BET inhibition (5). Whether these observations may be attributed to direct effects on PA remodeling and/or myocardial performance remains to be determined. These effects did not translate into changes in 6MWD and NT-proBNP, a discrepancy previously observed in the context of multiple background therapies or preserved functional capacity at baseline. Finally, two subjects experienced minimal elevations of transaminases that resolved despite continued therapy.

In conclusion, this single-arm open-label study documents that the evaluation of apabetalone for the treatment of patients with PAH in future clinical studies is feasible. Further studies are needed to confirm the efficacy signal suggesting that apabetalone may be associated with beneficial effects when added to current therapies in PAH. ■

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References

1. Lajoie AC, Lauzière G, Lega JC, Lacasse Y, Martin S, Simard S, *et al.* Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis. *Lancet Respir Med* 2016;4:291–305.
2. Humbert M, Sitbon O, Yaici A, Montani D, O'Callaghan DS, Jais X, *et al.* Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010;36:549–555.
3. Meloche J, Potus F, Vaillancourt M, Bourgeois A, Johnson I, Deschamps L, *et al.* Bromodomain-containing protein 4: the epigenetic origin of pulmonary arterial hypertension. *Circ Res* 2015;117:525–535.
4. Van der Feen DE, Kurakula K, Tremblay E, Boucherat O, Bossers GPL, Szulcek R, *et al.* Multicenter preclinical validation of BET inhibition for the treatment of pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2019;200:910–920.
5. Yeh TC, O'Connor G, Petteruti P, Dulak A, Hattersley M, Barrett JC, *et al.* Identification of CCR2 and CD180 as robust pharmacodynamic tumor and blood biomarkers for clinical use with BRD4/BET inhibitors. *Clin Cancer Res* 2017;23:1025–1035.
6. Ray KK, Nicholls SJ, Buhr KA, Ginsberg HN, Johansson JO, Kalantar-Zadeh K, *et al.*; BETonMACE Investigators and Committees. Effect of apabetalone added to standard therapy on major adverse cardiovascular events in patients with recent acute coronary syndrome and type 2 diabetes: a randomized clinical trial. *JAMA* 2020;323:1565–1573.
7. Paulin R, Courboulin A, Meloche J, Mainguy V, Dumas de la Roque E, Saksouk N, *et al.* Signal transducers and activators of transcription-3/pim1 axis plays a critical role in the pathogenesis of human pulmonary arterial hypertension. *Circulation* 2011;123:1205–1215.
8. Bonnet S, Rochefort G, Sutendra G, Archer SL, Haromy A, Webster L, *et al.* The nuclear factor of activated T cells in pulmonary arterial hypertension can be therapeutically targeted. *Proc Natl Acad Sci U S A* 2007;104:11418–11423.
9. Bourgeois A, Lambert C, Habbout K, Ranchoux B, Paquet-Marceau S, Trinh I, *et al.* FOXM1 promotes pulmonary artery smooth muscle cell expansion in pulmonary arterial hypertension. *J Mol Med (Berl)* 2018;96:223–235.
10. Stratton MS, Bagchi RA, Felisbino MB, Hirsch RA, Smith HE, Riching AS, *et al.* Dynamic chromatin targeting of BRD4 stimulates cardiac fibroblast activation. *Circ Res* 2019;125:662–677.

Normalization to Predicted Body Weight May Underestimate Mechanical Energy in Pediatric Acute Respiratory Distress Syndrome

To the Editor:

Mechanical power (MP) and mechanical energy (ME) have been proposed as unifying determinants of ventilator-induced lung injury (VILI). Theoretically, a ventilation strategy can be selected to minimize MP or ME, which should lower the risk for VILI, although this principle still needs to be tested in clinical trials. However, both MP and ME need to be normalized to account for differences in lung size because the energy per unit volume is a key determinant of VILI (1–3). Most typically, lung volume measurements are normalized to predicted body weight (PBW), in both adults and children. However, when considering patients with acute respiratory distress syndrome (ARDS), the "baby lung" concept reinforces that lung volumes, particularly FRC, are further reduced beyond what would be expected from PBW. As such, some suggest normalization of MP and ME to FRC, and in adult patients with ARDS, FRC-normalized MP is more associated with outcome than MP normalized to other parameters (4). However, FRC is often not available for clinical use. Respiratory system static compliance (Crs) may be a readily available surrogate for FRC in adult patients with ARDS, although lung compliance (C_L) is more precise and appears to be most proportional to FRC in adults (5). Unfortunately, C_L requires esophageal pressure (Pes) measurement.

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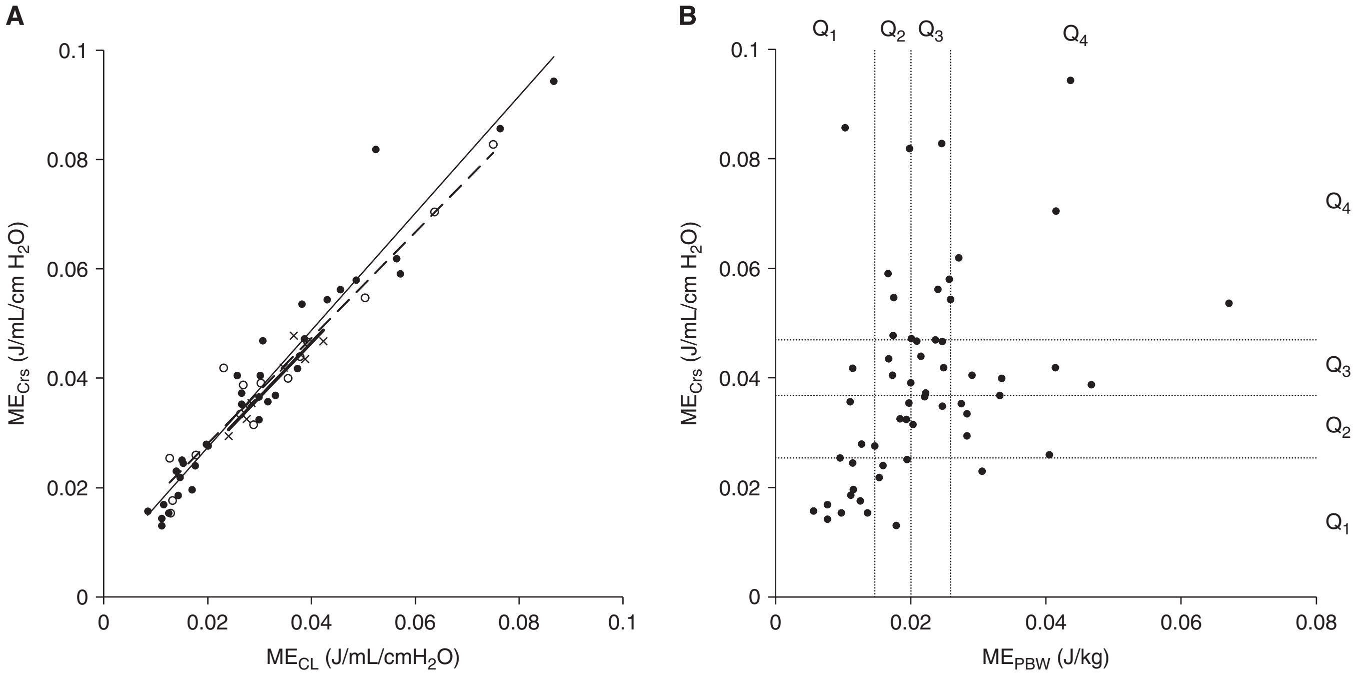

Figure 1. (*A*) Correlation between mechanical energy (ME) normalized to respiratory system static compliance (ME_{Crs}) and ME normalized to lung compliance (M_{CL}) by age group (x/thick line, <12 mo; open circle/dashed line, 12–60 mo; solid circle/normal line, >60 mo). The lines are the regression lines for each age group. ME_{Crs} and ME_{CL} in these patients were significantly correlated in all age groups. (*B*) Correlation between ME_{Crs} and ME normalized to predictive body weight (ME_{PBW}) and classification of each value grouped using interquartile range. Q_1–Q_4 on the *x*- and *y*-axes represent quartiles of ME_{Crs} and ME_{PBW}, respectively. There are some patients whose ME_{Crs} and ME_{PBW} differ greatly. Q = quartile.

There are no data in children surrounding methods to normalize lung volumes for the calculation of MP or ME. Such methods are crucial to develop and validate for use in children given developmental differences in lung volumes, FRC, and lung and respiratory system compliance. Errors in estimating ME may inadvertently lead to changes in ventilator management that may harm the patient. Therefore, we investigated differences in normalized ME according to the method of normalization (PBW, Crs, or C_L) in children with ARDS to identify whether the method of normalization could produce potentially important differences in the estimate of energy per unit lung volume. We present the analysis for normalized ME; similar results would be expected for the normalization of MP, as MP = ME × respiratory rate.

Methods

Population and settings. We performed a secondary analysis of physiologic data from mechanically ventilated children enrolled in an

Table 1. Characteristics of Subjects by Degrees of Difference between Classification Based on Respiratory System Static Compliance–normalized Mechanical Energy and Classification Based on Predictive Body Weight–normalized Mechanical Energy

Difference in Quartile	$ME_{PBW} < ME_{Crs}$ 2 or More (*n* = 6)	$ME_{PBW} < ME_{Crs}$ 1 (*n* = 11)	$ME_{PBW} = ME_{Crs}$ (*n* = 23)	$ME_{PBW} > ME_{Crs}$ 1 (*n* = 11)	$ME_{PBW} > ME_{Crs}$ 2 or More (*n* = 6)	*P* Value
Age, mo	150 (71–183)	93 (60–143)	65 (21–168)	62 (28–105)	65 (28–151)	0.762
PBW, kg	44.8 (21.9–50.4)	23.8 (14.7–46.9)	17.6 (10.3–50.1)	17.0 (12.3–25.7)	18.8 (9.7–28.0)	0.601
PIP, cm H_2O	35.5 (33.6–38.5)	30.1 (27.5–34.5)	26.3 (22.3–30.0)	26.5 (23.1–29.8)	27.0 (26.1–30.2)	0.009
PEEP, cm H_2O	8.0 (5.8–9.5)	10.8 (10.2–12.5)	10.3 (8.7–12.5)	10.3 (10.1–12.3)	11.0 (10.0–12.0)	0.6
DP, cm H_2O	16.9 (15.8–19.1)	15.8 (12.7–16.6)	12.9 (8.3–15.9)	12.7 (11.3–13.3)	11.3 (10.4–12.0)	0.013
V_T/PBW, ml/kg	4.6 (3.4–5.2)	6.6 (6.0–6.8)	7.5 (5.0–8.3)	9.1 (8.3–10.1)	11.0 (10.5–11.9)	<0.001
Crs/PBW, ml/cm H_2O/kg	0.28 (0.25–0.31)	0.43 (0.40–0.47)	0.56 (0.46–0.60)	0.72 (0.68–0.91)	0.93 (0.86–1.24)	<0.001
ME_{PBW}, J/kg	0.017 (0.013–0.018)	0.020 (0.016–0.024)	0.019 (0.011–0.024)	0.022 (0.019–0.031)	0.029 (0.028–0.033)	0.006
ME_{Crs}, J/ml/cm H_2O	0.057 (0.050–0.076)	0.044 (0.037–0.055)	0.033 (0.018–0.047)	0.035 (0.025–0.039)	0.032 (0.027–0.035)	0.004

Definition of abbreviations: Crs = respiratory system static compliance; DP = driving pressure; ME_{Crs} = mechanical energy normalized to respiratory system static compliance; ME_{PBW} = mechanical energy normalized to predictive body weight; PBW = predictive body weight; PEEP = positive end-expiratory pressure; PIP = peak inspiratory airway pressure.
Characteristics of the subjects whose quartiles changed by one or by two or more and those whose quartiles did not change are shown. ME_{Crs} is relatively larger than ME_{PBW}, which correlates with higher PIP, higher DP, lower V_T/PBW, and lower Crs/PBW.

ongoing randomized clinical trial testing a lung and diaphragm protective ventilation strategy (REDvent [Real-time Effort Driven ventilator management]; NIH/NHLBI grant R01HL124666) (ClinicalTrials.gov identifier NCT 03266016) at Children's Hospital Los Angeles. The parent REDvent study included children 1 month to 18 years old with ARDS who had no contraindications to the implementation of a lung and diaphragm protective ventilation strategy (6).

Data collection. Physiologic waveforms of Pes, flow, and airway pressure were recorded daily with a series of three inspiratory and expiratory holds to calculate the physiologic parameters described below. To be included in these analyses, patients had to be passive (no respiratory effort detected on Pes) on recordings from 1 of the first 2 study days. Patients were ventilated using Servo I (Maquet), Hamilton G5 (Hamilton Medical), or AVEA (CareFusion) ventilators using pressure-controlled ventilation.

We examined the correlation among ME normalized to Crs (ME_{Crs}), ME normalized to C_L (ME_{CL}), and ME normalized to PBW (ME_{PBW}). To illustrate potential differences among methods of normalization, subjects were divided into quartiles on the basis of the normalization methods, and parameters were compared among quartiles.

Definitions. ME, Crs, and C_L are calculated using the following formulas. Static measurements were computed. ME is calculated according to the simplified equation Becher and colleagues proposed (7).

$$\text{ME (joules)} = 0.000098 \cdot V_T \text{ (milliliters)} \cdot \text{PIP (centimeters of } H_2O)$$

$$\text{Crs} = V_T/(\text{Pplat} - \text{total PEEP}) \text{ (ml/cm } H_2O)$$

$$C_L = V_T/[(\text{Pplat} - \text{total PEEP}) - (\text{Pes}_{\text{plat}} - \text{Pes}_{\text{PEEP}})] \text{ (ml/cm } H_2O)$$

where V_T is tidal volume, PIP is peak inspiratory airway pressure, PEEP is positive end-expiratory pressure, Pplat is plateau pressure, Pes_{plat} is plateau pressure of Pes, and Pes_{PEEP} is end-expiratory pressure of Pes.

PBW was calculated using the Moore method (8).

Statistical analysis. Data are expressed as median (interquartile range). A *P* value of <0.05 was considered to indicate statistical significance on Kruskal-Wallis analysis. Correlation was evaluated using Spearman's correlation coefficient, and age stratification was performed using age groups of 12 months or less, 12–60 months, and 60 months or more. Analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (R Foundation for Statistical Computing).

Results

Fifty-seven patients were included. The median age of patients was 82.3 months (interquartile range, 27.5–151.4 mo). There was a very strong correlation between ME_{Crs} and ME_{CL}, regardless of age group (<12 mo, $r_s = 0.905$; 12–60 mo, $r_s = 0.92$; >60 mo, $r_s = 0.969$) (Figure 1A). However, there was only a modest correlation between ME_{PBW} and ME_{Crs} ($r_s = 0.481$; Figure 1B). When stratifying by quartiles of ME_{PBW} compared with ME_{Crs}, only 23 of 57 patients (40%) would be classified in the same quartile, and 12 (21%) were more than two quartiles disparate (Table 1). Patients with ME_{PBW} calculated lower than ME_{Crs} had higher PIP, higher driving pressure (DP), lower V_T/PBW, and lower Crs/PBW.

Discussion

Our results demonstrate potentially large differences in ME according to the method of normalization. When ME is normalized to PBW, patients with poor pulmonary compliance, high DP, but low V_T would likely be classified in a lower ME stratum, whereas if ME is normalized to Crs, the same patients would likely be in a higher stratum. This suggests that ME_{PBW} may underestimate the energy loaded per unit volume, especially in patients with low Crs and, possibly, low FRC, as in patients with severe ARDS. For this reason, we believe that ME normalization on the basis of PBW in children is not sufficient to reflect energy per unit lung volume.

The optimal method to normalize ME in children is unknown, and ultimately it will be important to evaluate normalization methods against clinical outcomes and other markers of VILI. Although normalization of ME to C_L may be a good surrogate for FRC, the limitations of esophageal manometry, particularly in children (9), make this impractical. Despite differences in chest wall mechanics as a function of age, ME_{Crs} and ME_{CL} had excellent correlation, regardless of age.

Conclusions

There are major differences in ME calculations according to the method of normalization of lung volume (PBW vs. static compliance). It is likely that ME_{PBW} will underestimate ME, particularly when V_T is low despite high DP and poor compliance. ME normalized to static compliance of the respiratory system should be a focus of investigation in children, particularly to determine if this variable has a relationship with clinically relevant outcomes. This requires routine measurement of Pplat to calculate Crs, which may suggest a need to change our standard practice in children (10). ■

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References

1. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, *et al.* Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med* 2016;42:1567–1575.
2. Marini JJ, Jaber S. Dynamic predictors of VILI risk: beyond the driving pressure. *Intensive Care Med* 2016;42:1597–1600.
3. Gattinoni L, Marini JJ, Collino F, Maiolo G, Rapetti F, Tonetti T, *et al.* The future of mechanical ventilation: lessons from the present and the past. *Crit Care* 2017;21:183.
4. Coppola S, Caccioppola A, Froio S, Formenti P, De Giorgis V, Galanti V, *et al.* Effect of mechanical power on intensive care mortality in ARDS patients. *Crit Care* 2020;24:246.
5. Chiumello D, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F, *et al.* Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2008;178:346–355.
6. Khemani RG, Hotz JC, Klein MJ, Kwok J, Park C, Lane C, *et al.* A phase II randomized controlled trial for lung and diaphragm protective ventilation (Real-time Effort Driven VENTilator management). *Contemp Clin Trials* 2020;88:105893.
7. Becher T, van der Staay M, Schädler D, Frerichs I, Weiler N. Calculation of mechanical power for pressure-controlled ventilation. *Intensive Care Med* 2019;45:1321–1323.
8. Moore DJ, Durie PR, Forstner GG, Pencharz PB. The assessment of nutritional status in children. *Nutr Res* 1985;5:797–799.
9. Hotz JC, Sodetani CT, Van Steenbergen J, Khemani RG, Deakers TW, Newth CJ. Measurements obtained from esophageal balloon catheters are affected by the esophageal balloon filling volume in children with ARDS. *Respir Care* 2018;63:177–186.
10. Bhalla AK, Klein MJ, Emeriaud G, Lopez-Fernandez YM, Napolitano N, Fernandez A, *et al.*; Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE) V.2. Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Adherence to lung-protective ventilation principles in pediatric acute respiratory distress syndrome: a Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology Study. *Crit Care Med* 2021;49: 1779–1789.

If Oral Breathing Does Not Determine Mask Choice for Continuous Positive Airway Pressure Delivery, What Does?

To the Editor:

As underlined by the 2020 American Thoracic Society Workshop Report, current evidence suggests that nasal masks should be the first option for the delivery of continuous positive airway pressure (CPAP) therapy for most patients with obstructive sleep apnea (1). Some patients, however, may require an oronasal mask to optimize their treatment, but evidence to support the choice is lacking. We read the study by Xavier and colleagues with interest, in particular their hypothesis that patients for whom an oronasal mask is well adapted breathe predominantly through the nose (2).

The data provided by Xavier and colleagues suggest that oral breathing is not the main pathophysiological endotype (PE) associated with the choice of an oronasal mask, because only 1 of the 12 patients investigated breathed exclusively through the mouth (2). These results therefore raise the question, If oral breathing is not the main reason for the choice of an oronasal mask, which other PEs determine the choice?

Oronasal masks are often used to prevent mouth opening, which disturbs the patient and leads to adverse effects, in particular leaks and a dry mouth. Mouth opening may therefore be the main PE that leads to the choice of an oronasal mask. In our opinion, three main factors explain mouth opening during CPAP therapy in patients with obstructive sleep apnea:

1. Nasal obstruction: Evidence supporting this is conflicting. Two pathophysiological observational studies in our group found that the choice of an oronasal mask was related to severe nasal obstruction (3, 4), although this was not found by Xavier and colleagues (2). This apparent discrepancy may be the result of differences in the severity of the nasal obstruction between the three studies. In the Xavier and colleagues study, only 1 of 12 patients was classified with severe nasal obstruction, and 4 of 12 were classified with moderate nasal obstruction (2). Current medical consensus is to treat nasal symptoms first to improve acceptance of the nasal mask and to switch to an oronasal mask only if nasal treatment fails and nasal mask tolerance remains poor (1).
2. Respiratory effort: During obstructive respiratory events, the mandible drops progressively as the respiratory effort increases, which can lead to leakage through the mouth (5).
3. Sleep stage: Variability in masseter tone with sleep stage could also contribute to mouth opening (5, 6).

We suggest that because oral breathing is an infrequent reason for the choice of an oronasal mask, as shown by Xavier and colleagues, clinicians should assess and manage mouth opening when possible (e.g., by treating nasal obstruction or sometimes increasing CPAP to reduce residual respiratory effort).

As interest in personalized medicine grows within the medical community, it is important to develop new tools to optimize mask selection for individual patients. We congratulate Xavier and colleagues (2) for providing new evidence regarding mask choice because this will lead to precision medicine and better patient outcomes. We fully agree with Xavier and colleagues that patients who breathe through the nose should switch to a nasal mask, but the question remains whether patients whose main problem is mouth opening should also be switched. It is our opinion that the reasons for the mouth opening should be managed first, in particular nasal obstruction and residual respiratory effort. ■

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