self-identified Black individuals puts them at a higher risk of developing cardiometabolic disease and, subsequently, heart failure with preserved ejection fraction. Therefore, iNO therapy in self-identified Black patients with respiratory failure may overcome these underlying deficiencies in NO production and degradation, which may improve oxygenation and clinical outcomes.

This *post hoc* analysis is limited by the use of self-identified race as a proxy for genetic ancestry and its sample size, which was not powered to assess the racial differences in treatment response. However, it has been shown previously that the proportion of African ancestry is ~90% in self-identified Black individuals from Birmingham, Alabama (a major recruitment center for Black patients in the trial) (10). The regions of practical equivalence were not depicted, as they were defined *a priori*.

To summarize, iNO therapy appeared to have a positive impact on systemic oxygenation and a potential reduction in the risk of mortality in self-identified Black individuals compared with self-identified White individuals. The suppressed NO system in self-identified Black individuals may be an effective therapeutic target in a range of clinical conditions, including ARDS. This *post hoc* analysis highlights that the effects of an intervention may vary by self-reported race and the need to represent self-identified Black individuals in prospective clinical trials to test these intriguing hypotheses. For validation of these findings, larger and well-powered prospective clinical trials are needed to assess the efficacy of therapies aimed at modulating the NO system to improve clinical outcomes among self-identified Black individuals with ARDS. ■

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

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## Respiratory System Compliance Accurately Assesses the "Baby Lung" in Pediatric Acute Respiratory Distress Syndrome

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*To the Editor*:

The concept of the "baby lung" has gained widespread recognition in acute respiratory distress syndrome (ARDS) and has significantly influenced the principles of protective mechanical ventilation (MV) (1). This concept is rooted in tomographic studies performed in adult patients with ARDS, which revealed the presence of a smaller, normally aerated lung compartment at the end of expiration and normal specific lung elastance. There is a strong correlation between end-expiratory lung volume (EELV) and respiratory system



The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions: P. Cruces conceived the study. P. Cruces and F.D. designed the study and participated in all stages of the research. P. Cruces and F.D. curated and analyzed the data. P. Caviedes, S.R., P. Cruces, and F.D. participated in data collection. P. Cruces wrote the initial draft. P. Caviedes, S.R., P. Cruces, and F.D. were involved in article preparation and provided critical feedback to the analysis and discussion. P. Caviedes, S.R., P. Cruces, and F.D. contributed to the final manuscript and approved the final version. P. Caviedes, S.R., P. Cruces, and F.D. have made substantial contributions to the research, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Table 1.** Clinical Characteristics of Patients with Pediatric Acute Respiratory Distress Syndrome Included in the Study

| Patient | Age (mo) | IBW (kg) | Etiology | Comorbidities | $C_{RS}$ (ml/cm $H_2O$) | EELV (ml/kg) |
|---|---|---|---|---|---|---|
| 1 | 8 | 8.1 | PIV3 | No | 4.9 | 33.2 |
| 2 | 1 | 5.3 | Bacterial pneumonia | No | 1.9 | 9.6 |
| 3 | 4 | 5.6 | RSV, PIV3 | Down syndrome | 3.7 | 18.2 |
| 4 | 1 | 4.1 | RSV, RV | No | 2.3 | 14.1 |
| 5 | 1 | 3.3 | RSV, HBoV | PNB 32 wk | 1.1 | 15.5 |
| 6 | 3 | 6.4 | hMPV | No | 2.8 | 12.4 |
| 7 | 3 | 6.2 | RSV, RV | No | 2.6 | 18.4 |
| 8 | 2 | 5.4 | RSV | No | 4.3 | 24.7 |
| 9 | 8 | 7.4 | Bacterial pneumonia | No | 4.6 | 14.1 |
| 10 | 1 | 3.2 | hMPV | PNB 31 wk | 2.0 | 11.8 |
| 11 | 1 | 3.6 | RSV | No | 0.9 | 27.6 |
| 12 | 9 | 8.6 | RSV, RV | No | 5.9 | 20.8 |
| 13 | 1 | 3.3 | RSV | PNB 33 wk | 1.1 | 10.0 |
| 14 | 11 | 7.5 | *Mycoplasma pneumoniae* | Down syndrome | 3.2 | 17.3 |
| 15 | 15 | 9.3 | Bacterial pneumonia | No | 7.2 | 19.9 |
| 16 | 1 | 4.3 | RSV, HBoV | No | 3.2 | 12.9 |
| 17 | 15 | 10.6 | Bacterial pneumonia | No | 5.7 | 14.6 |
| 18 | 2 | 4.3 | RSV | No | 2.4 | 33.5 |
| 19 | 2 | 6 | RSV, RV | No | 2.8 | 20.6 |
| 20 | 22 | 12.1 | Bacterial pneumonia | CHD | 7.0 | 13.1 |
| 21 | 14 | 9.3 | Bacterial pneumonia | No | 6.0 | 18.2 |
| 22 | 3 | 7.7 | RSV, EV | No | 3.1 | 12.1 |
| 23 | 12 | 10.4 | Bacterial pneumonia | No | 7.8 | 16.3 |
| 24 | 7 | 7.5 | RSV, EV | No | 2.9 | 6.4 |
| 25 | 22 | 12.7 | RSV, RV | No | 10.7 | 24.7 |
| 26 | 36 | 16.2 | Bacterial pneumonia | No | 15.4 | 23.2 |
| 27 | 24 | 15.5 | Bacterial pneumonia | No | 12.9 | 11.2 |
| 28 | 1 | 6.1 | Severe pertussis | No | 4.1 | 38.7 |
| 29 | 14 | 9.3 | PI3, RV | CHD | 7.2 | 24.9 |
| 30 | 22 | 10.9 | Bacterial pneumonia | No | 5.7 | 14.1 |
| 31 | 12 | 9.3 | RSV, RV, Flu A | No | 5.7 | 18.0 |

*Definition of abbreviations*: CHD = congenital heart disease; $C_{RS}$ = respiratory system compliance; EELV = end-expiratory lung volume; EV = enterovirus; Flu A = influenza A virus; HBoV = human bocavirus; hMPV = human metapneumovirus; IBW = ideal body weight; PARDS = pediatric acute respiratory distress syndrome; PIV3 = parainfluenza virus type 3; PNB = preterm newborn; RSV = respiratory syncytial virus; RV = rhinovirus.

compliance ($C_{RS}$) (2). Thus, monitoring the $C_{RS}$ provides a practical means of estimating the EELV at the bedside, but this hypothesis has not been tested in pediatric acute respiratory distress syndrome (PARDS). We sought to study the relationship between $C_{RS}$ and EELV through the modified nitrogen wash-in/washout method ($EELV_{N2}$) in PARDS.

## Methods

Ethical approval was obtained from the Servicio de Salud Metropolitano Central Ethics Committee in Santiago, Chile (ID 16/2022), with the need for informed consent waived. The study was conducted at Hospital El Carmen de Maipú, Chile, between May 1, 2022, and December 31, 2022. The inclusion criteria were as follows: *1*) children aged younger than 15 years, *2*) diagnosis of pulmonary PARDS (3), *3*) use of MV and neuromuscular blockade, and *4*) first 24 hours after the onset of PARDS. We excluded patients with endotracheal tube air leak >10% of $V_T$, uncorrected congenital heart disease, and treatment with bronchodilators. All patients were being treated in volume-controlled ventilation mode. We obtained the following MV parameters: peak inspiratory pressure, plateau pressure, extrinsic and intrinsic positive end-expiratory pressure (PEEP), driving pressure (ΔP), and expiratory $V_T$.

***Respiratory mechanics and $EELV_{N2}$ measurements.*** The following protocol was used:

1. $V_T$ was recorded.
2. A 3-second inspiratory hold and a 3-second expiratory hold were performed, and then we calculated ΔP (cm $H_2O$) and $C_{RS}$ ($ml \cdot cm\ H_2O^{-1}$).
3. EELV measurements were obtained by a ventilator-incorporated modified nitrogen wash-in/washout method ($EELV_{N2}$; Engström Carestation, GE Healthcare), calibrated according to the manufacturer's recommendations. $EELV_{N2}$ was calculated from at least two measurements of technically satisfactory trials (4).

Lung strain was calculated as $V_T/EELV_{N2}$. $V_T$ and $C_{RS}$ are also shown indexed by ideal body weight (IBW), as usually recommended in pediatrics (3). In addition, we reported $EELV_{N2}$ indexed by IBW for future comparisons.

***Statistics.*** We present data as median (interquartile range; according to Tukey's Hinges method). Normality was assessed by the Shapiro-Wilk test. We calculated the nonparametric Spearman's correlation (rho) between absolute values of $C_{RS}$, $EELV_{N2}$, and lung strain. Also, we added a correlation between $C_{RS}$ and $EELV_{N2}$

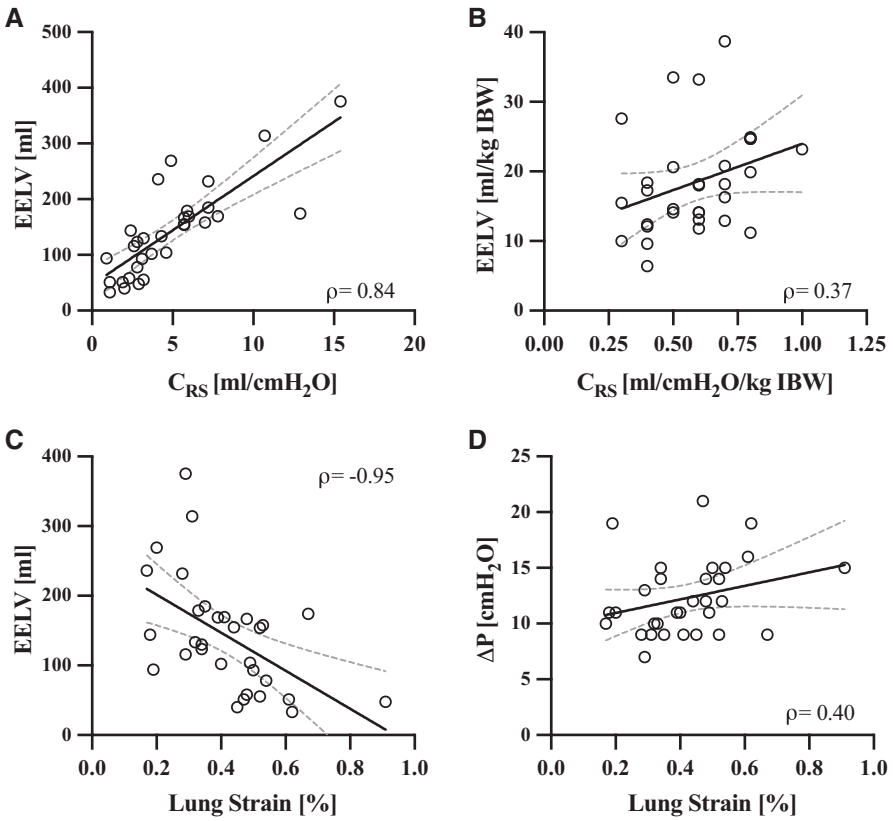


**Figure 1.** Spearman correlation plot between lung volumes and respiratory mechanics in patients with PARDS. (*A*) End-expiratory lung volume and respiratory system compliance. (*B*) End-expiratory lung volume and respiratory system compliance indexed by IBW. (*C*) End-expiratory lung volume and lung strain. (*D*) Driving pressure and lung strain. $C_{RS}$ = respiratory system compliance; EELV = end-expiratory lung volume; IBW = ideal body weight; PARDS = pediatric acute respiratory distress syndrome; ΔP = driving pressure.

indexed by IBW. We set the significance at $P < 0.05$. We used IBM SPSS Statistics version 28.1 and GraphPad Prism version 9.3.1 for the analyses.

## Results

We included 31 patients. Their median age was 7 (2–14) months, and their IBW was 7.5 (5.4–9.3) kg. The severity of PARDS was mild in 64.5% (20 of 31), moderate in 25.8% (8 of 31), and severe in 9.6% (3 of 31). Nineteen patients had severe viral infection, and 15 had respiratory syncytial virus (Table 1). Comorbidities were present in 7 of 31 patients, and 21 of 31 received vasoactive drugs. The $Pa_{O_2}/FI_{O_2}$ ratio was 192 (138–228) mm Hg, oxygenation index was 7 (6–9), and $Pa_{CO_2}$ was 49.1 (42.7–53.0) mm Hg.

$V_T$ was 6.7 (6.1–7.0) ml · $kg^{-1}$ IBW, peak inspiratory pressure was 25 (23–28) cm $H_2O$, plateau pressure was 18 (17–21) cm $H_2O$, total PEEP was 7 (6–7) cm $H_2O$, and ΔP was 11 (10–14) cm $H_2O$. $C_{RS}$ was 4.1 (2.7–6.0) ml · cm $H_2O^{-1}$, $EELV_{N2}$ was 134 (86–172) ml, and lung strain was 41.3% (31.2–51.0%). When indexed by IBW, $C_{RS}$ was 0.6 (0.4–0.7) ml · cm $H_2O^{-1}$ · $kg^{-1}$, and $EELV_{N2}$ was 17.3 (13.1–22.0) ml · $kg^{-1}$.

The correlations between $EELV_{N2}$ with $C_{RS}$ (rho = 0.84; $P < 0.001$) and lung strain (rho = −0.95; $P < 0.001$) were robust, whereas the correlation was moderate between ΔP and lung strain (rho = 0.40; $P = 0.031$). $EELV_{N2}$ indexed by IBW (ml · $kg^{-1}$) and $C_{RS}$ indexed by IBW (ml · cm $H_2O^{-1}$ · $kg^{-1}$) had a weak correlation (rho = 0.37; $P = 0.03$) (Figure 1).

## Discussion

The primary findings of this study in children with ARDS treated with a low-$V_T$ strategy were as follows: *1*) The correlation between $C_{RS}$ and $EELV_{N2}$ is robust, aligning with the epistemological basis of ARDS in adults; and *2*) ΔP is a satisfactory surrogate for lung strain, confirming the importance of this parameter when estimating the mechanical load of the lungs.

The relationship between tomographic EELV and $C_{RS}$ in ARDS has been investigated extensively, as documented in the literature (2). The evidence is certainly inadequate in pediatric patients. The correlation between EELV and $C_{RS}$ may seem counterintuitive in some patients with PARDS, owing to the current nuanced and evolving understanding of PARDS pathophysiology (5). Specifically, severe viral lower respiratory tract infections (also referred to as "critical bronchiolitis") are the most frequent PARDS etiology, and children frequently show signs of overdistention and ineffective ventilation by increased dead space (6). Reduced lung compliance in ARDS can arise from the classical etiology of aeration loss, typical in ARDS pathophysiology, and also because of overdistention (7). In the latter scenario, changes in $C_{RS}$ and EELV would theoretically establish an inverse relationship. However, in line with our previous work, we

reported that the elastic component is predominant in PARDS when mechanically ventilated with recommended lung-protective parameters (8, 9).

It is crucial to highlight that the ventilatory approach employed in our cohort likely minimized the risk of overdistention because of the use of recommended low $V_T$ and PEEP titration. Although escalating PEEP levels has the potential to enhance EELV through lung recruitment, it concurrently introduces the possibility of overdistention, particularly in alveoli that are already ventilated. This risk is exacerbated when measurements follow recruitment maneuvers or are influenced by tidal overdistention resulting from high $V_T$ in lungs with limited recruitment potential. Also, $C_{RS}$ measurement can be biased when PEEP is set below airway opening pressure (10). Our MV strategy, characterized by low $V_T$, PEEP adjustment based on $F_{I_{O_2}}$, the absence of recruitment maneuvers, and avoidance of fluid overload at the time of measurement, aligns with current recommendations in PARDS management (3, 7). Our findings are consistent with our earlier investigations, wherein we demonstrated that $\Delta P$ is a good surrogate for estimating the mechanical energy dissipated by the lung (11). With all these considerations, it is reasonable to extrapolate these results to the pediatric population within a lung-protective ventilation strategy framework. It is important to note that the correlation between EELV and $C_{RS}$ decreases when indexed by IBW. EELV is dependent on many factors, such as ethnicity, sex, age, height, and weight. In a heterogeneous cohort, the removal of one of the components (nonindependent) will make the correlation weaker. Thus, the mathematical coupling generated by indexing by IBW reduces the range of $C_{RS}$ values, attenuating the strength of the correlation.

Our study has some limitations. First, the number of patients with PARDS studied was small, mainly mild-to-moderate primary PARDS with a low-$V_T$ MV strategy. Thus, our findings may not be generalizable to severe or extrapulmonary PARDS or to those treated with a different MV strategy. Second, lung compliance was not measured, preventing the correlation of specific lung elastance with EELV. Nevertheless, it is noteworthy that when $C_{RS}$ and lung compliance were measured in a PARDS cohort, they were similar (5). This observation underscores the diminished influence of chest wall compliance in this context. Third, our study design focused on the early stage of PARDS to avoid the overuse of neuromuscular blockers in the following measurements. Fourth, the absence of respiratory muscle activity may have influenced our robust correlation. For example, patient respiratory efforts can increase lung volume and facilitate lung overdistention (12). In conclusion, the study's results indicate that the baby lung concept can be applied to children and that $\Delta P$ may be considered a lung-protective MV strategy parameter. ■

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