratory effort and transpulmonary driving pressure in extremely preterm infants during noninvasive respiratory support.

Study Design and Methods

Setting and Study Design

This was a prospective, observational pilot cohort study conducted in an academic referral neonatal ICU (NICU) during 2024. The study was pragmatic and noninvasive, using only data routinely collected during the usual clinical practice. As such, the study received ethical approval (CER-Paris Saclay-2023-055), adhered to the Declaration of Helsinki, and included written parental informed consent that was obtained on NICU admission. Data were recorded anonymously, and manuscript preparation followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[9] Surfactant was administered, if needed, using our customized intubation-surfactant-extubation procedure.[10] According to our NICU protocols, noninvasive NAVA is a pivotal part of the post-extubation respiratory support for these patients.[11] The rest of clinical management was provided according to our NICU protocols, essentially based on updated evidence and current international guidelines, and did not change during the study.

(M. P. and G. C.), IRCCS-Fondazione Policlinico "A. Gemelli," Roma; the Department of Biotechnology, Critical and Perioperative Medicine (M. P., G. C., M. A., and D. L. G.), Catholic University of the Sacred Heart, Rome; and the Intensive Care Unit (M. A. and D. L. G.), IRCCS-Fondazione Policlinico "A. Gemelli," Roma, Italy.

CORRESPONDENCE TO: Daniele De Luca, MD, PhD; email: dm.deluca@icloud.com

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Patients

Extremely preterm infants with gestational age $\leq 28^{+6}$ weeks were eligible if they were recovering from respiratory distress syndrome (RDS) or affected by evolving BPD and supported with noninvasive NAVA. Neonates were considered to be recovering from RDS if they (1) successfully and promptly responded to surfactant replacement, and (2) had a postnatal age <7 days at enrollment: this period was chosen because it corresponds to the time needed for the production of endogenous surfactant and for a full recovery from RDS.[12] RDS was diagnosed according to the Montreux consensus criteria (ie, respiratory distress signs appearing within the first day of life, with characteristic ultrasound findings,[13] and response to surfactant replacement).[14] Evolving BPD was diagnosed in extremely preterm infants if they (1) needed oxygen supplementation for ongoing hypoxemic respiratory failure at enrollment; (2) showed reduced lung aeration by ultrasound at enrollment; (3) needed invasive ventilation for at least 7 days in the first 2 weeks of life; (4) had a postnatal age $\geq$ 14 days at enrollment. Similar criteria have been used to study the pathophysiology of evolutive BPD[15] and predict the diagnosis of established BPD.[16] Patients were sampled once (ie, those recruited in the RDS group were not recruited again if they were developing BPD later). Neonates were not recruited if, besides recovering RDS or evolving BPD, another respiratory disorder (such as transient tachypnea, pneumonia, or neonatal ARDS) was present at the enrollment.

Additionally, a group of term neonates with no lung disease was considered as a control group if they fulfilled all the following criteria: (1) admitted to the NICU for nonrespiratory reasons (ie, no evidence of any neonatal respiratory disorder) and supported with post-extubation noninvasive NAVA after invasive ventilation for whole-body hypothermia or general anesthesia; (2) no need for supplemental oxygen to achieve pre-ductal peripheral hemoglobin saturation (Spo_2) $\geq$ 90%; (3) normal chest auscultation and lung ultrasound. For all groups of neonates, the exclusion criteria were: (a) complex malformations or chromosomal abnormalities; (b) congenital lung anomalies; (c) pneumothorax, pneumomediastinum, or pleural effusion; (d) need for thoracic surgery; (d) severe hemodynamic instability (defined as any need for inotropes).

Procedures

Noninvasive NAVA was provided using Servo-family ventilators (Getinge, Solna, Sweden), with esophageal catheters (6 Fr, 49 cm) used according to the manufacturer's recommendations. Catheter position was verified from the electrical activity of the diaphragm (EAdi) signal on the ventilator screen, as previously reported.[17] Adequately sized nasal masks (Flexytrunk, Fisher & Paykel Healthcare, Auckland, New Zealand) were chosen as the interface and used according to the manufacturer's recommendations. Leaks were reduced by patient positioning and chinstraps (Fisher & Paykel Healthcare, Auckland, New Zealand).[18] Our routine clinical protocol for the management of NAVA was as follows: positive end-expiratory pressure and NAVA level were set between 5 and 8 cm H_2O or 0.5 and 3 cm $H_2O/\mu V$, respectively; positive end-expiratory pressure was titrated to achieve an Spo_2 between 90% and 95% with the lowest Fio_2 possible. NAVA level was set to obtain adequate CO_2 clearance, minimize the work of breathing, and increase patient comfort; NAVA level was never increased beyond the NAVA breakpoint, which was serially evaluated by looking at EAdi and peak pressure tracings.[19] Crossing the NAVA breakpoint threshold may reduce EAdi, resulting in patient over-assistance and decreased spontaneous breathing effort; thus, by keeping the NAVA level below the breakpoint, we were able to create a more consistent and controlled situation. Patients were fully monitored according to our routine NICU protocols, which include vital parameters, as well as EDIN (Échelle de Douleur et d'Inconfort du Nouveau-né) and COMFORT scores.[20,21] Only nonpharmacological sedation (ie, pacifiers and dextrose solution) was used. Arterialized capillary blood gas analyses and transcutaneous blood gas monitoring were performed as needed per our routine care policy. Point-of-care lung and diaphragmatic ultrasound was performed whenever clinically indicated, as previously published.[22,23] Patients with evolving BPD were re-intubated if they had respiratory acidosis (pH < 7.20 with $Paco_2$ > 65 mm Hg) or severe hypoxia (Fio_2 $\geq$ 0.6 to reach Spo_2 between 90% and 95%) despite maximal noninvasive NAVA support and 6-hour prone positioning.[24] No procedure was performed solely for study purposes.

Data Collection and Calculations

The minimum and maximum EAdi as well as its waveform were recorded from the ventilator, when patients were peacefully asleep and analyzed in a breath-by-breath manner over 1 minute free of artifacts. For the same period, the maximal inspiratory pressure (P_{peak}) delivered by the ventilator was recorded for each breath. Timings of the beginning and end of cycles were

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identified, and a breath-by-breath visual inspection was performed with cursor adjustment if needed. For each breath, the maximal esophageal pressure swing (ΔP_{es}) was estimated by the EAdi peak using the equation previously reported by Essouri et al[25]:

$$\Delta P_{es}\ (cm\ H_2O) = 0.25 \times \text{EAdi}\ (\mu V) + 3.2$$

This equation had an $R^2 > 0.9$ in neonates and small infants supported with noninvasive NAVA who were studied with a special catheter comprising both EAdi electrodes and a balloon.[25] The end-inspiration dynamic transpulmonary driving pressure (ΔP_L) was then estimated, for each breath, by adding the delivered P_{peak} to the ΔP_{es}. If point-of-care ultrasound was performed within 1 hour from data recording, as a part of the clinical routine, the diaphragmatic thickening fraction (TF) was calculated,[23] and the Spo_2/Fio_2 ratio was simultaneously recorded. Demographics and clinical data were recorded in real time from electronic patient files and the monitoring system.

Statistics

No previous study has investigated inspiratory effort and transpulmonary driving pressure in extremely preterm infants, so a formal sample size calculation was unfeasible; this should be considered a pilot study. A convenience sample size was established to provide an indication of the magnitude of the effect size related to BPD. Thus, 25 infants with evolving BPD and 10 with RDS were enrolled. This population is similar to or larger than those analyzed in previous studies on lung mechanics in extremely preterm infants.[26,27]

The normality of the distribution was tested using the Shapiro-Wilk test, and the data were treated accordingly. EAdi, ΔP_{es}, ΔP_L, and TF were considered as outcomes, summarized as medians (25^{th}-75^{th} percentiles) and compared with the Kruskal-Wallis test. EAdi, P_{peak}, ΔP_{es}, and ΔP_L were averaged from breaths captured in 1-minute recordings for each patient. The coefficient of variance (CV, expressed in %) was calculated as the ratio of SD to mean for ΔP_{es} and ΔP_L to describe their heterogeneity, and compared with one-way analysis of variance followed by the Dunnett post hoc test.[28] Dichotomous data were compared with χ^2 or the Fisher test, as appropriate. Correlation analyses were performed between the main outcomes and the Spo_2/Fio_2 ratio, using the Spearman (ρ) coefficient and interpreted according to the *BMJ*'s Statistics classification.[29] Spearman correlation was chosen given the small sample size for this subgroup analysis. Results were subsequently adjusted for gestational age into multivariate linear regressions whose results were expressed as β-coefficients (95%CI). Analyses were performed with SPSS 30 (IBM), and $P < .05$ was considered statistically significant.

Results

Demographics and clinical characteristics of infants with RDS or evolving BPD are displayed in Table 1. The additional control group consisted of 5 term neonates (gestational age, 38.4 [SD: 1.1] weeks, birth weight = 2,564 [SD, 692] g, postnatal age = 3 [1.5-3.5] days). Mean NAVA level was similar in infants recovering from RDS (2.5 [1.9-2.5] cm H_2O/μV), with evolving BPD (2 [1.3-2.2] cm H_2O/μV) and in control infants (1.8 [1.6-2] cm H_2O/μV; $P = .211$), respectively. All enrolled patients survived and were successfully discharged from the NICU. Infants in the evolving BPD group were eventually diagnosed with mild BPD (ie, no cases of moderate-to-severe BPD were enrolled). No technical issues regarding data availability were observed, and data from all patients were suitable for the analysis.

Table 2 shows the main outcome results: EAdi, P_{peak}, ΔP_{es}, ΔP_L, and TF were not statistically different between the control group infants, patients with RDS, and patients with evolving BPD, although patients with BPD showed slightly higher median values. Interpatient variability of ΔP_{es} was higher in RDS (CV = 24 [9]%) and BPD (CV = 28 [8.5]%) patients than in control infants (CV = 10 [5.8]%; overall $P < .001$; Dunnett post hoc test: RDS vs controls, $P = .008$, BPD vs controls; $P < .001$). Similarly, ΔP_L variability was higher in RDS (CV = 24.6 [6.5]%) and BPD (CV = 27.3 [8.9]%) patients than in control infants (CV = 17.3 [7]%; overall $P = .05$; Dunnett post hoc test: BPD vs controls $P = .029$). Raw data visually illustrating the variability are shown in e-Figure 1.

Breaths showing ΔP_{es} values > 10 cm H_2O occurred more frequently in BPD (33 [2.9%] of 1,143 breaths) than in RDS patients (6 [1.2%] of 509 breaths; $P = .035$); both patient groups had more of these breaths than controls who never had ΔP_{es} values > 10 cm H_2O ($P = .006$; Fig 1 and e-Fig 1). ΔP_L > 20 cm H_2O was observed in 212 (41.6%) of 509 breaths, in 505 (44.2%) of 1,143 breaths, and in 38 (17.6%) of 216 breaths in

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TABLE 1] Demographics and Baseline Characteristics

	Whole Cohort (N = 35)	RDS (n = 10)	Evolving BPD (n = 25)
Gestational age, wk	26 (1.3)	26.6 (1.5)	26 (1.2)
Birth weight, g	757 (107)	752 (124)	758 (102)
Male sex	23 (65%)	8 (80%)	15 (60%)
Prenatal steroids	29 (82.9%)	8 (80%)	21 (84%)
Clinical chorioamnionitis	20 (57.1%)	3 (30%)	17 (68%)
Cesarean section	29 (82.9%)	9 (90%)	20 (80%)
5′ Apgar score	8 [7-9]	8 [6-10]	8 [7-9]
CRIB-II score	12 [9-13]	12 [9-14]	11 [9-13]
SGA neonates	3 (8.6%)	1 (10%)	2 (8%)
Postnatal age at enrollment, d	18 [4-28]	4 [3-6]	25 [19-35]
PEEP at enrollment, cm H_2O	6 [6-7]	6 [6-6.5]	7 [6-7]
F_{IO_2} at enrollment	0.21 [0.21-0.28]	0.21 [0.21-0.28]	0.25 [0.21-0.43]
Spo_2/F_{IO_2} ratio	445 [333-456]	443 [331-457]	437 [243-460]
Duration of O_2 supplementation, d	32 [22-54]	31 [23-52]	36 [17-51]
Duration of noninvasive support, d	56 [46-58]	41 [51-58]	57 [56-65]
NICU stay, d	69 [63-89]	67 [62-82]	70 [64-89]

Data are shown as mean (SD) or median [25th-75th percentile], as appropriate, or No. (%). Clinical chorioamnionitis was diagnosed using a dedicated score.[39] SGA status was diagnosed using Fenton curves.[40] Duration of noninvasive support was defined considering the cumulative duration of high-flow O_2 supplementation (>2 L/min), CPAP, biphasic positive airway pressure, or any mode of noninvasive ventilation. Apgar and CRIB-II are dimensionless variables. BPD = bronchopulmonary dysplasia; CRIB-II = critical risk index for babies-II; NICU = neonatal ICU; PEEP = positive end-expiratory pressure; RDS = respiratory distress syndrome; SGA = small for gestational age; Spo_2/F_{IO_2} ratio = preductal peripheral hemoglobin oxygen saturation to F_{IO_2} ratio.

patients with RDS or BPD and in control infants, respectively ($P < .001$; Fig 1 and e-Fig 1).

Significant correlations were found between EAdi and diaphragmatic TF (Fig 2A), TF and ΔP_{es} (Fig 2B), TF and Spo_2/Fio_2 (Fig 2C), and between ΔP_L and Spo_2/F_{IO_2} (Fig 2D). On adjustment for gestational age, all correlations, except that between TF and Spo_2/F_{IO_2} ($P = .373$), remain significant: EAdi and diaphragmatic TF ($\beta = 4.9$ [95%CI, 1.1 to 8.6; $P = .016$]), TF and ΔP_{es} ($\beta = 19.5$ [95%CI, 4.5 to 34; $P = .016$]), and ΔP_L and Spo_2/F_{IO_2} ($\beta = -0.02$ [95% CI, −0.04 to −0.007; $P = .01$]).

Discussion

In our population of extremely preterm infants supported with noninvasive NAVA, we found that (1) inspiratory effort and dynamic transpulmonary driving pressure, estimated through the EAdi signal, are overall similar amongst patients recovering from RDS, those with evolving BPD, and control infants; (2) inspiratory effort and dynamic transpulmonary driving pressure are significantly more variable in patients recovering from RDS or with evolving BPD than in control infants; (3) as a consequence, the number of breaths characterized by high inspiratory effort is greater in patients with BPD

TABLE 2] Main Outcome Results: Inspiratory Effort and Dynamic Transpulmonary Driving Pressure

	Control Participants (n = 5)	RDS (n = 10)	Evolving BPD (n = 25)	*P* Value
EAdi peak, μV	4.3 [2.1-12]	7.3 [4.2-8.5]	9.3 [4.3-13.1]	.259
EAdi swing, μV	3.3 [1.2-8]	3.8 [2.7-5.4]	6.1 [2.9-9.3]	.327
P_{peak}, cm H_2O	13.3 [9.3-14]	12 [10.6-17.1]	15.3 [11.6-18.8]	.182
ΔP_{es}, cm H_2O	4.3 [3.7-6.1]	5 [4.2-5.3]	5.3 [4.3-6.5]	.267
ΔP_L, cm H_2O	17.2 [14.2-19.4]	20.1 [15.9-22.5]	21 [16.6-25.4]	.216
TF, %	15.4 [10-23.3]	23.6 [15.8-51.3]	34 [8.7-47.2]	.704

Data are summarized as median [25th-75th percentile] and analyzed with the Kruskal-Wallis test. Electromyographic and pressure data are based on the mean of breaths, captured during 1-minute recordings (free of artifacts), in each patient with no lung disease (n = 5; 216 breaths), RDS (n = 10; 509 breaths) or evolving BPD (n = 25; 1,143 breaths). Ultrasound diaphragmatic measurements were obtained in a subgroup of 23 patients (4 control participants, 6 with RDS and 13 with evolving BPDΔP_{es} = esophageal pressure swing; ΔP_L = dynamic transpulmonary pressure;). BPD = bronchopulmonary dysplasia; EAdi = electrical activity of the diaphragm; P_{peak} = peak pressure; RDS = respiratory distress syndrome; TF = thickening fraction.

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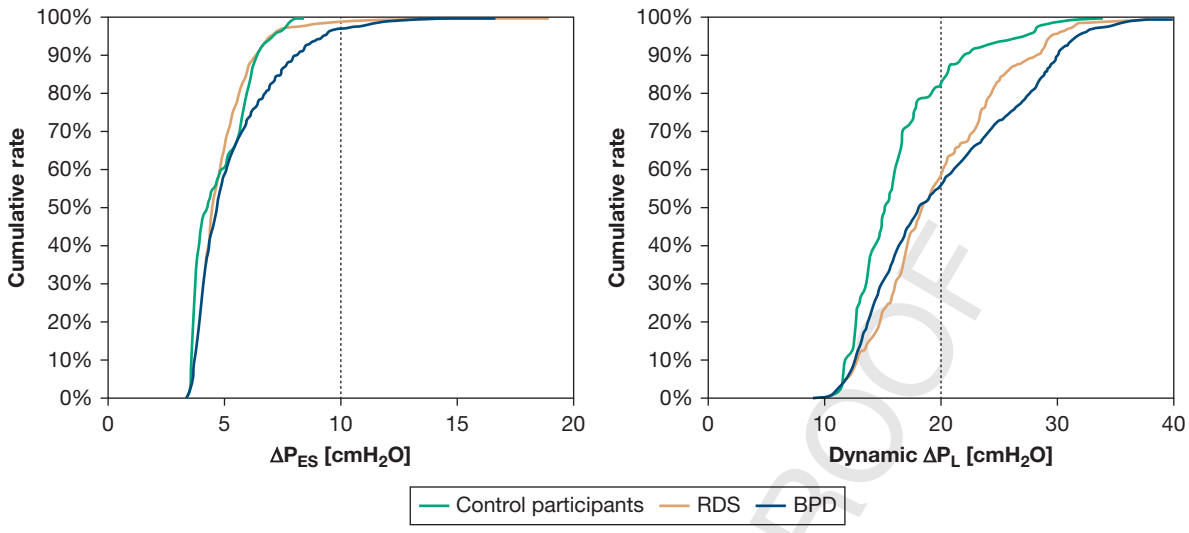

Figure 1 – *Cumulative frequency of breaths with high inspiratory effort and dynamic transpulmonary driving pressure. (A and B) Estimated esophageal pressure swing and dynamic transpulmonary driving pressure, respectively. Green, red, and blue curves represent data from control participants, and patients with RDS or evolving BPD, respectively.* ΔP_{es} *= esophageal pressure swing;* ΔP_L *= dynamic transpulmonary pressure; BPD = bronchopulmonary dysplasia; RDS = respiratory distress syndrome.*

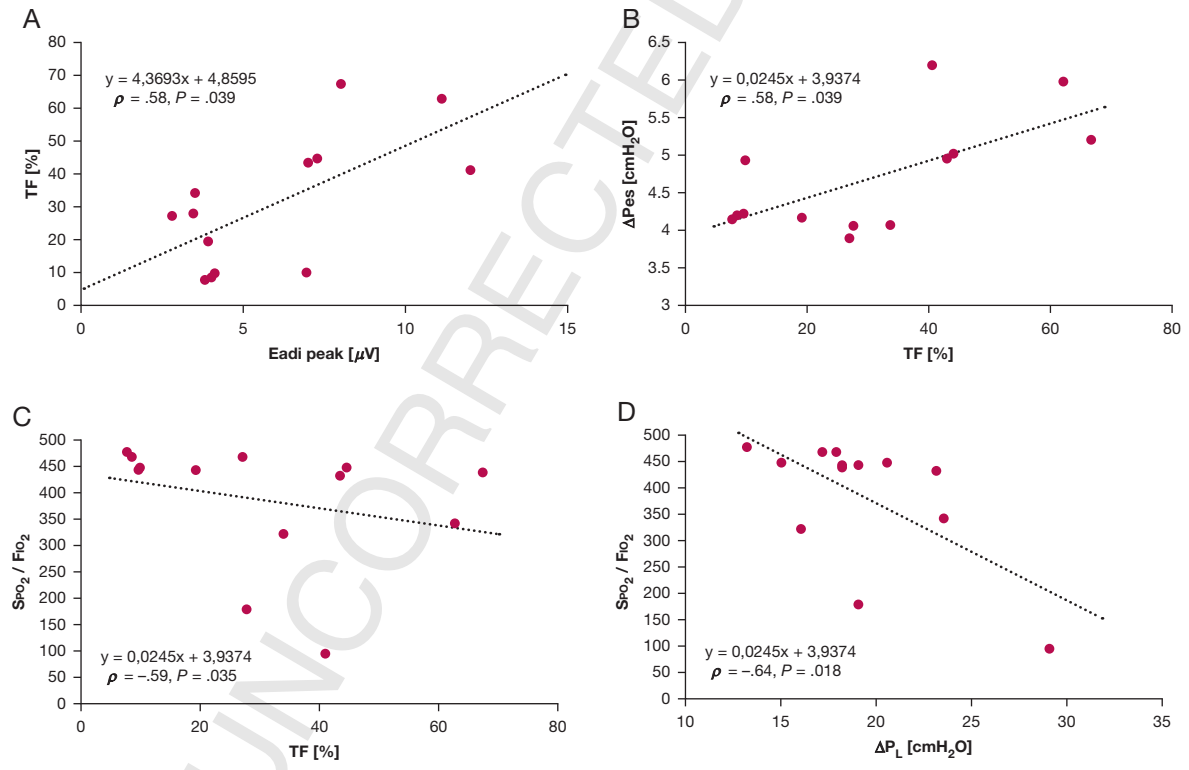

Figure 2 – *Correlations between diaphragmatic function, inspiratory effort, dynamic transpulmonary driving pressure, and oxygenation. Analyses performed on a subgroup of extremely preterm infants for whom data were available (n = 13, 9 with evolving BPD and 4 with RDS). Graphs show the correlation line, its equation, and the Spearman correlation coefficient. Coefficients of determination are shown and are calculated as* ρ^2*, representing the proportion of variance in the ranked data that is shared between the variables. (A) relationship between peak electrical activity of the diaphragm and its thickening fraction (*$\rho^2 = 0.34$*). (B) Relationship between the thickening fraction of the diaphragm and the esophageal pressure swing (*$\rho^2 = 0.34$*). (C) Relationship between the thickening fraction of the diaphragm and the* Spo_2/Fio_2 *ratio (*$\rho^2 = 0.35$*). (D) Relationship between dynamic transpulmonary driving pressure and the* Spo_2/Fio_2 *ratio (*$\rho^2 = 0.41$*). BPD = bronchopulmonary dysplasia; EAdi = electrical activity of the diaphragm;* ΔP_{es} *= esophageal pressure swing;* ΔP_L *= dynamic transpulmonary pressure; RDS = respiratory distress syndrome;* Spo_2/Fio_2 *= pre-ductal peripheral hemoglobin saturation/inspired oxygen fraction ratio; TF = thickening fraction of the diaphragm.*

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than in those with RDS or in healthy control infants; (4) breaths with high dynamic transpulmonary driving pressure occurred similarly in patients with BPD or RDS and more frequently than in control infants; (5) EAdi-based estimation of inspiratory effort is directly associated with the diaphragmatic TF; and, finally, (6) the estimated dynamic transpulmonary driving pressure is inversely associated with patient oxygenation.

These findings are consistent with current knowledge accumulated in adult critical care but also represent novel observations because this topic could not have been previously studied in extremely preterm infants. These data increase our understanding of respiratory pathophysiology in this particularly vulnerable population and might open the way toward more personalized respiratory support.

Despite a slight difference in median absolute values, ΔP_{es} and ΔP_L were generally similar between control infants and patients recovering from RDS or with evolving BPD. The similarity may be attributable to the relative mildness of respiratory failure in our patients: in fact, none of them required invasive ventilation. Consistently, in adults with acute hypoxemic respiratory failure, maintaining inspiratory effort and dynamic transpulmonary pressure within safe limits has been associated with the success of noninvasive support.[30] Conversely, excessive inspiratory effort may contribute to P-SILI, potentially worsening respiratory failure and increasing the likelihood of invasive ventilation.[4] The study is likely to be underpowered to assess outcomes on a per-participant basis rather than on a per-breath basis, and therefore, a more pronounced difference in ΔP_{es} and ΔP_L might be observed in sicker neonates with greater respiratory compromise requiring invasive ventilation. This might happen, for instance, in neonates in the acute phase of RDS or in those with more severe BPD who have not been enrolled in this study. In fact, a small physiologic study reported a lower static compliance of both lung and chest wall in a population of infants mainly diagnosed with established moderate-to-severe BPD.[27]

ΔP_{es} and ΔP_L have similar absolute values but are more variable in patients recovering from RDS or with evolving BPD than in healthy control infants, and this is consistent with earlier data showing that prematurity is associated with irregular and variable breathing patterns.[31-33] Because of the increased variability, breaths characterized by high effort and dynamic transpulmonary driving pressure occur more frequently in these patients. However, we do not know the thresholds of pressures or the exposure time to high effort that may be associated with harmful effects in extremely preterm infants. We analyzed the data using safety thresholds suggested in the adult critical care literature (ie, 10 and 20 cm H_2O for ΔP_{es} and ΔP_L, respectively),[34] but dedicated neonatal studies are urgently warranted to address these questions. In fact, clarifying safety thresholds for ΔP_{es} or ΔP_L would help in understanding whether noninvasive support is optimized or whether spontaneous breathing is, at least in some cases and for a certain period, more detrimental than controlled ventilation.

In a population subgroup, the EAdi-based estimations of inspiratory effort and dynamic transpulmonary driving pressure show interesting correlations. In fact, ΔP_{es} and EAdi directly correlate with the diaphragmatic TF, and this supports the reliability of the pressure estimations derived by EAdi. Furthermore, ΔP_L inversely correlates with oxygenation: because dynamic transpulmonary driving pressure estimates the ratio of tidal volume to compliance, higher ΔP_L values may reflect lower compliance and lung aeration.[35] However, these correlations are not very strong and were only produced in a subgroup of patients. Thus, despite being statistically significant, we cannot infer their clinical significance directly, and they should be considered "hypothesis generating" findings. Nonetheless, the correlation coefficients are classified as moderate/strong,[29] and they are consistent with findings reported in adult critical care.[35,36] They would need to be confirmed in larger, dedicated studies, which are more difficult to conduct with extremely preterm patients than with adults, given their rarity and vulnerability.

We acknowledge some study limitations. Ours was the first study on the topic to our knowledge, and although we enrolled a larger population than previous studies on similar patients,[26,27] it might be relatively underpowered. This could partially explain the similar ΔP_{es} and ΔP_L values observed in different study groups. Also, our study investigated a population receiving optimal perinatal care and noninvasive respiratory support, which are not always available in every center, and therefore results cannot always be generalized. Ours was a pragmatic study; thus, we lack the assessment of gas exchange metrics, lung mechanics, aeration, and biomarkers. These important aspects require different designs with dedicated interventions beyond routine care that will be applied in our future studies. Moreover, reliable markers for P-SILI are unavailable, making it

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challenging to assess its actual development. Nonetheless, we considered it important to have a first description of mechanisms not previously studied in extremely preterm infants, because this would be useful in the design of future research. None of the enrolled infants had failed noninvasive respiratory support; thus, to investigate the inspiratory effort and the dynamic transpulmonary driving pressure in intubated infants, a dedicated study is needed. This study should have strict enrollment criteria because the need for intubation also may depend on factors unrelated to respiratory failure itself.[37,38] We lack patient longitudinal evaluation and follow-up: this is important to understand whether the inspiratory effort and the dynamic transpulmonary driving pressure change during the clinical evolution and are eventually associated with long-term respiratory function, which is considered more relevant than BPD itself.[1] We estimated ΔP_{es} and ΔP_L but did not measure the actual esophageal pressure, because its measurement is unfeasible in extremely preterm infants. Our method has, however, been validated in neonates and small infants,[25] and it is supported by the diaphragmatic ultrasound findings. It has allowed us to study, for the first time, a homogeneous population of very vulnerable, extremely preterm infants, treated with consistent and optimized respiratory care.

Interpretation

Inspiratory effort and dynamic transpulmonary driving pressure in noninvasively supported extremely preterm infants recovering from RDS or with evolving BPD are similar to, but significantly more variable, than those of control neonates. Patients with evolving BPD show more breaths with high effort than RDS patients or controls. Breaths with high dynamic transpulmonary driving pressure occurred similarly in patients with BPD or RDS and more frequently than in controls. Dynamic transpulmonary driving pressure is inversely associated with oxygenation. Therefore, dedicated studies are urgently needed to determine whether these respiratory pattern features are associated with injurious inflation and contribute to P-SILI in extremely preterm infants.

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Q8 Q9

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Q10

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