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Determinants of pulmonary dead space in ventilated newborn infants

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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.

1. 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

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determination of the optimal targeted tidal volume, as a higher V_D would necessitate a higher delivered tidal volume [9].

2. Methods

2.1. 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 King's College Hospital NHS Foundation Trust 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 1 h prior to extubation. Extubation was considered, as per unit policy, if the fraction of inspired oxygen (F_IO_2) was <0.4, the infant had acceptable blood gases, that is a pH > 7.25 and a $PaCO_2$ < 8.5 kPa, and their breathing rate was above the set ventilator rate. Sedation was discontinued at least 12 h before extubation and all infants <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 <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 ≥30% supplemental oxygen and/or positive pressure [10].

2.2. 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 ($ETCO_2$) was measured with a Capnostat-5 mainstream, infrared absorption spectroscopy CO_2 sensor with dead space of less than one millilitre (ml) (Philips Respironics, Connecticut, USA).

2.3. Calculation of V_D

The measured dead space was calculated from the Bohr/Enghoff equation $V_D = V_T \times (1 - ETCO_2 / PaCO_2)$ 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 (<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).

2.4. 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.

2.5. 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_IO_2 and the $PaCO_2$ within 1 h prior to the measurement were also recorded from the nursing observation charts.

2.6. 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.

2.7. Statistical analysis

Data were tested for normality with the Kolmogorov–Smirnoff 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).

3. 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 1). Prematurely born infants were ventilated for a longer period compared to term infants and had significantly higher respiratory rates and $PaCO_2$ 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 ($r = 0.277$, $p = 0.002$), $PaCO_2$ ($r = 0.194$, $p = 0.028$), end tidal CO_2 ($r = -0.224$, $p = 0.011$), 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 Fig. 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 to −0.08, $p = 0.011$) independently of respiratory rate and days of ventilation. Infants born at <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,