Variability of Tidal Breathing Parameters in Preterm Infants and Associations with Respiratory Morbidity during Infancy: A Cohort Study

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Objective To test whether low variability of tidal volume (V_T) and capnographic indices are predictive of subsequent respiratory morbidity in preterm infants.

Study design In a birth cohort of 133 preterm infants, lung function was performed at 44 weeks postmenstrual age. Associations between the coefficient of variation (CV) of V_T (CV_{VT}) and of expired CO_2 volume per breath ($CV_{VE,CO2}$) with rehospitalization, wheeze, and inhalation therapy during infancy were assessed using logistic regression. Area under the curve (AUC) analysis was used to assess whether outcome prediction using bronchopulmonary dysplasia (BPD) classification was enhanced by CV_{VT} or $CV_{VE,CO2}$.

Results For each IQR decrease in CV_{VT} (range, 4%-35%) and $CV_{VE,CO2}$ (range, 5%-40%), the OR for rehospitalization increased by 2.25 (95% CI, 1.21-4.20) and 2.31 (95% CI, 1.20-4.45), respectively. The predictive value of BPD for rehospitalization was improved when CV_{VT} or $CV_{VE,CO2}$ was added to the model, with the AUC increasing from 0.56 to 0.66 in both models. No association was found for the other outcomes.

Conclusions Compared with BPD classification alone, including near-term variability of tidal breathing parameters improves the prediction of rehospitalization in infancy. These findings may inform parent counseling and monitoring strategies in preterm infants. *(J Pediatr 2019;205:61-9).*

Preterm born infants, particularly those with bronchopulmonary dysplasia (BPD), are at increased risk of respiratory morbidity during early childhood.[1-4] Early identification of such infants would be of value for clinical management, parental counseling, and monitoring strategies. Several previous studies have identified perinatal risk factors associated with a higher probability of respiratory symptoms and altered lung function in early childhood[1,4-6]; however, neither these clinical predictors[3,4,7] nor the degree of lung disease at 36 weeks postmenstrual age (PMA) can satisfactorily predict subsequent respiratory outcomes in an individual child.[3,4]

A series of studies have evaluated the ability of functional markers to predict subsequent respiratory morbidity in preterm infants.[3,8-11] Broughton at al measured functional residual capacity under sedation and found that lower lung volumes were associated with higher respiratory morbidity later in life.[9] Studies using noninvasive lung function tests, which can be easily performed in unsedated infants at bedside, are of particular interest.[3,8] In preterm born infants (<32 weeks gestation), higher airway resistance, R_{rs} (measured via the single-breath occlusion technique), at 36 weeks PMA predicted the occurrence of symptomatic respiratory syncytial virus infection during the first year of life.[8] Our group previously reported that a higher tidal volume (V_T) and a lower respiratory rate (RR) measured at term may be associated with later wheeze, although these parameters did not offer additional predictive value over standard clinical predictors.[3]

The physiological variability of breathing is the expression of an adaptive interaction between central breathing control mechanisms and the thoracopulmonary system to maintain optimal gas exchange under given environmental requirements.[12] Several studies have shown that the variability in breathing time, V_T, and airway resistance is positively associated with the maturity stage of preterm infants.[13-16]

AUC	Area under the curve
BPD	Bronchopulmonary dysplasia
CV	Coefficient of variation
EIP	Electromagnetic inductance plethysmography
MV	Minute ventilation
MV_{CO2}	CO_2 elimination per minute
$V_{E,CO2}$	Expired CO_2 volume per breath
PMA	Postmenstrual age
RR	Respiratory rate
V_T	Tidal volume

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Supported by the Swiss National Science Foundation (320030_163311) and a research fellowship from the University Children's Hospital Basel (to J.U.). The sponsors of this study did not have any influence on the study design, data interpretation, or manuscript preparation. The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2018.10.002

At 44 weeks PMA, the maturational aspects of breathing control mechanisms are less critical; however, tidal breathing must dynamically adapt to overcome any structural or functional lung changes related to preterm birth. We have recently shown that breath-to-breath variability in CO_2 clearance at term is strongly related to the degree of prematurity and the severity of lung injury.[17,18] In this context, reduced breathing variability in preterm born infants may reflect persistent pathophysiological lung changes, which led us to hypothesize that it also may be associated with respiratory morbidity later in infancy.

Because tidal breathing in infants can be measured in a normal hospital setting, the aims of the present study were to investigate whether the variability of tidal breathing and/or CO_2 clearance assessed near term is associated with respiratory morbidity during the first year of life of preterm born infants, and whether tidal breathing and/or CO_2 clearance variability can enhance the predictive power of the standard classification of BPD.

Methods

This prospective observational study was based on previously collected data from preterm infants (<37 weeks) and is part of the Basel Bern Infant Lung Development birth cohort study (http://www.bild-cohort.ch/). We recruited subjects between 1999 and 2009 within the region of Bern, Switzerland as described previously.[1,3,4] We excluded infants with severe illnesses, such as congenital diaphragmatic hernia, congenital heart diseases, neuromuscular disorders, and chromosomal aberrations and those with a history of lower respiratory tract infections. We performed lung function measurements at the age of 44 weeks PMA.[1,3] We sent standardized questionnaires to the parents at age >1 year to assess respiratory symptoms during the first year of life.[3] According to the American Thoracic Society (ATS) definitions, we classified preterm infants as healthy, mild, moderate, and severe BPD.[19] We recorded perinatal data using the institutional neonatology database (NEODAT 4.10, Tübingen, Germany) and the BILD study database.

Tidal breathing was assessed for 10 minutes as described previously.[17,18,20,21] Infants were studied while in the supine position, during quiet natural sleep, according to ATS/European Respiratory Society recommendations.[22,23] Measurements were performed using the Exhalyzer D (EcoMedics, Duernten, Switzerland), which incorporates an ultrasonic flowmeter and a mainstream CO_2 sensor. An infant face mask (size 1; Homedica, Cham, Switzerland) was used. The deadspace of the flowmeter and CO_2 sensor was estimated as 3.5 mL, and that of the face mask was 7.5 mL.[24]

Lung function data were processed using commercially available software (WBreath version 3.7.6.0; NDD Medizintechnik, Zurich, Switzerland). Data were corrected for body temperature, barometric pressure, vapor saturation, and flow offset. A subset of 100 consecutive regular breaths, excluding sighs and 10 breaths before and after each sigh, was selected for further analysis.[18] The expired CO_2 volume per breath ($V_{E,CO2}$) was obtained by integrating the CO_2 signal over V_T. The CO_2 elimination per minute (MV_{CO2}) was calculated as $V_{E,CO2} \times RR$. Details regarding correction for CO_2 signal delay and quality control criteria for the capnography parameters have been published previously.[17] Short-term variability in $V_{E,CO2}$, V_T, and RR was calculated using the coefficient of variation (CV) as CV (%) = SD/mean × 100, and is reported as $CV_{VE,CO2}$, CV_{VT}, and CV_{RR}, respectively. For each child, the relative breath-to-breath % change in $V_{E,CO2}$ ($\Delta V_{E,CO2}$) was plotted against the corresponding relative % change in V_T (ΔV_T), and the slope of the regression line was computed with a least squares approach (slope $\Delta V_{E,CO2}/\Delta V_T$) as described previously.[18] This slope describes the variability of CO_2 elimination in relation to the variability of V_T. The slope is equal to 1 when the relative breath-to-breath change in CO_2 is equal to the corresponding relative change in V_T and is >1 when the relative breath-to-breath change in CO_2 elimination is higher than the corresponding relative change in V_T. Breath-to-breath inspiratory and expiratory times and volumes were automatically calculated by WBreath; capnography parameters and variability indices were determined using algorithms implemented in MATLAB R2015a (MathWorks, Natick, Massachusetts).

We used questions adapted from the International Study on Asthma and Allergies in Childhood (ISAAC)[25,26] to assess binary outcomes for respiratory morbidity during the first year of life. The primary outcome was rehospitalization due to respiratory disease (excluding admissions for diagnostic purposes), as assessed with the following questions: (1) did your child receive medical attention due to coughing or wheezing during the first year of life? (here we don't mean the routine checkups for premature babies that we do in the hospital) (no/yes); (2) if yes, where? (a) as an emergency at the pediatrician (no/yes), (b) at a hospital emergency department (no/yes), (c) child admitted to the hospital for at least 1 night (no/yes); (d) at a specialist outpatient clinic (no/yes). Secondary outcomes were wheeze and inhalation therapy with beta-agonists for longer than 4 weeks. These outcomes can be reproducibly assessed.[4,26,27] The answers in the returned questionnaires were validated by study nurses and medical doctors using medical histories from hospital records. All returned questionnaires underwent quality control assessment performed by study nurses and medical doctors. The answers were futher validated using medical histories from hospital records.[3]

Statistical Analyses

The following parameters describing variability of tidal breathing and CO_2 were used as exposures: CV_{VT}, MV_{CO2}, $CV_{VE,CO2}$, slope $\Delta V_{E,CO2}/\Delta V_T$, and CV_{RR}. The associations between lung function parameters and clinical outcomes were investigated first by univariable logistic regression and then with a multivariable model adjusting for sex, gestational age, weight at time of the lung function test (in SDS), weight gain from birth until lung function (in SDS) (using the 1990 British Growth Reference), and duration of positive-pressure support (defined as days of mechanical ventilation plus days of continuous positive airway pressure). These parameters were chosen a priori based on clinical evidence[7] and experience in previous studies by our group using the same cohort.[3,4,28]

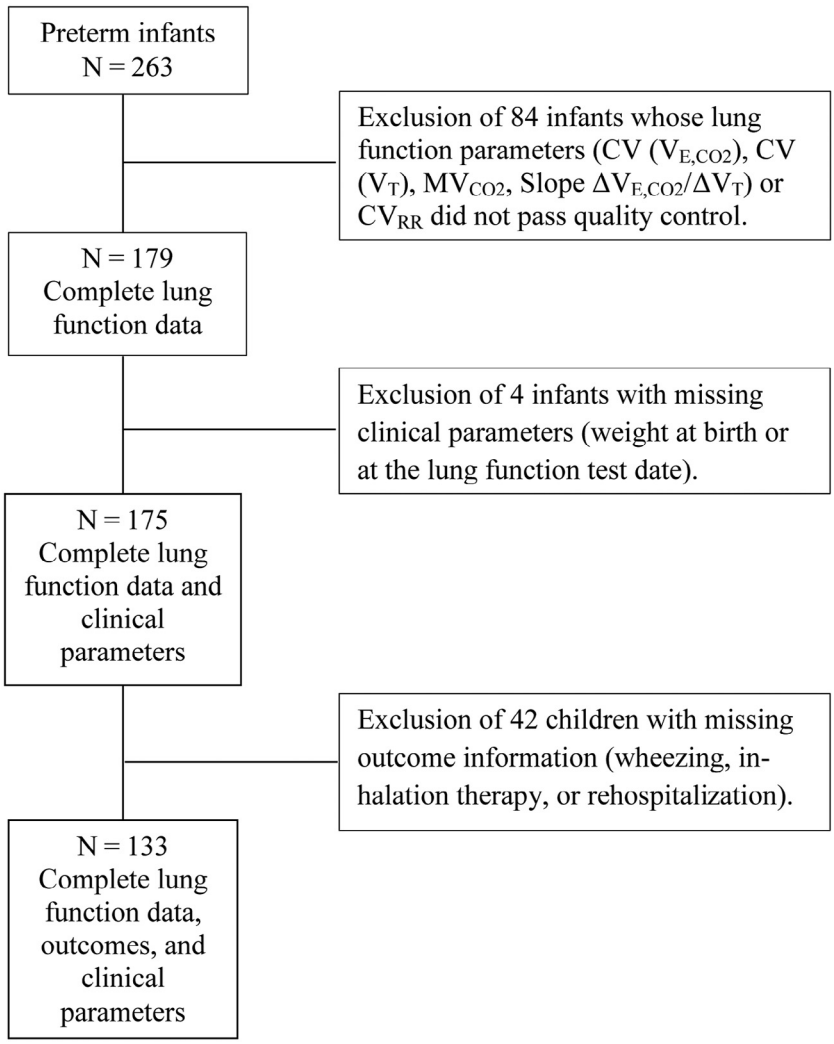

Figure 1. Flow chart of the study population.

To investigate the predictive ability of lung function parameters and BPD for subsequent respiratory outcomes, we compared adjusted regressions models including BPD classification with and without lung function parameters using the area under the receiver operating characteristic curve (AUC). Likelihood ratio tests were used to compare nested models. Lung function measures across BPD groups were compared using 1-way ANOVA with Bonferroni correction to account for multiple testing.

Data are expressed as mean ± SD (range) or as number (%); results of the regression models are given as OR with 95% CI per IQR of the exposure. Here $P < .05$ defines statistical significance. Data were analyzed using Stata 13 (StataCorp, College Station, Texas).

Results

Lung function measurements were performed in 263 preterm infants. Of these, 133 infants (51%) had complete data for exposures, outcomes, and clinical parameters and were used for analysis (**Figure 1**). Among the final study participants measured at 44 weeks PMA, 49 had no, 34 mild, 32 moderate, and 18 severe BPD. Wheezing was reported for 61 (46%), 53 (40%) had inhalation therapy, and rehospitalization due to respiratory disease was reported in 39 (29%). Further characteristics of the study participants are given in **Table I**. Infants with follow-up had higher birth weight, higher Apgar score, and fewer days on positive-pressure support and oxygen therapy compared with those lost to follow-up (**Table II**; available at www.jpeds.com).

Both the univariable and the multivariable analyses showed significant associations between variability parameters and subsequent rehospitalization. Per IQR decrease in CV_{VT} and $CV_{VE,CO2}$, the aOR for rehospitalization increased by 2.25 (95% CI, 1.21-4.20) and 2.31 (95% CI, 1.20-4.45), respectively. Regarding the variability of CO_2 elimination in relation to the variability in V_T, per IQR decrease in the slope $\Delta V_{E,CO2}/\Delta V_T$, the OR for rehospitalization increased by 1.97 (95% CI, 1.09-3.54). Per IQR decrease in CV_{RR}, the aOR for rehospitalization

Table I. Demographic, clinical, and lung function data for the 133 preterm infants in this study

Parameters	Values
Clinical perinatal parameters	
Male sex, n (%)	77 (58)
Gestational age at birth, wk, mean ± SD (range)	29.1 ± 2.8 (24-37)
Birth weight, kg, mean ± SD (range)	1.19 ± 0.55 (0.42-2.98)
Length at birth, cm, mean ± SD (range)	37.9 ± 4.2 (27-50)*
Apgar score at 5 min, mean ± SD (range)	7.7 ± 1.7 (2-10)†
Chorioamnionitis, n (%)	45 (37)‡
Patent ductus arteriosus, n (%)	55 (41)
Atrial septal defect, n (%)	8 (7)*
Prenatal corticosteroids, n (%)	115 (86)
Surfactant, n (%)	52 (43)§
Clinical postnatal parameters	
Positive-pressure support, d, mean ± SD (range)	25.5 ± 21.4 (0-81)
Duration of mechanical ventilation, d, mean ± SD (range)	5.0 ± 9.5 (0-63)
Duration of CPAP, d, mean ± SD (range)	20.5 ± 18.4 (0-80)
Oxygen therapy from birth, d, mean ± SD (range)	51.8 ± 56.6 (0-385)
Weight at study date, kg, mean ± SD (range)	3.88 ± 0.78 (1.59-6.80)
Length at study date, cm, mean ± SD (range)	52 ± 4 (39-63)
Weight at study date, SDS, mean ± SD (range)	−1.02 ± 1.33 (−4.7 to 3.9)
Weight gain, SDS, mean ± SD (range)	−0.3 ± 1.8 (−6.0 to 4.7)
Postmenstrual age at study date, wk, mean ± SD (range)	44.6 ± 1.9 (40-50.3)
Lung function parameters	
V_T, mL/kg, mean ± SD (range)	7.5 ± 1.7 (4.6-19)
CV_{VT}, %, mean ± SD (range)	8.5 ± 3.6 (3.7-34.9)
MV, mL/kg/min, mean ± SD (range)	373 ± 72 (229-624)
$V_{E,CO2}$, mL/kg, mean ± SD (range)	0.2 ± 0.06 (0.09-0.6)
$CV_{VE,CO2}$, %, mean ± SD (range)	10.3 ± 4.1 (5.3-39.7)
MV_{CO2}, mL/kg/min, mean ± SD (range)	11.2 ± 2.4 (4.7-19.1)
Slope $\Delta V_{E,CO2}/\Delta V_T$, mean ± SD (range)	1.1 ± 0.09 (0.9-1.3)
RR, breaths/min, mean ± SD (range)	51 ± 12 (29-96)
CV_{RR}, %, mean ± SD (range)	7.9 ± 2.3 (4.1-16.8)

CPAP, continuous positive airway pressure.
Clinical postnatal parameters at the study date were assessed at the lung function measurements at 44 weeks PMA.
*Data missing for 15 subjects.
†Data missing for 1 subject.
‡Data missing for 10 subjects.
§Data missing for 13 subjects.

increased by 1.57 (95% CI, 0.99-2.51) (**Table III**). When the analysis was further adjusted for BPD severity, the results remained similar (data not shown). For the outcomes of wheezing and inhalation therapy, we did not observe any significant associations with these exposures (**Table IV**; available at www.jpeds.com). MV_{CO2} was not associated with any of the outcomes (**Table III** and **Table IV**).

Figure 2 shows relevant lung function parameters stratified by the outcome rehospitalization. Although the mean V_T, $V_{E,CO2}$, and MV_{CO2} values did not differ between groups, all variability parameters were significantly lower in the infants with subsequent rehospitalization.

There was an overall difference in CV_{VT} ($P = .008$), $CV_{VE,CO2}$ ($P = .003$), and slope $\Delta V_{E,CO2}/\Delta V_T$ ($P > .001$) across BPD groups. $V_{E,CO2}$ did not differ across BPD groups. Further stratification of BPD groups in hospitalized and nonhospitalized infants yielded no difference in CV_{VT} (**Figure 3**) or any other lung function parameter (data not shown).

The model including BPD severity only had the lowest performance, with an AUC of 0.56. Models including CV_{VT}, $CV_{VE,CO2}$, the slope $\Delta V_{E,CO2}/\Delta V_T$ or CV_{RR}, and BPD better predicted rehospitalization than BPD classification alone (AUC of 0.66, 0.66, 0.62, and 0.64, respectively). A model including BPD classification and all variability parameters (CV_{VT}, $CV_{VE,CO2}$, slope $\Delta V_{E,CO2}/\Delta V_T$, and CV_{RR}) was not associated with further improvements in predictive value (**Table V** and **Figure 4**, A). All logistic regression models were adjusted, as defined in the legend of **Table V**. Diagnostic plots to predict subsequent hospitalization indicated that sensitivity and specificity of the model including CV_{VT} changed considerably depending on the CV_{VT} value. For example, at a CV_{VT} of 6%, sensitivity was 41% and specificity was 88%. At a CV_{VT} of 12%, specificity increased to 97%, but sensitivity decreased to 15% (**Figure 4**, B).

Discussion

In this prospective cohort of preterm infants with lung function measurements obtained at 44 weeks PMA, we assessed the association of breath-to-breath variability of V_T and CO_2 clearance with subsequent respiratory morbidity. We found that lower CV_{VT} and $CV_{VE,CO2}$ were associated with an increased risk of rehospitalization during the first year of life. Of note, the ability of the standard BPD classification[19] to predict rehospitalization was poor; however, it could be improved by including CV_{VT} and $CV_{VE,CO2}$ in the prediction models. Measurements of tidal breathing and CO_2 clearance can be easily

Table III. Associations among variability indices, CO_2 elimination, and subsequent rehospitalization during the first year of life (n = 133)

Outcome: rehospitalization due to respiratory disease (39 of 133)	Univariable association			Multivariable association*		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Exposure						
$CV_{VE,CO2}$, %	2.09	1.14-3.82	.017	2.31	1.20-4.45	.013
CV_{VT}, %	2.11	1.18-3.78	.012	2.25	1.21-4.20	.011
MV_{CO2}, mL/kg/min	1.08	0.71-1.67	.710	1.08	0.69-1.70	.740
Slope $\Delta V_{E,CO2}/\Delta V_T$	1.77	1.05-3.01	.034	1.97	1.09-3.54	.02
CV_{RR}, %	1.54	0.99-2.42	.050	1.57	0.99-2.51	.053

OR and 95% CI per IQR decrease for each exposure was determined by logistic regression.
*Adjusted for the following variables: sex, gestational age, weight gain (in SDS), duration of positive-pressure support (days of mechanical ventilation plus days of continuous positive airway pressure), weight at the time of lung function testing.

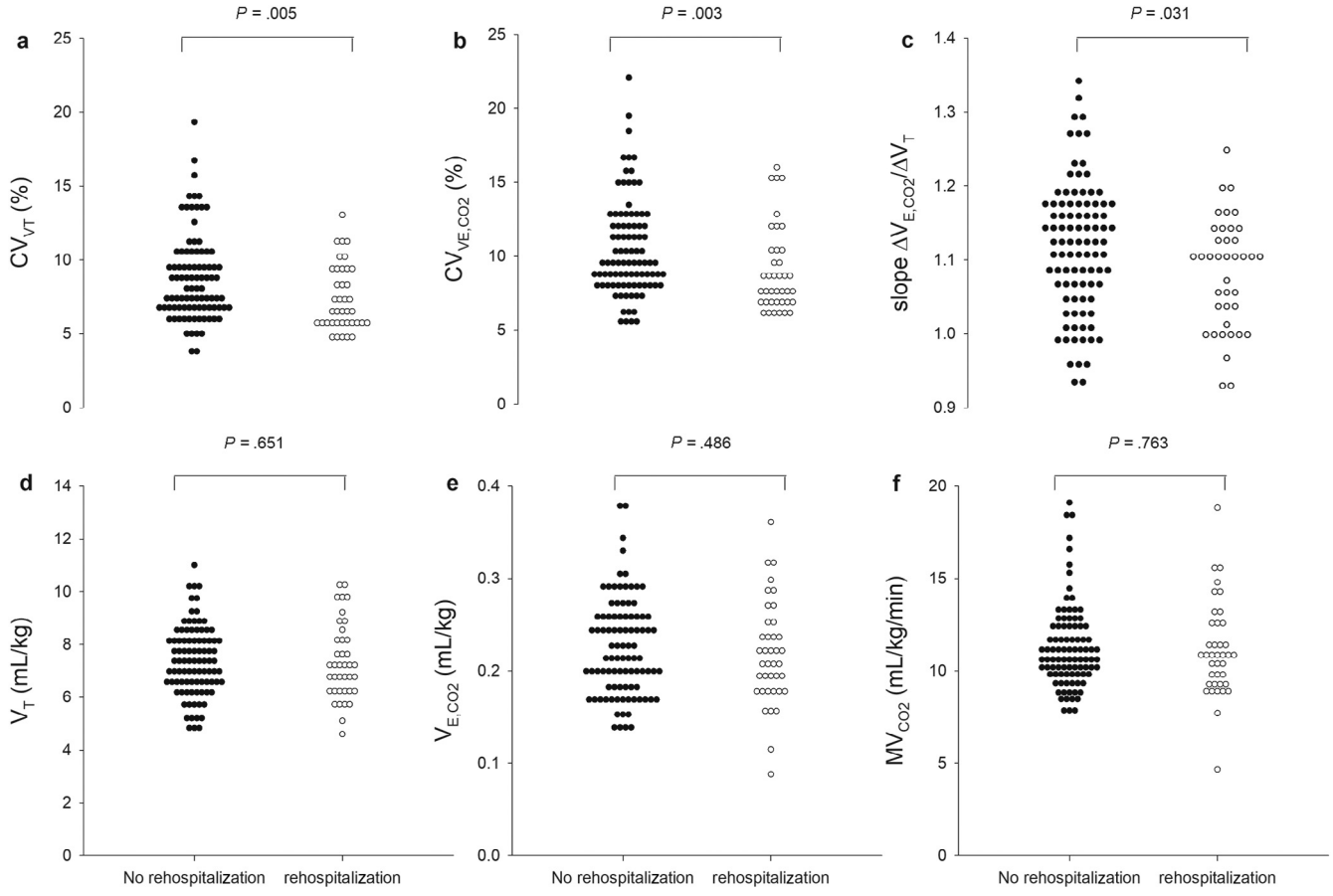

Figure 2. Comparison of lung function parameters between hospitalized and nonhospitalized preterm infants. Shown are boxplots of **A,** CV_{VT}; **B,** $CV_{VE,CO2}$; **C,** slope $\Delta V_{E,CO2}/\Delta V_T$; **D,** V_T; **E,** $V_{E,CO2}$; and **F,** MV_{CO2} at 44 weeks postmenstrual age, stratified by the outcome rehospitalization. The p values refer to the t test comparing rehospitalized and nonrehospitalized preterm born infants during the first year or life.

performed in unsedated infants at the bedside using portable devices. Therefore, CV_{VT} and $CV_{VE,CO2}$ measured near term may hold promise as predictors of respiratory morbidity during the first year of life in preterm born infants.

A limited number of studies[3,6,29] have used infant lung function parameters to predict subsequent respiratory morbidity in preterm born infants; however, these studies did not investigate the predictive value of CO_2 clearance variability. Our study was based on a large prospective cohort of preterm infants who underwent lung function measurements at 44 weeks PMA using standardized methodology. Infants were studied during natural sleep, which best reflects the natural state of breathing in infancy; this is particularly important because the variability of breathing parameters may be significantly influenced by sedation.[16] A minimum of 100 tidal breaths were recorded, providing more robust estimates of variability compared with the 30-breath recordings recommended in the literature.[23]

Using the same cohort, our group previously investigated the association of tidal breathing and inert gas washout test parameters with subsequent respiratory morbidity.[3] Other, more sophisticated and technically demanding lung function parameters (lung volume, lung clearance index) as assessed by inert gas washout test have not been identified as reliable predictors for subsequent respiratory morbidity in this population.[3] However, a significant association of decreased RR accompanied by higher V_T with wheezing during infancy has been reported.[3] Drysdale et al assessed the lung function of preterm infants at 36 weeks PMA and studied the associations with hospital admissions owing to viral lower respiratory tract infections in the first year of life.[29] The investigators reported higher airway resistance at 36 weeks PMA only in infants who were subsequently hospitalized with respiratory syncytial virus infections, but not in those hospitalized because of other respiratory viruses.[29] Lung function measurements were performed with another, technically more demanding technique (the single-breath occlusion technique) at an earlier PMA compared with our cohort; therefore, these findings cannot be directly compared with ours. Bentsen et al used the electromagnetic inductance plethysmography method (EIP) to study the association of tidal breathing parameters with rehospitalization.[6] Using a prediction model consisting of lung function measures (ratio of tidal expiratory flow at 50% of

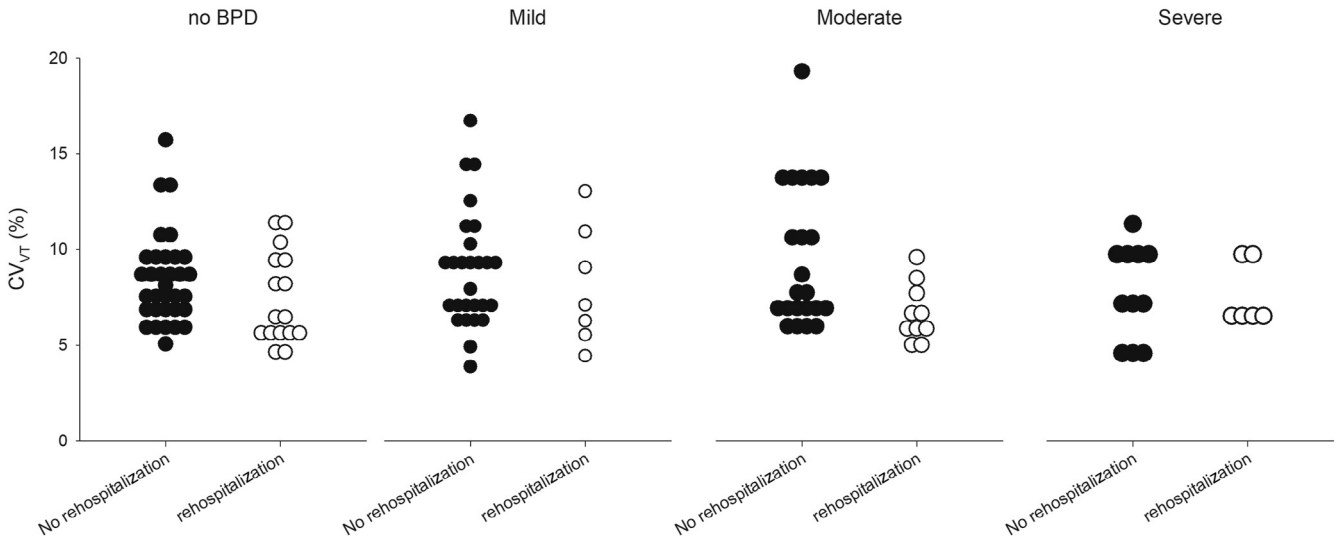

Figure 3. Comparison of CV_{VT} between hospitalized and nonhospitalized preterm infants across BPD severity grades. There was no difference in CV_{VT} between hospitalized (white circles) and nonhospitalized (black circles) preterm infants across infants with no (n = 49), mild (n = 34), moderate (n = 32), and severe (n = 18) BPD.

expired volume to peak tidal expiratory flow (TEF_{50}/PTEF), VT/kg,) and clinical parameters (BPD, birth weight, and sex), the authors reported an AUC of 0.818 to predict rehospitalization during the first year of life.[6] These lung function parameters were acquired in a small group of 35 extremely preterm infants, which may limit their generalizability. Although our direct lung function measurements are more accurate to quantitatively assess absolute V_T, EIP may be quite well suited for timing indices and variability indices (relative changes). Thus, our findings also may have relevance for future EIP studies and clinical applications.

The breathing pattern is naturally irregular in infancy. In very young preterm born infants, the exaggeration of this variability may be associated with an increased risk of apnea.[30] Near term, the structural and functional characteristics of the lung become more important than the autonomic control of breathing. Therefore, at this age, the variability of tidal breathing may provide information on lung mechanics, O_2 consumption, and CO_2 elimination.[31,32] Young infants have increased breathing variability due to their dynamic end-expiratory level and the proximity of their functional residual capacity to closure volume. Infants actively elevate their end-expiratory level to keep their small airways and alveoli open by using postinspiratory muscle activity, increasing breathing frequency, and adjusting upper airway resistance.[33] These breath-by-breath adaptations are altered in BPD,[34,35] where lung maturation occurs in a nonphysiological way, leading to structural alterations of lung periphery with well-known functional consequences in terms of airway obstruction,[6,36] lung restriction,[6,36-38] and reduced gas diffusion capacity.[39] Our group previously reported reduced variability in V_T and capnographic parameters in infants with moderate or severe BPD compared with their non-BPD counterparts.[18] This finding may reflect lung restriction[40] and/or structural simplification of lung periphery resulting in reduced efficiency in CO_2 elimination.[18] Moreover, the reduced variability may indicate that the range of working points at which the respiratory system can efficiently match the body's O_2 consumption and CO_2 elimination is narrower, and thus the system is less flexible. Therefore, because breath-to-breath variability of V_T and $V_{E,CO2}$ is likely influenced by the interplay of these factors, CV_{VT} and $CV_{VE,CO2}$ can be considered indirect markers of lung functional abnormalities in preterm infants and also may be considered markers for later respiratory outcome. Future studies are needed to evaluate whether these parameters can be extrapolated to a younger age (eg, at 36 weeks PMA), when the immaturity of breathing control mechanisms play the dominant role.

We hypothesized that reduced V_T and $V_{E,CO2}$ variability may reflect a reduced adaptability to environmental conditions. This

Table V. Additional value of adding variability of lung function parameters for predicting rehospitalization during the first year of life compared with a model including only BPD

Parameters	AUC	LRT
BPD	0.557	
BPD + CV_{VT}	0.657	0.008
BPD + $CV_{VE,CO2}$	0.662	0.014
BPD + slope $\Delta V_{E,CO2}/\Delta V_T$	0.616	0.063
BPD + CV_{RR}	0.644	0.060
BPD + CV_{VT} + $CV_{VE,CO2}$ + slope $\Delta V_{E,CO2}/\Delta V_T$ + CV_{RR}	0.680	0.026

LRT, likelihood ratio test.
Prediction of rehospitalization using BPD classification alone and in combination with variability of different lung function parameters. The AUC of the logistic regression models is shown. Models were adjusted for sex, gestational age, weight gain (in SDS), duration of positive-pressure support (days of mechanical ventilation plus days of continuous positive airway pressure), and weight (in SDS) at lung function test date. Models including variability of lung function parameters were compared with the corresponding model with only BPD as a predictor using the LRT. $P < .05$ suggests that the given model fits the data significantly better than the model with only BPD as a predictor.

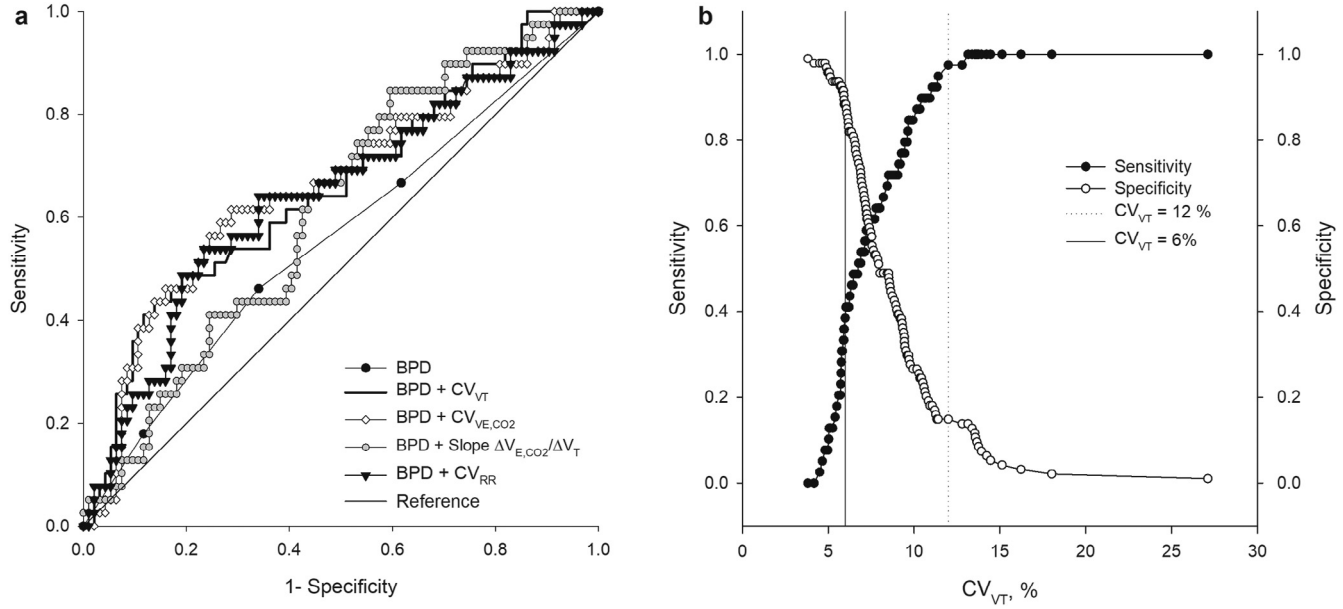

Figure 4. Sensitivity and specificity of BPD and lung function parameters for predicting hospitalization. **A,** Receiver operating characteristic curves comparing the basic model with BPD classification alone to models with CV_{VT}, $CV_{VE,CO2}$, the slope $\Delta V_{E,CO2}/\Delta V_T$, and CV_{RR} each added separately. The models are for prediction of rehospitalization during the first year of life. The lower left corner represents healthy infants with a higher CV, and the upper right corner represents sicker infants with lower values for the assessed parameters. **B,** Sensitivity and specificity differed considerably depending on the CV_{VT} value. At a CV_{VT} of 6%, sensitivity was 41% and specificity was 88%; at a CV_{VT} of 12%, specificity increased to 97%, but sensitivity decreased to 15%.

idea is consistent with the clinical observation that preterm born infants (even those with severe BPD) exhibit compensated gas exchange under normal conditions, although they breathe at their functional limits,[41] but when they experience a viral respiratory infection, they tend to decompensate rapidly, thus requiring hospitalization.

We acknowledge some limitations to our study. The device used for tidal breathing measurements (Exhalyzer D) has only limited applications in a clinical setting owing to its complex calibration algorithms. However, easy-to-apply devices have been developed and are currently being tested to assess the variability of tidal breathing in clinical settings.[42] The outcome parameters were assessed using retrospective questionnaires, thereby carrying the risk for reporting bias. However, there is little chance of reporting bias with the main outcome of rehospitalization due to the intensity of the event. From the initially recruited infants, only 51% were included in the final analysis. This high exclusion rate was attributed mainly to the systematic and rigorous quality control applied to our lung function tests, which let us exclude nearly 30% of the study sample. Infants lost to follow-up had a lower gestational age and birth weight, lower 5-minute Apgar scores, and a longer duration of respiratory support. This selection bias may have resulted in follow-up of infants with less severe BPD and a lower prevalence of respiratory outcomes (eg, rehospitalization, wheezing). Because of this selection bias, our methodology was applied in infants with less severe pulmonary disease and a larger birth weight, and thus our conclusions are not applicable to severely ill preterm born infants. Investigating tidal breathing variability in these infants would be of interest to assess whether our methodology is also applicable in infants with more severe pulmonary disease to predict later respiratory outcomes. However, performing lung function tests during natural sleep in that specific patient group, as was done in this study, may be challenging and result in a low success rate.

Although recent advances in perinatal care have resulted in higher survival rates of preterm infants, this did not affect the prevalence of BPD,[43] which represents an important factor in respiratory morbidity after hospital discharge.[4] Identification of infants at risk remains challenging, given that several studies have shown that the standard BPD classification cannot predict later outcomes.[3,6] In our study, the BPD score alone indeed had limited ability to estimate subsequent respiratory morbidity, and the addition of V_T and/or CO_2 variability to the predictive model improved its performance only modestly. This limited predictive value may reflect the fact that other, unmeasured factors have important influences on the rehospitalization of preterm infants with and without BPD during the first year of life.

In conclusion, we found that the variability in tidal breathing and CO_2 clearance was associated with early respiratory morbidity in preterm born infants. The strongest association was between a lower CV during tidal breathing and an increase in the risk of rehospitalization during the first year of life. Our results suggest that low variability of tidal breathing parameters in preterm infants is an expression of impaired lung function and gas exchange and can be used to identify infants at elevated risk for rehospitalization early in life. Reasons

underlying changes in variability, the optimal time point of lung function measurements, and its predictive value for other respiratory outcomes (eg, wheezing) or more objective measures (eg, lung function) await exploration in future studies. ■

Submitted for publication Jun 25, 2018; last revision received Sep 4, 2018; accepted Oct 2, 2018

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *The Journal of Pediatrics*

The Role of Marihuana in Patterns of Drug Abuse by Adolescents

Milman D. J Pediatr 1969;74:283-90

In the 1960s, the spreading use of marijuana and other drugs into high schools, colleges, and the armed forces serving in Vietnam lead to a clamor for legislative changes regarding marijuana distribution and use; this remains a topic of debate to this day.

In this case series, the author evaluates the use of marijuana among adolescents in relation to the development of schizophrenia and other chronic deleterious effects. The author contends that marijuana use was the precipitating event that lead to an episode of acute psychosis in 11 youths, an argument that had previously been proposed by Keeler regarding adverse reactions in college students using marijuana.[1] The author contends that marijuana should be considered a threat to adolescents, particularly those with preexisting personality disorders who may be predisposed to develop schizophrenia.

Half a century later, the mechanism of cannabis use as a trigger for the development of an acute psychotic episode and subsequent schizophrenia remains both unclear and contested. What has been established is that the high comorbidity rate of substance abuse in patients with schizophrenia, in particular marijuana, has been linked to worse clinical outcomes, such as increased loss of gray matter in the brain.[2] Marijuana use among individuals with psychosis is nearly 3-fold higher than in the general population and has been associated with earlier age of onset of psychosis.[3] With recent increases in cannabis use among 8th-12th graders to 24% in 2017 and the changing topography of marijuana legalization, Milman's original concerns about marijuana use among adolescents at risk for psychotic disorders remains valid 50 years later.[4]

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Table II. Comparison of infants followed up and those lost to follow-up

Parameters	Followed up (n = 133)	Lost to follow-up (n = 130)	*P* value
Clinical perinatal parameters			
Male sex, n (%)	77 (58)	83 (64)	.32
Gestational age at birth, wk, mean ± SD	29.1 ± 2.8	28.6 ± 3.0	.14
Birth weight, kg, mean ± SD	1.19 ± 0.52	1.10 ± 0.51*	.05
Length at birth, cm, mean ± SD	37.9 ± 4.2†	37.1 ± 4.9‡	.17
Apgar score at 5 min, mean ± SD	7.7 ± 1.7*	7.2 ± 1.9§	.04
Patent ductus arteriosus, n (%)	55 (41)	67 (52)	.1
Clinical postnatal parameters			
Positive-pressure support, d, mean ± SD	25.5 ± 21.4	35.2 ± 29.6	.02
Duration of mechanical ventilation, d, mean ± SD	5.0 ± 9.5	9.0 ± 16.7¶	.02
Duration of CPAP, d, mean ± SD	20.5 ± 18.4	25.9 ± 21.9¶	.07
Oxygen therapy from birth, d, mean ± SD	51.8 ± 56.6	78.2 ± 81.4**	.001
Weight at study date, kg, mean ± SD	3.88 ± 0.78	3.94 ± 0.95††	.88
Weight at study date, SDS, mean ± SD	−1.02 ± 1.33	−1.21 ± 1.19‡‡	.26
Weight gain, SDS, mean ± SD	−0.3 ± 1.8	−0.3 ± 1.6§§	.95
Length at study date, cm, mean ± SD	52 ± 3	52 ± 4.1¶¶	.97
Postmenstrual age at study date, wk, mean ± SD	44.6 ± 1.9	45.2 ± 4.6††	.16

CPAP, continuous positive airway pressure.
Clinical postnatal parameters at the study date were assessed at the lung function measurements at 44 weeks PMA. Comparisons between groups were performed using the Student *t* test, Kruskal–Wallis test, or χ^2 test as appropriate.
*Data missing for 1 subject.
†Data missing for 15 subjects.
‡Data missing for 22 subjects.
§Data missing for 3 subjects.
¶Data missing for 4 subjects.
**Data missing for 7 subjects.
††Data missing for 20 subjects.
‡‡Data missing for 25 subjects.
§§Data missing for 27 subjects.
¶¶Data missing for 26 subjects.

Table IV. Associations among variability indices, CO_2 elimination, and subsequent respiratory symptoms during the first year of life (n = 133)

	Univariable association			Multivariable association*		
Parameters	OR	95% CI	*P* value	OR	95% CI	*P* value
Outcome: wheezing† (61 of 133) exposure						
$CV_{VE,CO2}$, %	1.14	0.78-1.65	.50	1.05	0.69-1.58	.83
CV_{VT}, %	1.05	0.75-1.47	.77	0.96	0.67-1.37	.81
MV_{CO2}, mL/kg/min	1.29	0.86-1.92	.21	1.21	0.77-1.88	.41
Slope $\Delta V_{E,CO2}/\Delta V_T$	1.15	0.73-1.82	.55	1.13	0.67-1.91	.65
CV_{RR}, %	1.01	0.72-1.43	.91	1.12	0.77-1.61	.54
Outcome: inhalation therapy‡ (53 of 133) exposure						
$CV_{VE,CO2}$, %	1.42	0.90-2.23	.13	1.45	0.88-2.39	.14
CV_{VT}, %	1.42	0.92-2.20	.11	1.44	0.90-2.29	.13
MV_{CO2}, mL/kg/min	1.43	0.93-2.19	.10	1.37	0.88-2.15	.17
Slope $\Delta V_{E,CO2}/\Delta V_T$	0.83	0.52-1.32	.43	0.82	0.49-1.38	.46
CV_{RR}, %	1.02	0.72-1.43	.91	1.01	0.71-1.44	.97

OR and 95% CI per IQR decrease for each exposure determined by logistic regression.
*Adjusted for the following variables: sex, gestational age, weight gain (in SDS), duration of positive-pressure support (days of mechanical ventilation plus days of continuous positive airway pressure), and weight (in SDS) at lung function test date.
†Defined as any wheezing during the first year of life.
‡Defined as inhalation therapy with beta-agonists for >4 weeks during the first year of life.