Volumetric Capnography in Infants with Bronchopulmonary Dysplasia

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Objectives To assess the feasibility of using volumetric capnography in spontaneously breathing small infants and its ability to discriminate between infants with and without bronchopulmonary dysplasia (BPD).

Study design Lung function variables for 231 infants (102 term, 52 healthy preterm, 77 BPD), matched for post-conceptional age of 44 weeks, were collected. BPD was defined as supplemental oxygen requirement at 36 weeks post-menstrual age. Tidal breath-by-breath volume capnograms were obtained by mainstream capnography. The capnographic slope of phase II (S_{II}) and slope of phase III (S_{III}) were calculated and compared between study groups. The effect of BPD, tidal volume (V_T), respiratory rate (RR), and prematurity on the magnitude of the slopes was assessed.

Results S_{II} was steeper in infants with BPD (100 ± 28/L) compared with healthy preterm (88 ± 22/L; P = .007) and term infants (79 ± 18/L; $P < .001$), but this finding was attributed to differences in V_T, RR, and gestational age. S_{III} was steeper in the BPD group (26.8 ± 14.1/L) compared with healthy preterm (16.2 ± 6.2/L; $P < .001$) and term controls (14.8 ± 5.4/L; $P < .001$). BPD was a significant predictor of S_{III} independently of V_T, RR, and gestational age. The ability of S_{III} to discriminate between BPD and controls was significantly higher compared with lung clearance index (area under the curve 0.83 vs 0.56; $P < .001$).

Conclusions Volumetric capnography may provide valuable information regarding functional lung alterations related to BPD and might be considered as an alternative to more involved lung function techniques for monitoring chronic lung disease during early infancy. *(J Pediatr 2014;164:283-8)*.

Despite advances in prenatal and neonatal care, bronchopulmonary dysplasia (BPD) continues to be a major complication for the increasing number of extremely preterm neonates who survive.[1,2] Arrested alveolar growth is the pathologic hallmark of the contemporary disease, with enlarged airspaces and decreased alveolar numbers, disturbed septation, and various degrees of vascular injury.[3] This marked simplification of the lung periphery has certain functional consequences, which are reflected to various degrees by deviations in lung function, such as changes in lung volumes,[4-7] pulmonary mechanics,[5,7,8] and ventilation distribution.[4-7] However, lung function measurements during early infancy may be equally influenced by prematurity at one end and chronic lung disease at the other end of the spectrum and, as such, they cannot accurately reflect the severity of BPD.[4-8] Moreover, the direct functional consequences of the simplification in acinar structure are difficult to measure and have not been targeted in infants surviving extreme prematurity to date.

Volumetric capnography is a simple bedside technique that is used to provide information on deadspace ventilation and ventilation-perfusion (V'/Q') matching.[9-13] The volume-based capnogram is the breath-by-breath plot of expired CO_2 fraction against expired volume (V_E), and is typically divided into three phases[11]: phase I, which reflects the expiration of CO_2-free gas from the upper airways; phase II, which is characterized by a rapid S-shaped CO_2 increase due to the transition between airway and alveolar gas; and phase III, which is referred to as the alveolar plateau and reflects the expiration of alveolar gas. The slope of phase II (S_{II}) and slope of phase III (S_{III}) have been used to describe changes in the capnographic profile related to underlying respiratory pathology.[10-14] The magnitude of these slopes is substantially influenced by tidal volume (V_T) and respiratory rate (RR),[9,15-17] which may hinder the interpretation of capnography in infants and small children.[9] However, modeling studies of pulmonary CO_2 washout have shown that S_{III} is particularly dependent on the structural complexity of the acinus, and that this relationship is more evident for smaller V_T independently of RR.[16,17] In this regard, the simplified acinar structure in BPD[2,3] provides an ideal opportunity to examine the effect of hampered alveolar growth on the magnitude of S_{III} and the shape of the capnogram.

BPD	Bronchopulmonary dysplasia	S_{III}	Slope of phase III
$F_{E,CO2}$	Mixed expired CO_2 fraction	S_{nII}	Normalized S_{II}
$F_{et,CO2}$	End-expiratory CO_2 fraction	S_{nIII}	Normalized S_{III}
KPIv	Capnographic index	V_E	Expired volume
LCI	Lung clearance index	$V_{E,CO2}$	Expired CO_2 volume per breath
MBW	Multiple-breath washout	V'/Q'	Ventilation-perfusion
MM	Molar mass	$V_{ds,aw}$	Airway dead space
RR	Respiratory rate	V_T	Tidal volume
S_{II}	Slope of phase II		

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The aim of the present study was to examine the hypothesis that specific capnographic indices may reflect functional lung alterations related to BPD better than more complex lung function techniques, such as multiple-breath inert-gas washout. Based on this premise, we analyzed lung function data from a large cohort of spontaneously breathing term and preterm infants and explored the ability of volumetric capnography to discriminate between infants with and without BPD. With this approach, we were also able to explore the feasibility of a simpler and less time-consuming method, which utilizes an endogenous gas and does not require complicated procedures and advanced technical skills that are often not available.

Methods

This cross-sectional observational study was based on previously-collected lung function data from healthy term and preterm infants with and without BPD, matched for a post-conceptional age of 44 weeks and recruited from 1999-2007 within the region of Bern, Switzerland. The study protocol was approved by the Bernese Cantonal Ethics Committee and written informed parental consent was obtained for each subject prior to enrollment.

Term-born participants were infants without postnatal respiratory morbidities recruited within a prospective birth cohort study.[18] Preterm participants were infants born at <37 weeks gestation admitted to the University Children's Hospital of Bern. BPD was defined as supplemental oxygen requirement at 36 weeks post-menstrual age. The healthy-preterm group consisted of preterm infants with a duration of supplemental oxygen requirement of <21 days. Infants with congenital heart disease, neuromuscular disorders, and chromosomal aberrations, as well as those with a history of lower respiratory tract infection, were excluded. Information regarding demographics, clinical prenatal and perinatal data, and postnatal respiratory outcomes (**Table I**; available at www.jpeds.com) was obtained during the initial hospital stay and at the time of lung function measurement.

Lung Function Measurements

Lung function measurements were performed by specialized study nurses and physicians at the Infant Lung Function Laboratory of the University Children's Hospital of Bern, using a commercially available device (Exhalyzer D; EcoMedics AG, Dürnten, Switzerland) incorporating an ultrasonic flowmeter and a mainstream CO_2 sensor (single beam infrared technology; range 0%-14%; rise time <120 ms; sampling rate 100 Hz) and an infant face mask (size 1; Homedica AG, Cham, Switzerland). Details on the technical characteristics of the ultrasonic flowmeter have been published elsewhere.[19] The CO_2 sensor was placed between the flowmeter and the face mask. The deadspace of the measurement head (including the CO_2 sensor) and that of the face mask were previously determined to be 3.5 and 7.5 mL, respectively.[20]

All measurements were performed with the infants in supine position during quiet natural sleep after regular feeding and according to American Thoracic Society/European Respiratory Society standards.[21] After allowing for adjustment of breathing pattern, 10 minutes of tidal breathing were recorded, followed by three multiple-breath washout (MBW) measurements using 4% sulfur hexafluoride as previously described.[19,22] In each case, a subset of 100 consecutive regular breaths, carefully inspected to exclude sighs or variability in breathing pattern indicative of non-quiet sleep, was used for tidal breathing analysis. Functional residual capacity at the airway opening and lung clearance index (LCI) were measured via MBW.

Volumetric Capnography

Volume-based capnograms were obtained by plotting the momentary CO_2 fraction against the corresponding V_E after correcting for signal delay. Details regarding correction for signal delay and calculation of capnographic indices are presented in the **Appendix** (available at www.jpeds.com). S_{II} and S_{III} were calculated by fitting a linear regression line over empirically chosen intervals as follows: (1) for S_{II} between 5% and 60% of the end-expiratory CO_2 fraction ($F_{et,CO2}$),[10] and (2) for S_{III} between 65% and 95% of V_E. The 65% V_E cutoff was chosen based on previously published data from spontaneously breathing neonates[23] in order to ensure that the starting point of S_{III} would be on the 'alveolar' phase of the capnogram. The 95% V_E end point was chosen to exclude the very final part of the capnogram in which cardiogenic oscillations may appear.[9] The expired CO_2 volume per breath ($V_{E,CO2}$) was calculated by integrating the CO_2 concentration curve over V_E, and the mixed expired CO_2 fraction ($F_{E,CO2}$) as $V_{E,CO2}/V_E$. S_{II} and S_{III} were normalized by the corresponding $F_{E,CO2}$ (normalized S_{II} (S_{nII}) and normalized S_{III} [S_{nIII}], respectively) in order to allow comparisons among different rates of CO_2 exhalation.[9,17] S_{III}/S_{II}, also known as the capnographic index (KPIv), was calculated and $F_{et,CO2}$ was also noted. The airway dead space ($V_{ds,aw}$) was obtained by the equal-area method as proposed by Fowler.[24] Breaths with V_E <2.5% or >97.5% of each participant's V_E distribution were not included in the analysis. Capnograms in which slope or $V_{ds,aw}$ calculation failed were also excluded. All indices were calculated breath-by-breath and averaged. Construction of volume-based capnograms, calculation of capnographic indices, and application of quality control criteria were performed automatically using algorithms implemented in the language and environment for statistical computing 'R'.[25]

Statistical Analyses

Categorical variables were compared using chi-square test. Continuous variables were compared by *t* test or one-way ANOVA (multiple group comparisons) with Bonferroni correction. A posterior power analysis showed that both sample size and between-groups distribution of cases were adequate to achieve a statistical power of 97.3% given the observed differences in S_{nIII} (**Table II**). The effect of