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(Article begins on next page)

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)/ F_{iO_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/F_{iO_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

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 infants, 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

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

(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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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.

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.

221 Patients

222 Extremely preterm infants with gestational age $\leq 28^{+6}$ 277
 223 weeks were eligible if they were recovering from respira- 278
 224 tory distress syndrome (RDS) or affected by evolving 279
 225 BPD and supported with noninvasive NAVA. Neonates 280
 226 were considered to be recovering from RDS if they (1) 281
 227 successfully and promptly responded to surfactant 282
 228 replacement, and (2) had a postnatal age < 7 days at 283
 229 enrollment: this period was chosen because it corre- 284
 230 sponds to the time needed for the production of endo- 285
 231 genous surfactant and for a full recovery from RDS.¹² RDS 286
 232 was diagnosed according to the Montreux consensus 287
 233 criteria (ie, respiratory distress signs appearing within 288
 234 the first day of life, with characteristic ultrasound find- 289
 235 ings,¹³ and response to surfactant replacement).¹⁴ 290
 236 Evolving BPD was diagnosed in extremely preterm in- 291
 237 fants if they (1) needed oxygen supplementation for 292
 238 ongoing hypoxemic respiratory failure at enrollment; 293
 239 (2) showed reduced lung aeration by ultrasound at 294
 240 enrollment; (3) needed invasive ventilation for at least 295
 241 7 days in the first 2 weeks of life; (4) had a postnatal 296
 242 age ≥ 14 days at enrollment. Similar criteria have been 297
 243 used to study the pathophysiology of evolutive BPD¹⁵ 298
 244 and predict the diagnosis of established BPD.¹⁶ Patients 299
 245 were sampled once (ie, those recruited in the RDS group 300
 246 were not recruited again if they were developing BPD 301
 247 later). Neonates were not recruited if, besides recovering 302
 248 RDS or evolving BPD, another respiratory disorder (such 303
 249 as transient tachypnea, pneumonia, or neonatal ARDS) 304
 250 was present at the enrollment. 305

251 Additionally, a group of term neonates with no lung 306
 252 disease was considered as a control group if they ful- 307
 253 filled all the following criteria: (1) admitted to the 308
 254 NICU for nonrespiratory reasons (ie, no evidence of 309
 255 any neonatal respiratory disorder) and supported with 310
 256 post-extubation noninvasive NAVA after invasive 311
 257 ventilation for whole-body hypothermia or general 312
 258 anesthesia; (2) no need for supplemental oxygen to 313
 259 achieve pre-ductal peripheral hemoglobin saturation 314
 260 (SpO_2) $\geq 90\%$; (3) normal chest auscultation and lung 315
 261 ultrasound. For all groups of neonates, the exclusion 316
 262 criteria were: (a) complex malformations or chromo- 317
 263 somal abnormalities; (b) congenital lung anomalies; 318
 264 (c) pneumothorax, pneumomediastinum, or pleural 319
 265 effusion; (d) need for thoracic surgery; (d) severe hemo- 320
 266 dynamic instability (defined as any need for inotropes). 321

272 Procedures

273 Noninvasive NAVA was provided using Servo-family 322
 274 ventilators (Getinge, Solna, Sweden), with esophageal 323

274 catheters (6 Fr, 49 cm) used according to the manufac- 275
 276 turer's recommendations. Catheter position was verified 276
 277 from the electrical activity of the diaphragm (EAdi) 278
 279 signal on the ventilator screen, as previously reported.¹⁷ 280
 281 Adequately sized nasal masks (Flexytrunk, Fisher & 281
 282 Paykel Healthcare, Auckland, New Zealand) were cho- 282
 283 sen as the interface and used according to the manufac- 283
 284 turer's recommendations. Leaks were reduced by 284
 285 patient positioning and chinstraps (Fisher & Paykel 285
 286 Healthcare, Auckland, New Zealand).¹⁸ Our routine 286
 287 clinical protocol for the management of NAVA was as 287
 288 follows: positive end-expiratory pressure and NAVA 288
 289 level were set between 5 and 8 cm H₂O or 0.5 and 289
 290 3 cm H₂O/ μV , respectively; positive end-expiratory 290
 291 pressure was titrated to achieve an SpO_2 between 291
 292 90% and 95% with the lowest FiO_2 possible. NAVA level 292
 293 was set to obtain adequate CO₂ clearance, minimize the 293
 294 work of breathing, and increase patient comfort; NAVA 294
 295 level was never increased beyond the NAVA break- 295
 296 point, which was serially evaluated by looking at EAdi 296
 297 and peak pressure tracings.¹⁹ Crossing the NAVA 297
 298 breakpoint threshold may reduce EAdi, resulting in pa- 298
 299 tient over-assistance and decreased spontaneous breath- 299
 300 ing effort; thus, by keeping the NAVA level below the 300
 301 breakpoint, we were able to create a more consistent 301
 302 and controlled situation. Patients were fully monitored 302
 303 according to our routine NICU protocols, which 303
 304 include vital parameters, as well as EDIN (Échelle de 304
 305 Douleur et d'Inconfort du Nouveau-né) and COM- 305
 306 FORT scores.^{20,21} Only nonpharmacological sedation 306
 307 (ie, pacifiers and dextrose solution) was used. Arterial- 307
 308 ized capillary blood gas analyses and transcutaneous 308
 309 blood gas monitoring were performed as needed per 309
 310 our routine care policy. Point-of-care lung and dia- 310
 311 phragmatic ultrasound was performed whenever clini- 311
 312 cally indicated, as previously published.^{22,23} Patients 312
 313 with evolving BPD were re-intubated if they had respi- 313
 314 ratory acidosis ($\text{pH} < 7.20$ with $\text{PaCO}_2 > 65$ mm Hg) or 314
 315 severe hypoxia ($\text{FiO}_2 \geq 0.6$ to reach SpO_2 between 315
 316 90% and 95%) despite maximal noninvasive NAVA 316
 317 support and 6-hour prone positioning.²⁴ No procedure 317
 318 was performed solely for study purposes. 318
 319 320 321

322 Data Collection and Calculations

323 The minimum and maximum EAdi as well as its wave- 323
 324 form were recorded from the ventilator, when patients 324
 325 were peacefully asleep and analyzed in a breath-by- 325
 326 breath manner over 1 minute free of artifacts. For the 326
 327 same period, the maximal inspiratory pressure (P_{peak}) 327
 328 delivered by the ventilator was recorded for each breath. 328
 329 Timings of the beginning and end of cycles were 329
 330 331

331 identified, and a breath-by-breath visual inspection was
 332 performed with cursor adjustment if needed. For each
 333 breath, the maximal esophageal pressure swing (ΔP_{es})
 334 was estimated by the EAdi peak using the equation pre-
 335 viously reported by Essouri et al²⁵:
 336

$$337 \Delta P_{es} \text{ (cm H}_2\text{O)} = 0.25 \times \text{EAdi } (\mu\text{V}) + 3.2$$

338 This equation had an $R^2 > 0.9$ in neonates and small in-
 339 fants supported with noninvasive NAVA who were
 340 studied with a special catheter comprising both EAdi
 341 electrodes and a balloon.²⁵ The end-inspiration dy-
 342 namic transpulmonary driving pressure (ΔP_L) was
 343 then estimated, for each breath, by adding the delivered
 344 P_{peak} to the ΔP_{es} . If point-of-care ultrasound was per-
 345 formed within 1 hour from data recording, as a part
 346 of the clinical routine, the diaphragmatic thickening
 347 fraction (TF) was calculated,²³ and the $\text{SpO}_2/\text{FiO}_2$ ratio
 348 was simultaneously recorded. Demographics and clin-
 349 ical data were recorded in real time from electronic pa-
 350 tient files and the monitoring system.
 351
 352

353 Statistics

354 No previous study has investigated inspiratory effort
 355 and transpulmonary driving pressure in extremely pre-
 356 term infants, so a formal sample size calculation was
 357 unfeasible; this should be considered a pilot study. A
 358 convenience sample size was established to provide an
 359 indication of the magnitude of the effect size related
 360
 361

362 Results

363 Demographics and clinical characteristics of infants
 364 with RDS or evolving BPD are displayed in [Table 1](#). The
 365 additional control group consisted of 5 term neonates
 366 (gestational age, 38.4 [SD: 1.1] weeks, birth weight =
 367 2,564 [SD, 692] g, postnatal age = 3 [1.5-3.5] days).
 368 Mean NAVA level was similar in infants recovering
 369 from RDS (2.5 [1.9-2.5] cm H₂O/ μ V), with evolving
 370 BPD (2 [1.3-2.2] cm H₂O/ μ V) and in control infants
 371 (1.8 [1.6-2] cm H₂O/ μ V; $P = .211$), respectively. All
 372 enrolled patients survived and were successfully
 373 discharged from the NICU. Infants in the evolving BPD
 374 group were eventually diagnosed with mild BPD (ie, no
 375 cases of moderate-to-severe BPD were enrolled). No
 376 technical issues regarding data availability were
 377 observed, and data from all patients were suitable for
 378 the analysis.
 379
 380

381 [Table 2](#) shows the main outcome results: EAdi, P_{peak} ,
 382 ΔP_{es} , ΔP_L , and TF were not statistically different
 383 between the control group infants, patients with RDS,
 384
 385

386 to BPD. Thus, 25 infants with evolving BPD and 10
 387 with RDS were enrolled. This population is similar to
 388 or larger than those analyzed in previous studies on
 389 lung mechanics in extremely preterm infants.^{26,27}
 390

391 The normality of the distribution was tested using the
 392 Shapiro-Wilk test, and the data were treated accord-
 393 ingly. EAdi, ΔP_{es} , ΔP_L , and TF were considered as out-
 394 comes, summarized as medians (25th-75th percentiles)
 395 and compared with the Kruskal-Wallis test. EAdi, P_{peak} ,
 396 ΔP_{es} , and ΔP_L were averaged from breaths captured in
 397 1-minute recordings for each patient. The coefficient of
 398 variance (CV, expressed in %) was calculated as the ra-
 399 tio of SD to mean for ΔP_{es} and ΔP_L to describe their
 400 heterogeneity, and compared with one-way analysis of
 401 variance followed by the Dunnett post hoc test.²⁸
 402 Dichotomous data were compared with χ^2 or the Fisher
 403 test, as appropriate. Correlation analyses were per-
 404 formed between the main outcomes and the $\text{SpO}_2/\text{FiO}_2$
 405 ratio, using the Spearman (ρ) coefficient and inter-
 406 preted according to the *BMJ's* Statistics classification.²⁹
 407 Spearman correlation was chosen given the small sam-
 408 ple size for this subgroup analysis. Results were subse-
 409 quently adjusted for gestational age into multivariate
 410 linear regressions whose results were expressed as β -co-
 411 efficients (95%CI). Analyses were performed with SPSS
 412 30 (IBM), and $P < .05$ was considered statistically
 413 significant.
 414
 415

416 and patients with evolving BPD, although patients with
 417 BPD showed slightly higher median values. Interpatient
 418 variability of ΔP_{es} was higher in RDS (CV = 24 [9%])
 419 and BPD (CV = 28 [8.5%]) patients than in control
 420 infants (CV = 10 [5.8%]; overall $P < .001$; Dunnett post
 421 hoc test: RDS vs controls, $P = .008$, BPD vs controls;
 422 $P < .001$). Similarly, ΔP_L variability was higher in RDS
 423 (CV = 24.6 [6.5%]) and BPD (CV = 27.3 [8.9%])
 424 patients than in control infants (CV = 17.3 [7%];
 425 overall $P = .05$; Dunnett post hoc test: BPD vs controls
 426 $P = .029$). Raw data visually illustrating the variability
 427 are shown in [e-Figure 1](#).
 428
 429

430 Breaths showing ΔP_{es} values > 10 cm H₂O occurred
 431 more frequently in BPD (33 [2.9%] of 1,143 breaths)
 432 than in RDS patients (6 [1.2%] of 509 breaths; $P =$
 433 .035); both patient groups had more of these breaths
 434 than controls who never had ΔP_{es} values > 10 cm H₂O
 435 ($P = .006$; [Fig 1](#) and [e-Fig 1](#)). $\Delta P_L > 20$ cm H₂O was
 436 observed in 212 (41.6%) of 509 breaths, in 505 (44.2%)
 437 of 1,143 breaths, and in 38 (17.6%) of 216 breaths in
 438
 439
 440

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 ₂ O	6 [6-7]	6 [6-6.5]	7 [6-7]
FiO ₂ at enrollment	0.21 [0.21-0.28]	0.21 [0.21-0.28]	0.25 [0.21-0.43]
SpO ₂ /FiO 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 O₂ 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; SpO₂/FiO₂ ratio = preductal peripheral hemoglobin oxygen saturation to FiO₂ 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 SpO₂/FiO₂ (Fig 2C), and between ΔP_L and SpO₂/FiO₂ (Fig 2D). On adjustment for gestational age, all correlations, except that between TF and SpO₂/FiO₂ ($P = .373$), 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 SpO₂/FiO₂ ($\beta = -0.02$ [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 ₂ O	13.3 [9.3-14]	12 [10.6-17.1]	15.3 [11.6-18.8]	.182
ΔP_{es} , cm H ₂ O	4.3 [3.7-6.1]	5 [4.2-5.3]	5.3 [4.3-6.5]	.267
ΔP_L , cm H ₂ O	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 BPD). ΔP_{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.

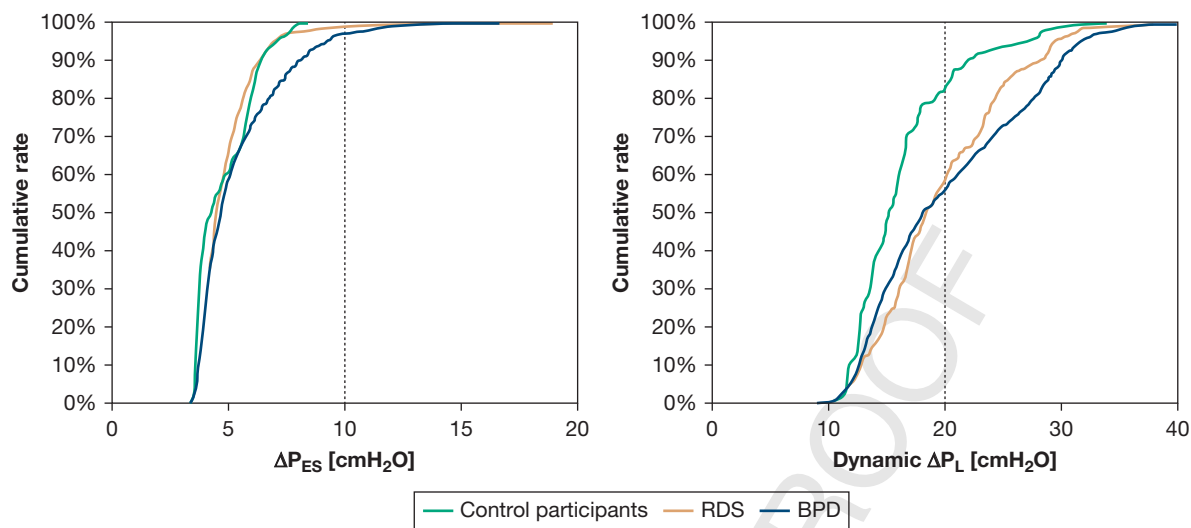


Figure 1 – Cumulative frequency of breaths with high inspiratory effort and dynamic transpulmonary driving pressure. (A and B) Estimated esophageal pressure swing and dynamic transpulmonary driving pressure, respectively. Green, red, and blue curves represent data from control participants, and patients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

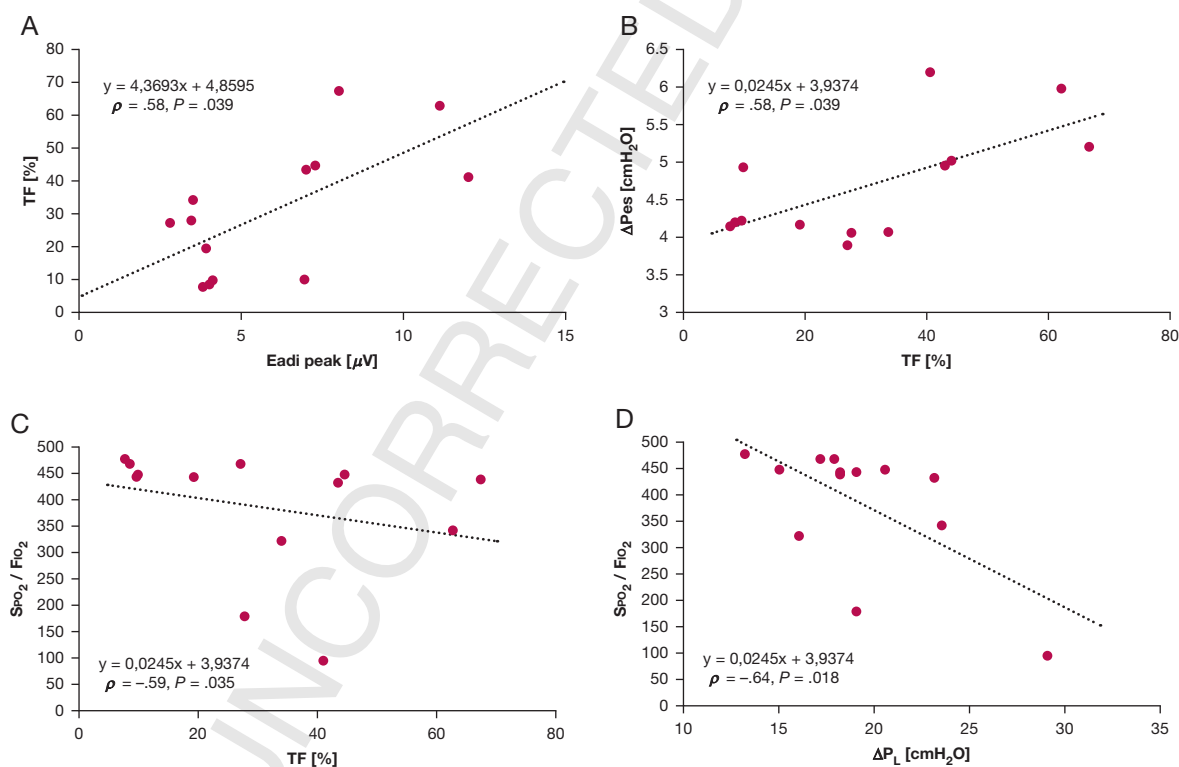


Figure 2 – Correlations between diaphragmatic function, inspiratory effort, dynamic transpulmonary driving pressure, and oxygenation. Analyses performed on a subgroup of extremely preterm infants for whom data were available ($n = 13$, 9 with evolving BPD and 4 with RDS). Graphs show the correlation 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.

661 than in those with RDS or in healthy control infants; (4)
 662 breaths with high dynamic transpulmonary driving
 663 pressure occurred similarly in patients with BPD or
 664 RDS and more frequently than in control infants; (5)
 665 EAdi-based estimation of inspiratory effort is directly
 666 associated with the diaphragmatic TF; and, finally, (6)
 667 the estimated dynamic transpulmonary driving pressure
 668 is inversely associated with patient oxygenation.
 669

670 These findings are consistent with current knowledge
 671 accumulated in adult critical care but also represent
 672 novel observations because this topic could not have
 673 been previously studied in extremely preterm infants.
 674 These data increase our understanding of respiratory
 675 pathophysiology in this particularly vulnerable
 676 population and might open the way toward more
 677 personalized respiratory support.
 678

679 Despite a slight difference in median absolute values,
 680 ΔP_{es} and ΔP_L were generally similar between control
 681 infants and patients recovering from RDS or with
 682 evolving BPD. The similarity may be attributable to the
 683 relative mildness of respiratory failure in our patients:
 684 in fact, none of them required invasive ventilation.
 685 Consistently, in adults with acute hypoxemic
 686 respiratory failure, maintaining inspiratory effort and
 687 dynamic transpulmonary pressure within safe limits has
 688 been associated with the success of noninvasive
 689 support.³⁰ Conversely, excessive inspiratory effort may
 690 contribute to P-SILI, potentially worsening respiratory
 691 failure and increasing the likelihood of invasive
 692 ventilation.⁴ The study is likely to be underpowered to
 693 assess outcomes on a per-participant basis rather than
 694 on a per-breath basis, and therefore, a more
 695 pronounced difference in ΔP_{es} and ΔP_L might be
 696 observed in sicker neonates with greater respiratory
 697 compromise requiring invasive ventilation. This might
 698 happen, for instance, in neonates in the acute phase of
 699 RDS or in those with more severe BPD who have not
 700 been enrolled in this study. In fact, a small physiologic
 701 study reported a lower static compliance of both lung
 702 and chest wall in a population of infants mainly
 703 diagnosed with established moderate-to-severe BPD.²⁷
 704

705 ΔP_{es} and ΔP_L have similar absolute values but are more
 706 variable in patients recovering from RDS or with
 707 evolving BPD than in healthy control infants, and this is
 708 consistent with earlier data showing that prematurity is
 709 associated with irregular and variable breathing
 710 patterns.³¹⁻³³ Because of the increased variability,
 711 breaths characterized by high effort and dynamic
 712 transpulmonary driving pressure occur more frequently
 713
 714
 715

716 in these patients. However, we do not know the
 717 thresholds of pressures or the exposure time to high
 718 effort that may be associated with harmful effects in
 719 extremely preterm infants. We analyzed the data using
 720 safety thresholds suggested in the adult critical care
 721 literature (ie, 10 and 20 cm H₂O for ΔP_{es} and ΔP_L ,
 722 respectively),³⁴ but dedicated neonatal studies are
 723 urgently warranted to address these questions. In fact,
 724 clarifying safety thresholds for ΔP_{es} or ΔP_L would help
 725 in understanding whether noninvasive support is
 726 optimized or whether spontaneous breathing is, at least
 727 in some cases and for a certain period, more detrimental
 728 than controlled ventilation.
 729

730 In a population subgroup, the EAdi-based estimations
 731 of inspiratory effort and dynamic transpulmonary
 732 driving pressure show interesting correlations. In fact,
 733 ΔP_{es} and EAdi directly correlate with the diaphragmatic
 734 TF, and this supports the reliability of the pressure
 735 estimations derived by EAdi. Furthermore, ΔP_L
 736 inversely correlates with oxygenation: because dynamic
 737 transpulmonary driving pressure estimates the ratio of
 738 tidal volume to compliance, higher ΔP_L values may
 739 reflect lower compliance and lung aeration.³⁵ However,
 740 these correlations are not very strong and were only
 741 produced in a subgroup of patients. Thus, despite being
 742 statistically significant, we cannot infer their clinical
 743 significance directly, and they should be considered
 744 “hypothesis generating” findings. Nonetheless, the
 745 correlation coefficients are classified as moderate/
 746 strong,²⁹ and they are consistent with findings reported
 747 in adult critical care.^{35,36} They would need to be
 748 confirmed in larger, dedicated studies, which are more
 749 difficult to conduct with extremely preterm patients
 750 than with adults, given their rarity and vulnerability.
 751
 752
 753

754 We acknowledge some study limitations. Ours was the
 755 first study on the topic to our knowledge, and although
 756 we enrolled a larger population than previous studies on
 757 similar patients,^{26,27} it might be relatively
 758 underpowered. This could partially explain the similar
 759 ΔP_{es} and ΔP_L values observed in different study groups.
 760 Also, our study investigated a population receiving
 761 optimal perinatal care and noninvasive respiratory
 762 support, which are not always available in every center,
 763 and therefore results cannot always be generalized. Ours
 764 was a pragmatic study; thus, we lack the assessment of
 765 gas exchange metrics, lung mechanics, aeration, and
 766 biomarkers. These important aspects require different
 767 designs with dedicated interventions beyond routine
 768 care that will be applied in our future studies. Moreover,
 769 reliable markers for P-SILI are unavailable, making it
 770

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

800 Interpretation

801 Inspiratory effort and dynamic transpulmonary driving
 802 pressure in noninvasively supported extremely preterm
 803 infants recovering from RDS or with evolving BPD are
 804

826 similar to, but significantly more variable, than those of
 827 control neonates. Patients with evolving BPD show
 828 more breaths with high effort than RDS patients or
 829 controls. Breaths with high dynamic transpulmonary
 830 driving pressure occurred similarly in patients with
 831 BPD or RDS and more frequently than in controls.
 832 Dynamic transpulmonary driving pressure is inversely
 833 associated with oxygenation. Therefore, dedicated
 834 studies are urgently needed to determine whether these
 835 respiratory pattern features are associated with
 836 injurious inflation and contribute to P-SILI in extremely
 837 preterm infants.
 838
 839

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