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Determinants of pulmonary dead space in ventilated newborn infants

Abstract

Background: Pulmonary dead space (V_D) is an index of ventilation inhomogeneity and one of the determinants of the magnitude of tidal volume to maintain optimal blood gases.

Aims: To identify the determinants of V_D in ventilated newborns and to investigate differences in V_D between prematurely born and term infants and those prematurely born infants who did or did not develop bronchopulmonary dysplasia (BPD).

Methods: Sixty-one mechanically ventilated infants (15 term, 46 preterm) were studied at a median age of 8 (IQR 2-31) days; 32 of the preterm infants developed BPD. V_D was determined from the difference between arterial and end tidal carbon dioxide (CO_2) using a low dead space CO_2 detector using the Bohr/Enghoff equation and was related to body weight (V_D/kg) at the time of study. The time to peak tidal expiratory flow/expiratory time (T_{PTEF}/T_E) was measured during spontaneous breathing using a fixed orifice pneumotachograph.

Results: V_D/kg was related to gestational age ($r=-0.285$, $p=0.001$), birth weight ($r=-0.356$, $p<0.001$), weight ($r=-0.316$, $p<0.001$) and postmenstrual age ($r=-0.205$, $p=0.020$) at measurement, days of ventilation ($r=0.322$, $p<0.001$) and T_{PTEF}/T_E ($r=-0.397$, $p=0.003$). The median V_D/kg was higher in prematurely born infants [2.3 (IQR: 1.7-3.0) ml/kg] compared to term infants [1.5 (1.3-2.1) ml/kg, ($p=0.003$)] and in premature infants that developed BPD [2.6 (IQR 1.8-3.4) ml/kg] compared to those who did not [1.7 (IQR 1.1-1.9) ml/kg], ($p<0.001$).

Conclusions: Numerous factors influence pulmonary dead space and thus an optimum tidal volume will differ according to the underlying demographics and respiratory status.

Introduction

Pulmonary dead space (V_D) is an index of pulmonary inhomogeneity and is the sum of anatomical dead space (nose, pharynx and conducting airways) and the alveolar dead space that is, ventilated alveoli that do not receive blood flow [1]. It is the fraction of the tidal volume that does not participate in gas exchange [2]. Delivery of inappropriately high tidal volumes during mechanical ventilation can lead to alveolar over distention and contribute to the development of bronchopulmonary dysplasia (BPD) [3]. An inappropriately low V_T is also disadvantageous as it is associated with prolonged mechanical ventilation and a pro-inflammatory state [4]. Hence, it is important to be able to assess the magnitude of V_D .

V_D has been successfully used to predict survival in adults with acute respiratory distress syndrome [5], however, few studies have reported values of V_D in ventilated infants: Schmalisch et al measured V_D in 22 ventilated infants with a median gestation of 34.5 weeks and reported a median V_D /kg of 2.3 ml/kg [2]. They used a combined flow/ CO_2 detector with a dead space of 2.6 ml which, given the small tidal volume of the premature infants, might have impacted on the results via rebreathing from the apparatus dead space [6]. In another study, the molar mass signal of an ultrasonic flow meter was used in 43 ventilated neonates with a mean gestational age of 28 weeks and a mean V_D of 2.51 ml/kg was reported [7]. It has also been demonstrated that the ratio of V_D/V_T is higher in prematurely born infants and influences the results of the lung clearance index in term and prematurely born ventilated infants with and without BPD [8].

Recent technological advances in sensitive, low-dead space carbon dioxide detectors have enhanced the reliability of real time pulmonary function monitoring as an adjunct to clinical decision making. Our aim was using such a system to assess the clinical determinants of V_D , as such data have not been previously reported in ventilated newborns. In addition, we wished to determine whether V_D correlated with abnormal airway function as assessed by the time to peak tidal expiratory flow as a proportion of the total expiratory time (T_{PTEF}/T_E). Furthermore, we aimed to determine whether V_D differed between preterm and term infants or between those who subsequently did or did not develop

BPD. Such results would be important as they would inform the determination of the optimal targeted tidal volume, as a higher V_D would necessitate a higher delivered tidal volume [9].

Methods

Subjects and Protocol

A retrospective analysis was undertaken of data collected during a study that assessed readiness for extubation using a spontaneous breathing trial (SBT test). Flow, volume and expired carbon dioxide (CO_2) during mechanical ventilation were recorded before the commencement of the SBT. The study was approved by the London – Surrey Borders Research Ethics Committee (REC Reference 15/LO/2111) and written, informed parental consent was obtained.

Infants born without congenital anomalies ventilated at [REDACTED] were included in the study. The infants were ventilated with a Cole's endotracheal tube (size 2.5-3.5 mm) on volume-targeted or pressure-controlled time-cycled ventilation with the SLE5000 neonatal ventilator or the SLE2000 infant ventilator (SLE, Croydon, UK).

The infants were studied when they were clinically stable and ready for extubation. The arterial pressure of carbon dioxide (PaCO_2) was assessed within one hour prior to extubation. Extubation was considered, as per unit policy, if the fraction of inspired oxygen (F_iO_2) was less than 0.4, the infant had acceptable blood gases, that is a $\text{pH} > 7.25$ and a $\text{PaCO}_2 < 8.5$ kPa, and their breathing rate was above the set ventilator rate. Sedation was discontinued at least 12 hours before extubation and all infants less than 34 weeks of postmenstrual age were receiving caffeine. BPD was defined as any need for supplemental oxygen at 36 weeks of postmenstrual age in infants born at less than 32 weeks of gestation and classified to mild, moderate or severe: mild disease was defined as breathing room air, moderate disease was defined as need for supplemental oxygen at $<30\%$ and severe disease was defined as need for $\geq 30\%$ supplemental oxygen and/or positive pressure [10].

Monitoring equipment

A respiratory function monitor (NM3 respiratory profile monitor (RPM) (Philips Respironics, Connecticut, USA) was used. The monitor was connected to a Laptop (Dell Latitude, Dell, Bracknell, UK) with customised Spectra software (3.0.1.6, 2016) (Grove Medical, London, UK). The NM3 RPM had a combined carbon dioxide, pressure and flow sensor which was placed between the endotracheal tube and the ventilator circuit. End-tidal carbon dioxide (ETCO₂) was measured with a Capnostat-5 mainstream, infrared absorption spectroscopy CO₂ sensor with dead space of less than one millilitre (ml) (Philips Respironics, Connecticut, USA).

Calculation of V_D

The measured dead space was calculated from the Bohr/Enghoff equation $V_D = V_T \times (1 - \text{ETCO}_2 / \text{PaCO}_2)$ from patient-triggered mechanical breaths with a plateau during mechanical ventilation where V_T was the expired tidal volume [2]. As the endotracheal tube bypasses part of the anatomical dead space, this modified index of dead space corresponds to the carbon dioxide sensor dead space (less than 1 ml), the endotracheal tube dead space (approximately 0.9 ml) and the part of the anatomical dead space below the endotracheal tube and the alveolar dead space. V_D was corrected for body weight by dividing V_D with the weight at measurement (V_D/kg).

Calculation of T_{PTEF}/T_E

The time to reach peak (maximum) tidal expiratory flow as a proportion of total expiratory time (T_E) (T_{PTEF}/T_E) was measured during the SBT test. The mean T_{PTEF}/T_E ratio was calculated from the mean of at least five breaths with a repeatable flow waveform.

Information from the medical records

Gender, gestational age, birth weight, postmenstrual age, postnatal age and weight at the time of measurement were recorded. A patent ductus arteriosus (PDA) was diagnosed clinically and confirmed by echocardiography. Administration of antenatal corticosteroids was recorded as positive

if at least two doses were given. The $F_{I}O_2$ and the $PaCO_2$ within one hour prior to the measurement were also recorded from the nursing observation charts.

Sample size calculation

The sample size calculation was based on the assumption that a difference in V_T/kg of 0.92 ml/kg between prematurely and term born infants was clinically significant [11]. The standard deviation of V_D/kg was 0.61 ml/kg [7]. Ten subjects in each group enabled detection of a difference in V_D/kg of 0.92 ml/kg between the two groups with 90% power at the 5% level.

Statistical analysis

Data were tested for normality with the Kolmogorov–Smirnov test and found to be non-normally distributed. The relationships of V_D/kg with birth weight, gestational age, weight, postmenstrual age, day of life, $PaCO_2$, days of ventilation and T_{PTEF}/T_E were examined with the Kendall-tau rank correlation coefficient (r). The factors with the highest correlation coefficients with V_D were analysed with bivariate regression analysis and the corresponding curve was constructed. Differences between term and prematurely born infants and differences between prematurely born infants that did or did not develop BPD were assessed for statistical significance using the Mann-Whitney rank sum test or Chi-squared test, as appropriate. The factors that were statistically different (p value <0.05) were inserted into a multivariate logistic regression model with V_D/kg as the outcome. Variables without normal distribution were logarithmically transformed. Multi-collinearity among the independent variables in the regression analysis was assessed by calculation of the tolerance for the independent variables.

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago IL).

Results

Between 1 February 2016 and 1 August 2016, 113 infants were ventilated on the Neonatal Unit. Fifty-two infants were excluded from the study as they had congenital anomalies or were extubated before the SBT could be performed. Sixty one infants were included in the study (Table). Prematurely born infants were ventilated for a longer period compared to term infants and had significantly higher respiratory rates and PaCO₂ levels and lower T_{PTEF}/T_E compared to term infants.

V_D/kg was related to gestational age (r=-0.285, p=0.001), postmenstrual age (r=-0.205, p=0.020), birth weight (r=-0.356, p<0.001), weight at measurement (r=-0.316, p<0.001), postnatal age (r=0.277, p=0.002), PaCO₂ (r=0.194, p=0.028), end tidal CO₂ (r=-0.224, p=0.011), days of ventilation (r=0.322, p<0.001) and T_{PTEF}/T_E (r=-0.397, p=0.003). The relation of V_D/kg against birth weight is presented in figure 1.

Prematurely born infants had higher V_D/kg and V_D/V_T compared to term infants. Multivariate regression analysis revealed that V_D/kg was significantly related to birth weight (Odds ratio: -0.353, 95% Confidence intervals: -0.55- -0.08, p=0.011) independently of respiratory rate and days of ventilation. Infants born at less than 32 weeks of gestational age that developed BPD had significantly lower gestational ages, birth weight, T_{PTEF}/T_E and higher postnatal age, days of ventilation, PaCO₂ and FiO₂ at measurement than the infants who did not develop BPD (Table). The infants of the preterm-BPD group had significantly higher V_D/kg than the infants of the preterm-no BPD group (Table, Figure 2). Eleven out of 32 (34%) of the infants of the preterm-BPD group had a PDA compared to none in the preterm-no BPD group (p=0.014). Twenty-seven out of 32 (84%) of the infants of the preterm-BPD group had antenatal steroids compared to 11 of 14 (79%) in the preterm-no BPD group (p=0.745). Multivariate regression analysis revealed that V_D/kg was significantly higher in the infants of the preterm-BPD group compared to the infants of the preterm-no BPD group (p<0.001) independently of gestational age, FiO₂ at measurement and presence of PDA.

The median V_D/kg in the infants of the preterm-BPD group who developed moderate disease [2.4 (IQR: 1.8-2.9) ml/kg, N=11] was not significantly different compared to the median V_D/kg in the

infants of the preterm-BPD group who developed severe disease [2.7, (IQR: 1.7-4.2) ml/kg, $N=21$, $p=0.197$]. The infants of the preterm-no BPD group did not have significantly different V_D /kg compared to the term infants ($p=0.813$).

Discussion

We have demonstrated that pulmonary dead space in ventilated newborn infants was significantly related to gestation, anthropometry, days of ventilation and expiratory airway function. V_D was higher in prematurely born compared to term infants and higher in prematurely born infants who developed BPD compared to those who did not develop BPD.

Previous studies have reported values of V_D in ventilated newborn infants with different techniques to the one we employed, they had used either higher dead space capnographs [2] or the molar mass signal of an ultrasonic flowmeter [7]. We report values of V_D which are lower in term infants than those previously reported, but they had used higher dead space capnographs, which would have influenced their results [2]. Our study highlights that V_D /kg is significantly higher than that of term born infants in preterm infants, but only in those who develop BPD. We also report a significant association of V_D with the duration of mechanical ventilation. It is known that preterm compared to term infants have a proportionately higher anatomical dead space in relation to their tidal volume [11]. Our results suggest that in certain preterm infants an additional early increase in pulmonary dead space occurs, possibly as a consequence of their evolving lung disease and the effect of mechanical ventilation. Our results highlight the early origins of respiratory morbidity in premature infants as the infants that developed BPD had significantly greater dead spaces at a median postmenstrual age of 29 weeks, which corresponds to seven weeks before the subsequent diagnosis of BPD. Furthermore, the significant association of the size of the dead space with the duration of mechanical ventilation underlines the contribution of ventilator-induced lung injury in the early origin of chronic lung disease in premature infants [12].

In our study, the increased values of V_D might be associated with underlying pathophysiological disturbances: The presence of an intrapulmonary right to left shunt would result in arterial blood gas tensions closer to that of mixed venous blood, thus increasing the apparent V_D by increasing the PaCO_2 . Furthermore, a decreased ventilation/perfusion (V/Q) ratio would increase the alveolar dead space by increasing the venous admixture from lung regions with lower V/Q [13].

We measured tidal volume and end-tidal CO_2 when the median ventilation frequency was in the range of 50-70 per minute. If the ventilator frequency was 40 per minute or lower, in order to maintain minute ventilation, the tidal volume would be higher, resulting thus in a higher end-tidal CO_2 and the calculation of a lower V_D .

We report significantly lower values of T_{PTEF}/T_E in the preterm compared to the term infants, as well as in the prematurely born infants who later developed BPD compared to those who did not. T_{PTEF}/T_E results have been reported in previous studies: Infants who later developed wheezing had significantly lower values of T_{PTEF}/T_E [14], and T_{PTEF}/T_E was significantly lower in infants that developed cough and wheeze during the first year after birth compared to the ones that did not [15].

The strengths of our study include the use of the Capnostat-5 which is a low-dead space, mainstream CO_2 detector which introduced less than one millilitre of apparatus dead space. We measured pulmonary dead space in a cohort of 61 subjects that included extremely prematurely born infants and used the Bohr/Enghoff equation, which is the most reliable method to calculate dead space in extremely low birth weight infants [16]. We also measured T_{PTEF}/T_E in ventilated infants during spontaneous breathing thus avoiding the error relating to mechanical ventilation in our assessment of expiratory airway function. We did not account for “endotracheal tube leak” in our measurements [17] as it is standard practice in our unit to use shouldered endotracheal tubes which minimise any potential leak [18]. Our sample size was adequate to detect differences of V_D that were clinically significant. The infants who developed BPD were born more prematurely than the ones that did not and thus it might be that developing BPD per se was not responsible for the higher dead space, but rather it was related to extreme prematurity. We suggest it is likely to be a combination of those

factors as extremely prematurely born infants are more likely to require prolonged ventilation with its injurious effect on the lung and develop BPD.

In conclusion, numerous factors such as gestation, anthropometry and duration of ventilation influence pulmonary dead space and thus an optimum tidal volume will differ according to the underlying demographics and respiratory status.

Legends to figures

Figure 1: Regression analysis of V_D/kg with birth weight. The regression line and 95% confidence intervals are presented. The type of non-linearity was tested by visual inspection of the residuals and the quadratic model was found to accommodate the best non-linear fit.

△ Preterm-no BPD

■ preterm-BPD

○ term infants

Figure 2: Boxplot of V_D/kg in preterm infants without BPD, preterm infants with BPD and term infants. In each data bar the horizontal line represents the median, the bottoms and tops of the bars represent the 25th and 75th percentiles, and the whisker bars represent the 5th and 95th percentiles.

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Table: Demographics and respiratory parameters. Data are presented as median (IQR) or n (%)

	Premature N=46	Term N= 15	P value	Premature - no BPD N=14	Premature – BPD N= 32	P value
GA (weeks)	26 (25-29)	39 (38-40)	<0.001	30 (28-31)	26 (24-28)	<0.001
PMA (weeks)	30 (27-33)	40 (38-41)	<0.001	31 (29-32)	29 (27-33)	0.860
BW (kg)	0.88 (0.73-1.10)	3.30 (3.00-3.71)	<0.001	1.36 (1.06-1.74)	0.78 (0.63-0.92)	<0.001
Male gender	23 (50)	8 (53)	0.529*	7 (50)	16 (50)	0.847*
Weight (kg)	1.19 (0.93-1.61)	3.43 (3.00-4.28)	<0.001	1.36 (1.22-1.74)	1.03 (0.84-1.44)	0.040
Postnatal age (days)	9 (3-40)	2 (1-6)	0.003	2 (1-4)	24 (8-61)	<0.001
Days of ventilation	8 (2-32)	1 (1-5)	0.003	2 (1-3)	23 (7-47)	<0.001
FiO ₂	0.27 (0.22-0.34)	0.28 (0.21-0.32)	0.429	0.22 (0.21-0.28)	0.28 (0.23-0.39)	0.002
MAP (cmH ₂ O)	8 (7-9)	8 (8-9)	0.922	8 (6-9)	8 (7-9)	0.413
PEEP (cmH ₂ O)	5.6 (4.8-6.2)	5.2 (4.1-5.7)	0.139	5.6 (4.9-6.2)	5.6 (4.7-6.3)	0.989
Backup rate	40 (38-40)	30 (30-40)	0.021	40 (30-40)	40 (40-44)	0.221
Respiratory rate	71 (58-84)	58 (42-68)	0.029	65 (55-85)	74 (61-83)	0.222
T _{PTEF/TE}	0.25 (0.15-0.32)	0.40 (0.35-0.44)	<0.001	0.36 (0.24-0.45)	0.23 (0.15-0.29)	0.018
PaCO ₂ (mmHg)	47 (39-53)	40 (34-43)	0.003	39 (34-47)	50 (44-56)	0.003
ET CO ₂ (mmHg)	27 (20-33)	28 (22-31)	0.802	27 (19-32)	28 (20-34)	0.351
V _T (ml)	6.7 (5.2-8.7)	16.6 (14.8-24.8)	<0.001	6.3 (4.2-7.5)	6.8 (6.0-9.8)	0.082
V _T /kg (ml)	5.4 (4.2-7.5)	5.35 (4.1-6.1)	0.604	4.1 (3.5-4.7)	6.7 (4.9-8.0)	<0.001
V _D (ml)	2.6 (2.0-3.7)	5.1 (4.3-7.9)	<0.001	2.4 (1.7-2.8)	2.9 (2.2-4.8)	0.047
V _D /kg (ml)	2.3 (1.7-3.0)	1.5 (1.3-2.1)	0.003	1.7 (1.1-1.9)	2.6 (1. 8-3.4)	0.001

V_D/V_T	0.39 (0.29-0.56)	0.31 (0.21-0.38)	0.018	0.38 (0.29-0.52)	0.40 (0.29-0.59)	0.668
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Mann Whitney U Test

* Chi Square Test

GA: gestational age, PMA: postmenstrual age, BW: birth weight, FIO₂: fraction of inspired oxygen, MAP: Mean airway pressure on mechanical ventilation, PEEP: Positive end expiratory pressure, T_{PTEF}/T_E: time to peak tidal expiratory flow/expiratory time, PaCO₂: arterial partial pressure of carbon dioxide, ET CO₂ end-tidal carbon dioxide, V_T: inspiratory tidal volume, V_D: dead space.

