Tidal Breathing Measurements in Former Preterm Infants: A Retrospective Longitudinal Study

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Objectives To investigate, in infants born preterm with or without bronchopulmonary dysplasia (BPD), the trajectory of tidal breathing flow-volume (TBFV) parameters in the first 2 years of life; the association between TBFV parameters and perinatal risk factors; and the predictive value of TBFV parameters for rehospitalizations due to respiratory infections and wheeze.

Study design We retrospectively analyzed TBFV measurements performed at 0-6, 6-12, and 12-24 months of corrected age in 97 infants <32 weeks of gestation and <1500 g. We assessed the association between TBFV parameters and perinatal risk-factors using linear regressions and the predictive capacity for subsequent respiratory morbidity using logistic regressions. We used the area under the curve and likelihood ratio test (LRT) to compare nested models.

Results Time to peak tidal expiratory flow/expiratory time ratio (tPTEF/tE) was lower than normal for the first 2 years of corrected age. Longer duration of oxygen supplementation, intubation, and respiratory support were associated with reduced tPTEF/tE at all time points. For each z-score increase in tPTEF/tE, the OR for rehospitalizations decreased by 0.70. tPTEF/tE added significantly to BPD classifications alone in predicting rehospitalizations (area under the receiver operating characteristic curve = 0.81 vs 0.76, *P* value for LRT = .0012), and wheeze (area under the receiver operating characteristic curve = 0.76 vs 0.71, *P* value for LRT <.001).

Conclusions Infants born preterm, with and without BPD, display persistent airway obstruction during the first 2 years of life. tPTEF/tE may identify infants at greater risk of severe respiratory morbidity. *(J Pediatr 2021;230:112-8)*.

Advances in neonatal care have improved survival of infants born preterm at extremely low gestational age[1]; however, the rate of bronchopulmonary dysplasia (BPD) has not decreased accordingly.[2] Infants born preterm have impaired lung function[3-5] that can persist into adulthood[6] and are at greater risk of respiratory illnesses.[7-9] Functional markers of lung disease to inform the clinical management of infants born preterm at risk of respiratory impairment are lacking. The standard tool to identify respiratory outcomes after preterm birth is the definition of BPD itself, which classifies infants according to oxygen requirement at specific time points.[10-12] However, all proposed definitions of BPD describe the treatment provided rather than distinct, pathophysiologic features. Current BPD definitions poorly suit the need for longitudinal monitoring, assessing the lung status at a specific time point. Finally, infants without BPD also may experience substantial respiratory morbidity.[2,13]

Lung function testing may assist clinicians in monitoring infants born preterm who are at risk of respiratory morbidity early in life[14] and in guiding the management of infants with BPD.[15] Tidal breathing flow-volume (TBFV) measurements are easy to perform at all postnatal ages, do not require sedation, and enable identification of expiratory airway obstruction.[16] Few studies have assessed the role of TBFV in infants born preterm,[4,17-22] and limited data are available about the trajectories of TBFV parameters during infancy, their association with the perinatal history, and subsequent respiratory morbidity.

We hypothesized that TBFV parameters would differ in infants with more severe lung disease and could identify in advance infants at greater risk of respiratory morbidity in early infancy. To test this hypothesis, we retrospectively analyzed longitudinal TBFV measurements performed over the first 2 years of life in infants born preterm <32 weeks of gestational age and birth weight <1500 g. We aimed to describe the trajectories of TBFV parameters; evaluate the association between TBFV parameters

AUC	Area under the receiver operating characteristic curve
BPD	Bronchopulmonary dysplasia
LRT	Likelihood ratio test
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
PDA	Patent ductus arteriosus
RR	Respiratory rate
TBFV	Tidal breathing flow-volume
tPTEF/tE	Ratio of time to reach peak tidal expiratory flow to expiratory time
V_T	Tidal volume

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and perinatal risk factors; and assess the predictive capability of TBFV parameters for subsequent respiratory morbidity.

Methods

We offer to all infants hospitalized at the Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico the opportunity to participate in a multidisciplinary postdischarge follow-up program. The current study is a retrospective analysis of the respiratory follow-up data collected between June 2010 and March 2019. Parents prospectively consented to the use of the anonymized data for research purposes. The local ethical committee approved the retrospective study.

We included in the analysis all infants <32 weeks of gestation or <1500 g who completed 3 follow-up visits at 0-6, 6-12, and 12-24 months of corrected age. We excluded infants with genetic disorders, congenital malformations, or incomplete pulmonary function assessments.

We extracted data related to the demography and perinatal course from electronic medical records. We calculated birth weight z scores by the INTERGROWTH-21st newborn birth weight standards[23] and postnatal weight z scores by the World Health Organization Child Growth Standards.[24] Perinatal risk factors included duration of oxygen supplementation, intubation, and any respiratory support; patent ductus arteriosus (PDA); pulmonary hypertension requiring either inhaled nitric oxide or sildenafil; and neonatal sepsis. We additionally assessed BPD and its severity using 4 different classifications: (1) Vermont Oxford Network (a requirement for supplemental oxygen at 36 weeks of postmenstrual age); (2) Jobe–Bancalari[11]; (3) *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) 2016[12]; and (4) Jensen et al.[25] In the prediction models, we considered weight gain in SDS and exposure to passive smoking as additional confounders.

We performed respiratory function testing with the infants in the supine position, during quiet, natural sleep, according to American Thoracic Society/European Respiratory Society recommendations.[26] TBFV measurements occurred through an infant's facemask using Exhalyzer D (EcoMedics). After allowing adaptation to the mask, we recorded tidal breathing flow volume loops for ≥2 minutes or ≥20 artifact-free breaths. Using commercially available software (WBreath; NDDMedizintechnik), we extracted tidal breathing parameters from the flow–volume loops. We included the following parameters in the analysis: the ratio of time to reach peak tidal expiratory flow to expiratory time (tPTEF/tE), tidal volume (V_T), and respiratory rate (RR). We focused on tPTEF/tE because it is a reproducible and reliable marker of airway obstruction.[27,28] tPTEF/tE can detect severe expiratory airway obstruction in infants with respiratory complaints[16] and is associated with subsequent wheezing in infancy.[29] We expressed all parameters as z scores, as determined by Nguyen et al.[30] Parents' reports and searches on the local hospital electronic medical records documented the rehospitalizations for respiratory reasons and need for wheezing medications over the first 2 years of life.

Statistical Analyses

We calculated the sample size that allowed a 95% power at a 5% significant level for one-way ANOVA with 3 repeated measurements (0-6, 6-12, and 12-24 months of corrected age) and effect size of 0.4[20,31]; 80% power at a 5% significant level for a multiple linear regression model with 4 independent predictors of medium effect size = 0.2[4]; and 80% power at a 5% significant level for a logistic model with a probability of the outcome of 0.25 and an OR of 2.[20] A minimum of 78 infants would fulfill the aforementioned requirements.

We assessed differences between different time points using one-way ANOVA for repeated measurements, and differences between infants with and without BPD using 2-way ANOVA with BPD classification and time as factors. We assessed the association between tidal breathing parameters and perinatal risk factors using linear regression models, considering each factor separately. We coded PDA as 0 = none, 1 = pharmacologic closure, 2 = surgical closure; pulmonary hypertension and sepsis were binary coded. We coded exposure to passive smoking as 0 = none of the patents smoked; 1 = the father smoked; 2 = the mother smoked; 3 = both parents smoked. Linear models were adjusted for the following predefined confounders: sex, gestational age, and birth weight z score.

To investigate the predictive ability of tidal breathing parameters for subsequent rehospitalizations for respiratory reasons or the need for wheezing medications (binary outcomes), we applied logistic regressions considering each tidal breathing parameter separately. We also evaluated the associations between subsequent respiratory morbidity and BPD classification, testing each of the 3 BPD definitions separately. Finally, we developed a multivariable logistic regression model, including the regressors that were significant in the univariable analysis. To determine whether adding TBFV parameters improved the prediction compared with BPD classification alone, we compared the areas under the receiver operating characteristic curves (AUC) and applied likelihood ratio tests (LRTs). Logistic models were adjusted for sex, gestational age, birth weight z score, weight gain in SDS, and exposure to passive smoke.

We expressed data as median and IQR; results of the linear regression models as coefficients and SE; and results of logistic regression models as OR with 95% CI. We considered P values <.05 as statistically significant. We performed the data analysis using SigmaPlot v11 (Systat Software, Inc) and Matlab R2019b (MathWorks).

We estimated an adequate sample size to limit random errors. To reduce systematic errors, 2 investigators separately checked the information extracted from electronic medical records. To assess the risk of selection bias, we compared the baseline characteristics of the study population with those of infants lost to follow-up. To minimize the effect of confounders, we adjusted all the analyses for age, birth weight z score, and sex.

Results

Between June 2010 and March 2019, 269 infants less than 32 weeks of gestation, less than 1500 g birth weight, and without major malformations had TBFV assessments during the postdischarge follow-up. We included in the analysis 97 subjects with 3 valid assessments at regular time intervals and no missing data. The median (IQR) gestational age of the study population was 27.8 (26.0; 29.1) weeks, and birth weight was 885 (729; 1060) g. In total, 89% of infants received antenatal steroids, and 64% had endotracheal surfactant. The rate of BPD was 45% following Vermont Oxford Network classification; 69% according to Jobe–Bancalari definition[11]; 65% for the NICHD 2016[12]; and 54% based on Jensen et al.[25] We reported the baseline and clinical characteristics of the study subjects in **Table I**. We found no statistically significant differences between the infants included in the analysis and those excluded for missing data (**Table II**; available at www.jpeds.com).

Body weight z score was lower than normal between 0 and 6 months and significantly increased over the first 2 years of life. tPTEF/tE and V_T were on average lower, and RR was greater than normal between 0 and 6 months of corrected age. V_T and RR improved over the first 2 years of life, whereas tPTEF/tE did not (**Figure 1**). **Figure 2** (available at www.jpeds.com) shows the trajectories of TBFV parameters expressed as absolute values. Infants with BPD tended to have lower tPTEF/tE and V_T than infants without BPD (**Figure 3**; available at www.jpeds.com). Infants with moderate or severe BPD had significantly lower tPTEF/tE than infants with no or mild BPD over the first 2 years of life (**Figure 4**; available at www.jpeds.com).

A longer duration of oxygen supplementation, intubation, and any respiratory support was associated with reduced tPTEF/tE z score over the first 2 years of life and tended to be associated with reduced V_T z score (**Table I**). PDA and neonatal sepsis were associated with reduced V_T z score at 0-6 months of corrected age (**Table I**). RR was not associated with perinatal risk factors at any time point.

Infants with low tPTEF/tE at 0-6 months of corrected age and BPD NICHD were at significantly increased risk of respiratory morbidity requiring rehospitalization and wheezing medications, after adjusting for sex, gestational age, birth weight z score, weight gain in SDS, and exposure to passive smoke (**Figure 5**). A model including tPTEF/tE and BPD NICHD classification predicted rehospitalizations and need for wheezing medication better than BPD NICHD classifications alone (rehospitalizations: AUC = 0.81 vs 0.76, *P* value for LRT = .0012; need for wheezing medication: AUC = 0.76 vs 0.71, *P* value for LRT < .001).

A multivariable regression model including tPTEF/tE, BPD NICHD 2016, sex, gestational age, birth weight z score, weight gain in SDS, and exposure to passive smoke had a strong predictive value for re-hospitalizations (AUC = 0.81, **Figure 6**, left panel). At a cutoff value of −2 z scores, the sensitivity and specificity of tPTEF/tE alone to rehospitalization were 0.78 and 0.52, respectively (**Figure 6**, right panel).

Table I. Associations between perinatal risk factors and tidal breathing parameters over the first 2 years of life

	0-6 months	6-12 months	12-24 months
tPTEF/tE, z score			
O_2 supplementation, 10 d	−0.17 (0.04)*	−0.11 (0.03)*	−0.13 (0.04)*
Intubation, 10 d	−0.27 (0.12)†	−0.19 (0.09)†	−0.22 (0.11)†
Respiratory support, 10 d	−0.23 (0.06)*	−0.12 (0.05)†	−0.19 (0.06)*
PH	−0.62 (0.45)	−0.54 (0.34)	−0.73 (0.40)
PDA	−0.47 (0.28)	−0.44 (0.21)†	−0.28 (0.26)
Sepsis	−0.06 (0.44)	.19 (0.34)	−0.30 (0.40)
V_T, z score			
O_2 supplementation, 10 d	−0.12 (0.06)	−0.16 (0.08)†	−0.12 (0.05)†
Intubation days, 10 d	−0.33 (0.16)†	−0.42 (0.19)†	−0.24 (0.13)
Respiratory support, 10 d	−0.17 (0.09)	−0.18 (0.11)	−0.15 (0.08)†
PH	0.19 (0.61)	−0.35 (0.75)	−0.56 (0.51)
PDA	−0.96 (0.37)†	−0.52 (0.43)	−0.61 (0.32)
Sepsis	−1.51 (0.57)†	−1.04 (0.73)	−0.10 (0.50)

PH, pulmonary hypertension.
Data reported as linear regression coefficient and SE. We included 1 risk factor at a time and adjusted for sex, gestational age, and birth weight z score.
*$P < .01$.
†$P < .05$.

Discussion

TBFV parameters are associated with perinatal risk factors; reduced tPTEF/tE, in particular, is strongly associated with the duration of respiratory support, intubation, and oxygen supplementation. tPTEF/tE assessed at 0-6 months of corrected adds to BPD classification in predicting rehospitalizations for respiratory reasons and wheeze in the first 2 years of life.

BPD is characterized by large simplified alveolar structure, reduced and dysmorphic vascular bed, and airway smooth muscle thickening, leading to functional consequences in terms of airway obstruction, lung restriction, and reduced gas exchange. BPD represents a continuum of these structural and functional abnormalities, which may not all be present in all patients at all times, leading to different phenotypes. Due to the complex pathophysiology, TBFV analysis cannot capture all functional abnormalities of infants born preterm with or without BPD. Functional residual capacity or pulmonary compliance is necessary to assess lung restriction. The diffusing capacity of the lung for carbon monoxide may capture alveolar underdevelopment and functional echocardiography can detect vascular abnormalities. TBFV measurements are useful in evaluating breathing patterns and airway obstruction. Combining TBFV measurements with morphologic data from magnetic resonance imaging of the lung may help identify BPD phenotypes and evaluate the pathophysiologic causes of lung disease on an individual basis.

In the present study, we focused on V_T and RR, and on tPTEF/tE, an index of airway obstruction. The breathing pattern is a complex result of lung mechanics and control of breathing: it aims at minimizing elastic and resistive work of breathing while assuring the adequate alveolar

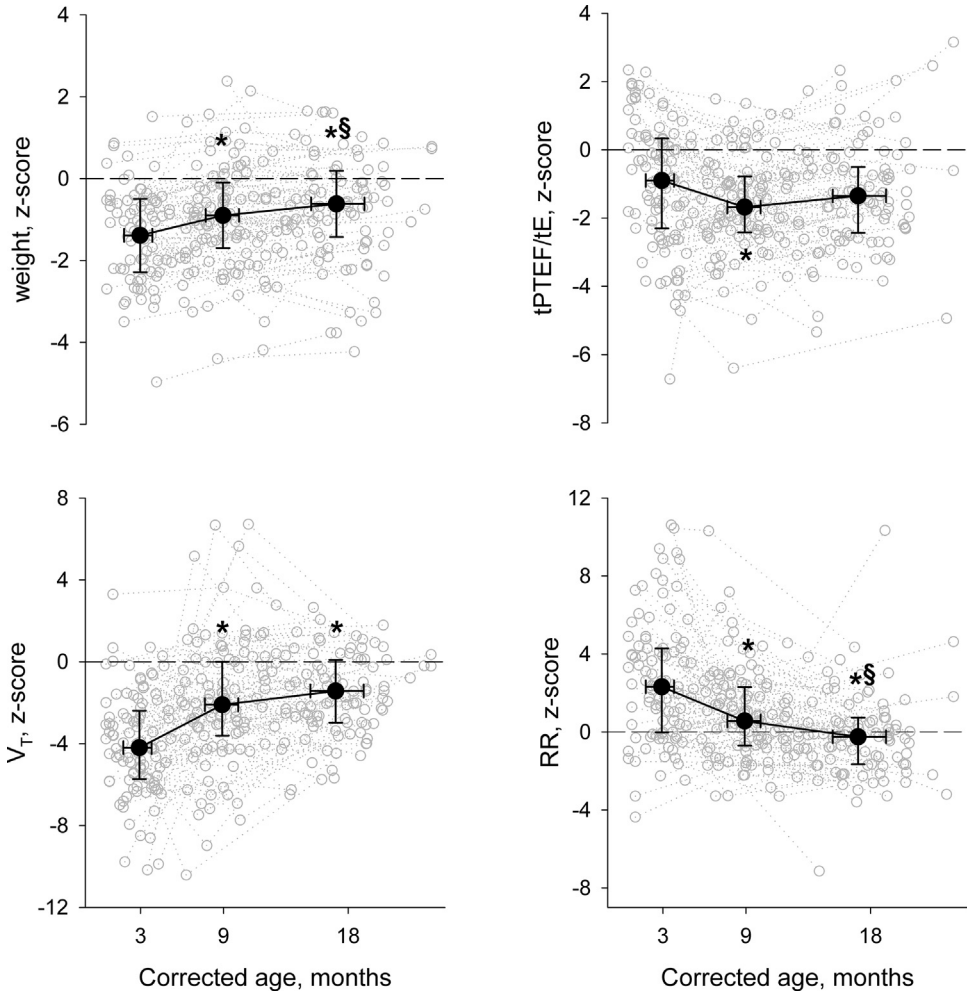

Figure 1. Trajectories of body weight and tidal breathing parameters z scores over the first 2 years of life in infants with very low birth weight and <32 weeks of gestation. Data expressed as individual values (in *gray*) and as medians and IQR (in *black*). **P* < .05 vs 0-6 months. §*P* < .05 vs 6-12 months.

ventilation. In infants, the breathing pattern also contributes to the dynamic elevation of end-expiratory lung volume above functional residual capacity. Several other conditions affect the breathing pattern, such as sleep stage, temperature, or stress. By contrast, tPTEF/tE is a more direct indicator of airway obstruction, and this is why it was more consistently associated with the severity of lung disease. Airway obstruction is common among former preterm infants whereas in contrast to alveolar underdevelopment is less likely to resolve during early childhood. In our study, tPTEF/tE was reduced in most infants regardless of BPD classification, and we did not observe an improvement over the first 2 years of life.

tPTEF/tE may be used to quantify the outcome of different perinatal respiratory support strategies and to follow-up infants born very preterm at risk of respiratory morbidity. The BPD NICHD 2016 classification was sensitive to subsequent rehospitalizations for respiratory reasons (80% of infants who were rehospitalized had a BPD diagnosis[12]) but was not specific (only 32% of infants with BPD were rehospitalized). Adding tPTEF/tE to BPD classification helped in identifying infants at greater risk of severe respiratory complaints (eg, leading to rehospitalizations). Therefore, tPTEF/tE and BPD classification provide complementary information. Infants without BPD may have expiratory airway obstruction. In contrast, infants with BPD may have variable phenotypes, with prevailing restrictive features and/or pulmonary hypertension, which are not captured by tPTEF/tE or other TBFV parameters. Therefore, in our opinion, the composed model has a greater predictive value. tPTEF/tE at 0-6 months of corrected age was also significantly associated with subsequent need for wheezing medications, confirming the hypothesis that tPTEF/tE can identify infants with obstructive airway disease.

Preterm birth is associated with multisystem immaturity, and infants who develop a pulmonary disease may have other comorbidities that contribute to the development of respiratory morbidities during infancy. TBFV measurements cannot

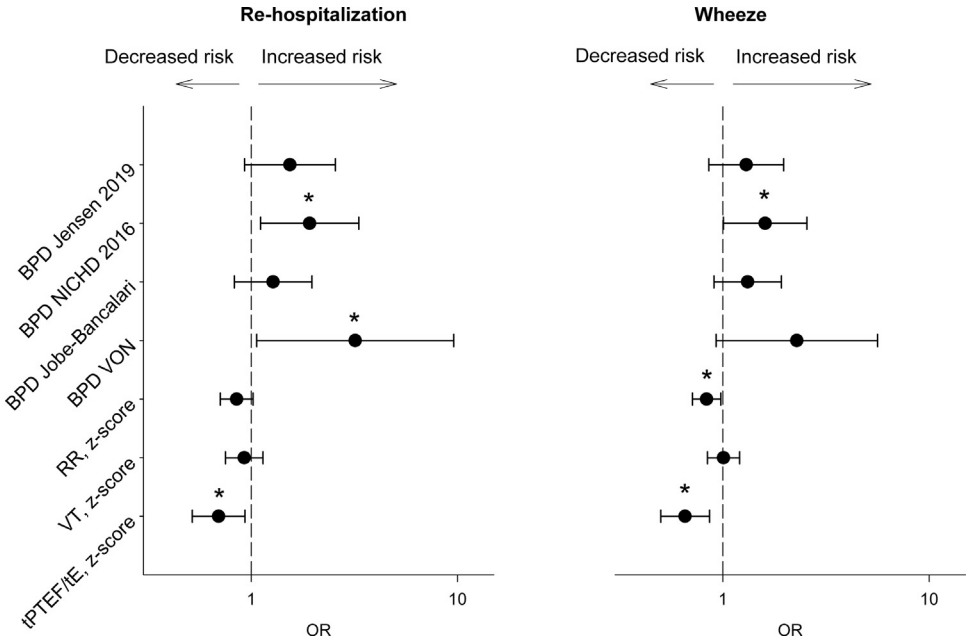

Figure 5. Association of TBFV parameters at 0-6 months of corrected age with rehospitalization for respiratory reasons and wheeze in the first 2 years of life in infants with very low birth weight and <32 weeks of gestation. Data are expressed as OR and 95% CIs on a log scale. The models adjusted for sex, gestational age, birth weight z score, weight gain in SDS, and exposure to passive smoke. *$P < .05$.

capture all risk factors associated with prematurity and respiratory morbidity, but tPTEF/tE could contribute to disentangling the complexity of chronic lung disease of prematurity, identifying the obstructive phenotype. tPTEF/tE also has the potential of informing the clinical management of the patient, for example, assessing the severity of intercurrent acute pathologies, guiding pharmacologic treatment, and evaluating the effect of therapies.

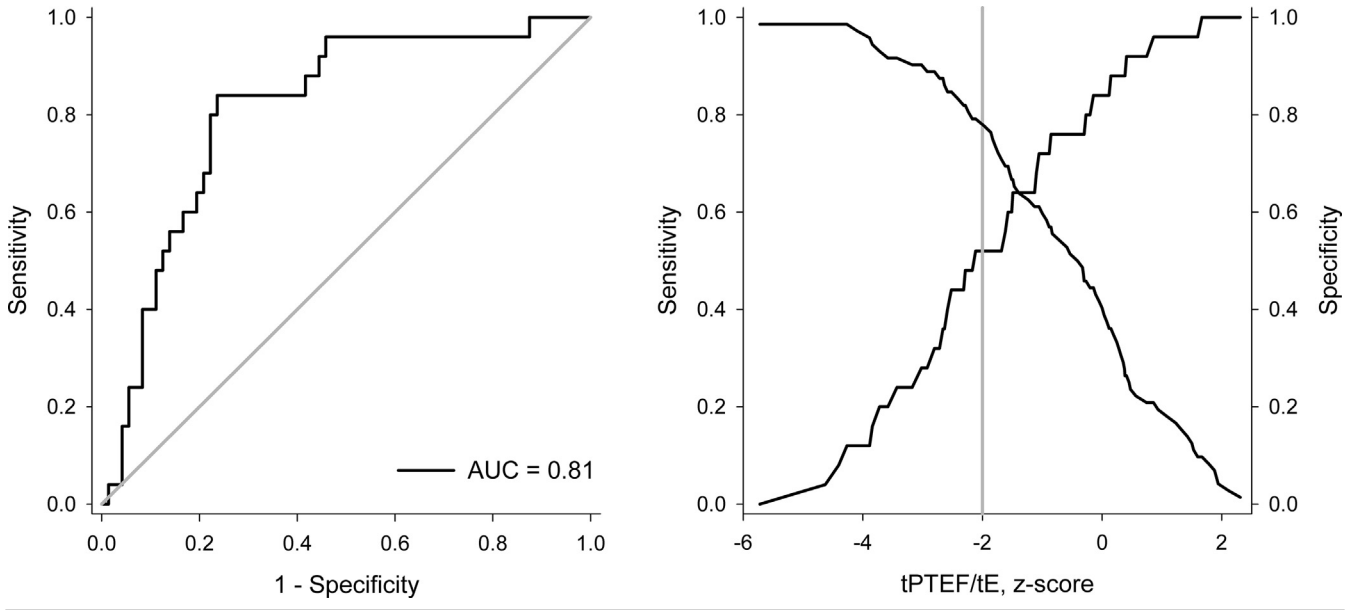

Figure 6. Predicting power of tPTEF/tE for rehospitalizations in the first 2 years of life in infants with very low birth weight and <32 weeks of gestation. *Left panel*, receiver operating characteristic curves for the multivariable logistic model, including tPTEF/tE, BPD NICHD 2016, sex, gestational age, body weight z score, weight gain in SDS, and exposure to passive smoke. *Right panel*, sensitivity and specificity as a function of the tPTEF/tE cut-off value. At a tPTEF/tE of −2 z score, sensitivity was 0.52, and specificity was 0.78.

Finally, tPTEF/tE as a marker of airways obstruction in former preterm infants may play a role in investigating the pathophysiology of sudden infant death syndrome. Different authors highlighted the association between airways obstruction and sudden infant death syndrome both by functional assessment in survivors and by postmortem findings.[32,33]

Our results echo a common finding to previous studies: even though abnormal lung function tends to be more pronounced with BPD,[4,21,22] both infants born preterm with or without BPD have abnormal lung function compared with healthy infants born at term.[4,19,21,22] We found increased RR in infants born preterm, in agreement with most of the previous literature.[4,19,21,34] In our cohort, V_T tended to be lower than normal, in agreement with Chen et al.[34] By contrast, other studies reported that V_T adjusted for somatic growth does not differ between infants with BPD and healthy infants born at term[19] nor between infants born preterm with or without BPD,[18] whereas Bentsen et al reported that infants born extremely preterm have greater V_T than healthy controls born at term.[22] The epidemiologic and methodologic heterogeneity may partially explain the mixed results about V_T. Most studies reported increased expiratory obstruction in infants born preterm, particularly in those with BPD,[4,21,22,34] in agreement with our findings. To our knowledge, only 2 studies described the longitudinal course of TBFV parameters in infants born preterm.[18,34] The authors documented a tendency of RR to decrease and of V_T adjusted for body weight to increase, in agreement with our results.

Few studies investigated the predictive capability of TBFV measurements for subsequent respiratory morbidity in infants born preterm.[20-22,35] Ren et al found that TBFV parameters measured near hospital discharge did not differentiate infants with respiratory morbidity in the first year of life.[21] Proietti et al found that TBFV parameters did not add significantly to BPD classification and standard clinical risk factors in predicting the risk of subsequent respiratory morbidity in an individual infant.[20] In contrast, we found that TBFV parameters added significantly to BPD classification and standard clinical parameters in predicting the risk of respiratory morbidity requiring rehospitalization. A possible explanation for the different results is that we performed measurements later after birth, when the parameters may capture more persistent abnormalities. Moreover, compared with Proietti et al, we limited our analysis to infants at high risk, <32 weeks of gestation, and <1500 g birth weight. In agreement with our results, Bentsen et al found that TBFV parameters measured at term equivalent can predict rehospitalizations for respiratory morbidity or need for wheezing medications in the first year of life.[22]

Strengths of our study include the longitudinal characterization of TBFV parameters in the same subjects without missing data and the detailed clinical information available for the patients. Moreover, all measurements were performed by the same investigator, using the same equipment and protocol. We managed to perform all the assessments with spontaneously breathing infants during natural sleep, without sedation.

The limitations of our study are the retrospective study design and the lack of a control group of healthy infants[36] and the limited time frame of 2 years for the assessment of both lung function assessment and clinical outcomes. In addition, the study lacked other measurements (other lung function tests, imaging, bronchoscopy, echocardiography) that could have captured other relevant physiopathological characteristics of former preterm infants. A potential source of selection bias is the participation in a follow-up program, which may have selected the sickest infants. Nevertheless, our rate of participation in the follow-up for this category of infants is >80%. Also, comparing infants included in the study (having assessment at 3 time points) with infants lost to follow-up, we found no significantly different baseline characteristics. Finally, despite presenting a study report from a single study site, the sample size, the reproducibility and standardization of the TBFV technique, and the agreement with previous reports suggest the generalizability of our findings to other populations of similar age and level of care.

In conclusion, tPTEF/tE added to BPD classification in the prediction of subsequent rehospitalization for respiratory problems and was a marker of the degree of respiratory assistance during the neonatal intensive care unit stay (intubation, duration of respiratory support, and supplemental oxygen). Therefore, TBFV measurements may play a role in the follow-up management of former preterm infants at risk of subsequent respiratory morbidity. ■

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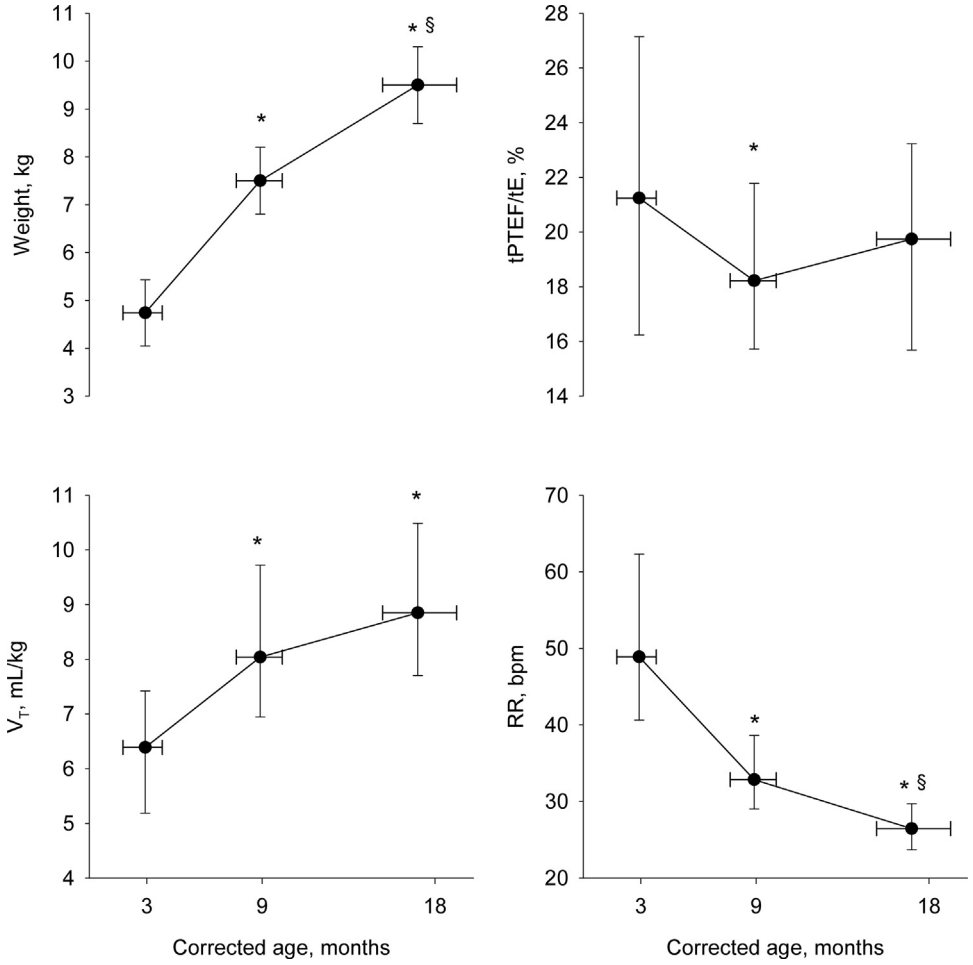

Figure 2. Trajectories of body weight and tidal breathing parameters over the first 2 years of life in infants with very low birth weight and <32 weeks of gestation. Data are expressed as median and IQR. *P < .05 vs 0-6 months. §P < .05 vs 6-12 months.

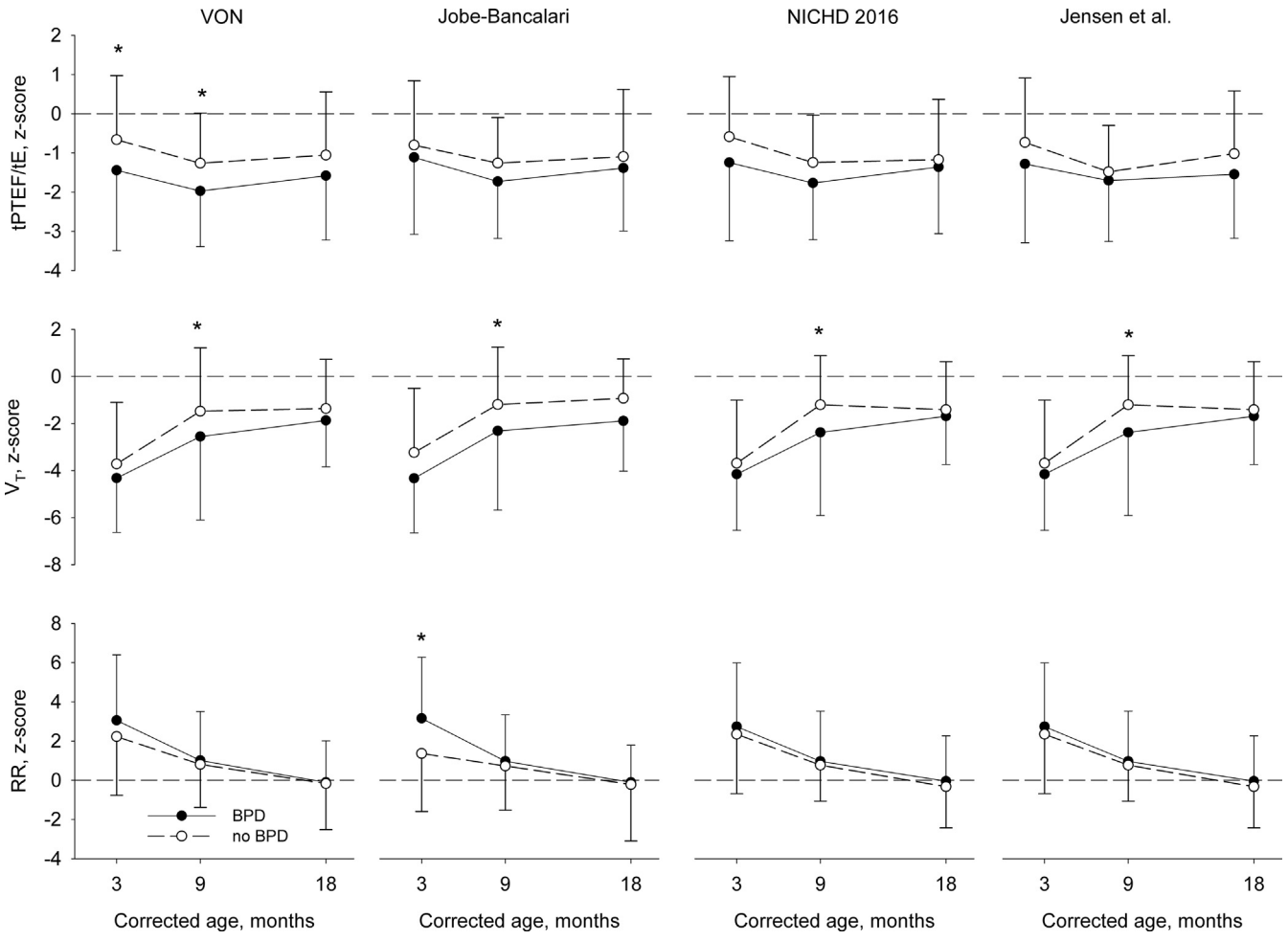

Figure 3. Trajectories of tidal breathing parameters z scores over the first 2 years of life in infants with very low birth weight and <32 weeks of gestation with and without BPD according to different BPD definitions. *Closed symbols, solid lines*: infants with BPD. *Open symbols, dashed lines*: infants without BPD. Data are expressed as means and SD. *$P < .05$ vs no BPD. *VON*, Vermont Oxford Network.

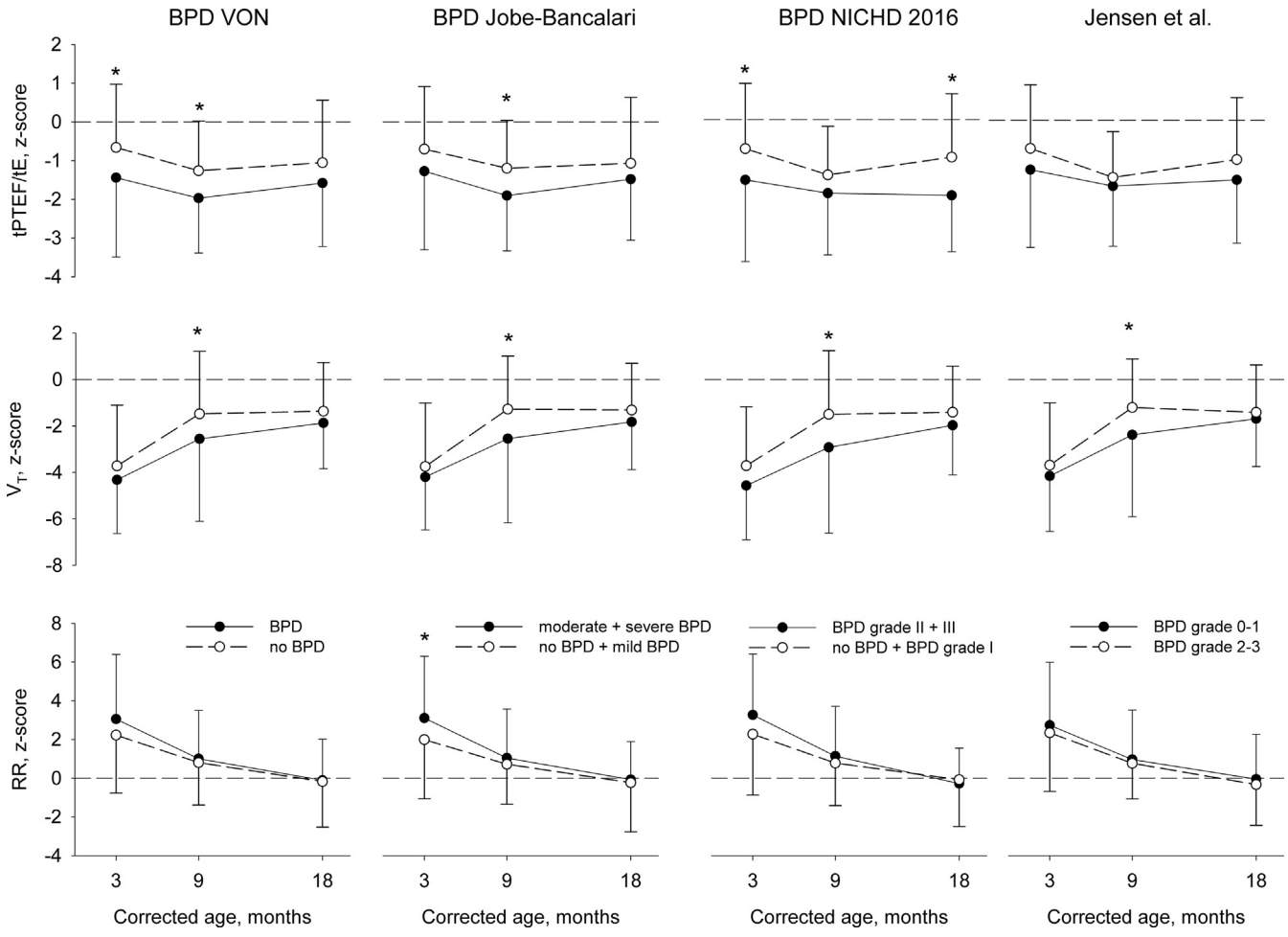

Figure 4. Trajectories of tidal breathing parameters z scores over the first 2 years of life in infants with very low birth weight and <32 weeks of gestation without BPD or with mild BPD vs infants with moderate-to-severe BPD according to different BPD definitions. *Closed symbols, solid lines*: infants with moderate-to-severe BPD. *Open symbols, dashed lines*: infants without BPD or with mild BPD. Data are expressed as means and SD. *$P < .05$ vs no BPD or moderate BPD.

Table II. Comparison of infants included and excluded in the analysis

	Included	Excluded
Subjects, n	97	172
Demographics		
Sex, %male	53%	60%
Gestational age, postmenstrual weeks	27.8 (26.0, 29.1)	28.0 (26.0, 29.6)
Body weight, g	885 (729, 1060)	880 (735, 1185)
Body weight, z score	−0.31 (−1.22, 0.22)	−0.17 (−1.5, 0.29)
SGA, %	18%	26%
Perinatal clinical parameters		
Respiratory support, d	52 (34, 77)	49 (26, 77)
Intubation, d	6 (0, 23)	5 (0, 23)
Oxygen supplementation, d	38 (20, 769)	34 (12, 73)
Pulmonary hypertension, %	26%	27%
PDA, %	44%	49%
Neonatal sepsis, %	57%	49%
BPD classification		
BPD VON, %	45%	41%
BPD Jobe–Bancalari, %	69%	59%
BPD NICHD 2016, %	65%	52%
BPD Jensen et al, %	54%	45%

SGA, small for gestational age; *VON*, Vermont Oxford Network.
Data are presented as median (IQR) unless otherwise stated.