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Physiological and anatomical dead space in mechanically ventilated newborn infants

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Keywords:	Neonatal Pulmonary Medicine, Mechanical Ventilation
Other Keywords:	physiological dead space, anatomical dead space, newborn infants, premature, capnography
Abstract:	<p>Objectives: To compare the anatomical (VD-Ana) and alveolar dead space (VD-Alv) in term and prematurely-born infants and identify the clinical determinants of those indices.</p> <p>Working hypothesis: VD-Ana and VD-Alv will be higher in prematurely born compared to term born infants.</p> <p>Study design: Retrospective analysis of data collected at King's College Hospital NHS Foundation Trust, London, UK. Patient selection: Fifty-six infants (11 term, 45 preterm) were studied at a median age of 8 (IQR 2-33) days.</p> <p>Methodology: VD-Ana was determined using Fowler's method of volumetric capnography. VD-Alv was determined by subtracting VD-Ana from the physiological dead space which was determined by the Bohr-Enghoff equation. VD-Ana and VD-Alv were related to body weight at the time of study.</p> <p>Results: The median VD-Ana/kg was higher in prematurely-born infants [3.7 (IQR: 3.0 – 4.5) ml/kg] compared to term infants [2.4 (IQR: 1.9 – 2.9) ml/kg, adjusted p=0.001]. The median VD-Alv/kg was not higher in prematurely-born infants [0.3 (IQR: 0.1 – 0.5)] compared to term infants [0.1 (IQR: 0.0 – 0.2) ml/kg] after adjusting for differences in respiratory rate and days of ventilation (p=0.482). VD-Ana/kg was related to postmenstrual age (r=-0.388, p<0.001), birth weight (r=-0.397, p<0.001) and weight at measurement (r=-0.476, p<0.001). VD-Alv/kg was related to postmenstrual age (r=-0.254, p<0.001), birth weight (r=-0.291, p=0.002) and weight at measurement (r=-0.281, p=0.003) and related to days of ventilation (r=0.194, p=0.044).</p> <p>Conclusions: VD-Ana/kg and VD-Alv/kg increased with decreasing weight and gestation. VD-Alv was higher in infants that have undergone prolonged mechanical ventilation.</p>

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Physiological and anatomical dead space in mechanically ventilated newborn infants

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Running head: Dead space in newborns

Key words: Physiological dead space, anatomical dead space, newborn infants, premature, capnography

ABSTRACT

Objectives: To compare the anatomical (V_{D-Ana}) and alveolar dead space (V_{D-Alv}) in term and prematurely-born infants and identify the clinical determinants of those indices.

Working hypothesis: V_{D-Ana} and V_{D-Alv} will be higher in prematurely born compared to term born infants.

Study design: Retrospective analysis of data collected at King's College Hospital NHS Foundation Trust, London, UK.

Patient selection: Fifty-six infants (11 term, 45 preterm) were studied at a median age of 8 (IQR 2-33) days.

Methodology: V_{D-Ana} was determined using Fowler's method of volumetric capnography. V_{D-Alv} was determined by subtracting V_{D-Ana} from the physiological dead space which was determined by the Bohr-Enghoff equation. V_{D-Ana} and V_{D-Alv} were related to body weight at the time of study.

Results: The median V_{D-Ana}/kg was higher in prematurely-born infants [3.7 (IQR: 3.0 – 4.5) ml/kg] compared to term infants [2.4 (IQR: 1.9 – 2.9) ml/kg, adjusted $p=0.001$]. The median V_{D-Alv}/kg was not higher in prematurely-born infants [0.3 (IQR: 0.1 – 0.5)] compared to term infants [0.1 (IQR: 0.0 – 0.2) ml/kg] after adjusting for differences in respiratory rate and days of ventilation ($p=0.482$). V_{D-Ana}/kg was related to postmenstrual age ($r=-0.388$, $p<0.001$), birth weight ($r=-0.397$, $p<0.001$) and weight at measurement ($r=-0.476$, $p<0.001$). V_{D-Alv}/kg was related to postmenstrual age ($r=-0.254$, $p<0.001$), birth weight ($r=-0.291$, $p=0.002$) and weight at measurement ($r=-0.281$, $p=0.003$) and related to days of ventilation ($r=0.194$, $p=0.044$).

Conclusions: V_{D-Ana}/kg and V_{D-Alv}/kg increased with decreasing weight and gestation. V_{D-Alv} was higher in infants that have undergone prolonged mechanical ventilation.

INTRODUCTION

The physiological dead space is the part of the tidal volume that doesn't participate in gas exchange and is an index of ventilation inhomogeneity¹. The physiological dead space (V_{D-Phys}) is the sum of the anatomical dead space (V_{D-Ana}) (the conducting non-gas exchanging airways) and the alveolar dead space (V_{D-Alv}) which corresponds to the ventilated alveoli that are not perfused by the pulmonary circulation². The physiological dead space (V_{D-Phys}) is elevated in adults with chronic obstructive pulmonary disease³ and pulmonary embolism⁴ and it has been used to predict mortality in acute respiratory distress syndrome⁵.

Dead space can be calculated using the concentration of carbon dioxide (CO_2) in expired breaths measured by capnography. Few studies, however, have used capnography to calculate dead space in ventilated infants^{6,7} as it has previously been problematic in prematurely born infants because of technical limitations arising from their high respiratory rates and small tidal volumes and the use of un-cuffed endotracheal tubes (ET) as there may be leakage around such ETs^{8,9}. Recently, sensitive, low dead-space CO_2 sensors combined with flow sensors have made the application of real time capnography feasible as a tool to estimate pulmonary dead space at the bedside.

Estimation of the concurrent arterial CO_2 , which is a surrogate for the alveolar CO_2 ², can be used in the calculation of the total physiological dead space and (by subtraction), the corresponding alveolar dead space¹⁰. To our knowledge, the associations of alveolar and anatomical dead space with anthropometric and clinical parameters have not been previously reported using low dead space capnography. We have recently demonstrated that V_{D-Phys} per kilogram of body weight increases with decreasing weight and gestation⁷ but it is not known

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3 whether this relationship is a reflection of lung disease severity or of anthropometric
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5 differences in anatomical dead space. The latter is plausible as it has been shown that term-
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7 born newborn infants have higher anatomical dead space per kilogram compared to older
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9 children ¹¹. Furthermore, it is not known how V_{D-Ana} and V_{D-Alv} change with decreasing
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11 gestation and birth weight and with increasing severity of lung disease.
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16 Our hypotheses were that weight-adjusted V_{D-Alv} and V_{D-Ana} would be higher in prematurely-
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18 born compared to term infants and that these indices will increase with decreasing body
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20 weight and gestation and with increasing duration of mechanical ventilation, used as a proxy
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22 for the severity of lung disease. Our aims were to test these hypotheses using a low-dead
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24 space capnograph and concurrent measurements of arterial CO_2 .
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METHODS

Subjects and protocol

We retrospectively analysed data collected during a study that assessed readiness for extubation using a spontaneous breathing trial (SBT)¹². Flow, volume and expired CO₂ 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. Two groups of infants were recruited: infants born at less than 34 completed weeks of gestation (preterm) and term infants born at equal or more than 37 completed weeks of gestation. The infants were ventilated via Cole's shouldered endotracheal tubes (sizes 2.5 to 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 (PaCO₂) was assessed within 30 minutes prior to extubation. Infants that did not have an arterial CO₂ value 30 minutes preceding the SBT were excluded from the study. Extubation was considered, as per unit policy, if the fraction of inspired oxygen (F_IO₂) was less than 0.4, the infant had a pH > 7.25 and a PaCO₂ < 8.5 kPa and their breathing rate was above the set ventilator rate¹². Sedation was discontinued at least

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3 12 hours before the SBT and all infants less than 34 weeks of postmenstrual age were
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5 receiving caffeine¹³.
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8 9 10 **Measuring equipment**

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12 The NM3 respiratory profile monitor (RPM) (Philips Respironics, Connecticut, USA) was
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14 used to measure flow, volume and the concentration of expired CO₂. The monitor was
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16 connected to a Laptop (Dell Latitude, Dell, Bracknell, UK) with customised Spectra software
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18 (3.0.1.6, 2016) (Grove Medical, London, UK). The NM3 RPM had a combined CO₂ and flow
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20 sensor which was placed between the endotracheal tube and the ventilator circuit. Expired
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22 CO₂ was measured with a Capnostat-5 mainstream, infrared absorption spectroscopy CO₂
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24 sensor with dead space of less than one millilitre (ml) (Philips Respironics, Connecticut,
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26 USA).
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33 **Calculation of V_{D-Ana} and V_{D-Alv}**

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35 The measured physiological dead space (V_{D-Phys}) was calculated from the Bohr/Enghoff
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37 equation: $V_D = V_T \times (1 - P_{E\text{CO}_2} / P_{a\text{CO}_2})$ from patient-triggered mechanical breaths with a
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39 plateau, during mechanical ventilation where V_T was the expired tidal volume and P_ECO₂
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41 was the volume-averaged expired CO₂⁶. The measured V_{D-Ana} was calculated using the
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43 Fowler method of volumetric capnography where the expired CO₂ was plotted against the
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45 expired tidal volume^{14, 15}. The resulting “volumetric capnogram” comprised of three phases:
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47 an initial phase where no CO₂ is expired, a second phase, where expired CO₂ rises rapidly
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49 (indicating the expiration of mixed air from the airways and from the alveoli) and a final
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51 plateau phase which represents pure alveolar gas. A tangent line was constructed at the
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53 alveolar plateau and a vertical line was inserted in the middle of the second phase so that two
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3 equal triangles were created. V_{D-Ana} was measured from the beginning of expiration to the
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5 point where the vertical line crosses the volume axis (Figure 1)¹⁶. The calculation of the V_{D-}
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7 Ana was made by a researcher who was unaware of the demographics of the infants. As the
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9 endotracheal tube bypasses the upper airways, this modified index of dead space corresponds
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11 to the capnograph dead space (less than 1 ml), the endotracheal tube dead space
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13 (approximately 0.9 ml) and the part of the airways below the endotracheal tube. V_{D-Alv} was
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15 calculated by subtracting the V_{D-Ana} from the V_{D-Phys} . The CO_2 and volume signals were
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17 synchronised by aligning the maximum of tidal CO_2 with the end of expiration¹⁷. V_{D-Ana} and
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19 V_{D-Alv} were corrected for body weight at the time of measurement.
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26 **Information from the medical records**

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28 Gender, gestational age, birth weight, postmenstrual age, postnatal age and weight at the time
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30 of measurement were recorded. The F_{IO_2} and the $PaCO_2$ within 30 minutes prior to the
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32 measurement were also recorded from the nursing observation charts.
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38 **Sample size calculation**

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40 The sample size calculation was based on the observation that a difference in tidal volume of
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42 0.92 ml/kg was observed in premature infants between the first and twenty-first day after
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44 birth despite permissive hypercapnia¹⁸. The standard deviation of V_D/kg had been previously
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46 shown to be 0.61 ml/kg¹⁹. Ten subjects in each group enabled detection of a difference in
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48 V_D/kg of 0.92 ml/kg between the two groups with 90% power at the 5% level.
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Statistics

Data were tested for normality with the Kolmogorov–Smirnov test and found to be non-normally distributed. Hence, differences in V_{D-Ana}/kg and V_{D-Alv}/kg between term and prematurely born infants were assessed for statistical significance using the Mann-Whitney rank sum test or Chi-squared test, as appropriate. The factors that were significantly different (p value <0.05) were inserted into a multivariate logistic regression model with V_{D-Ana}/kg or V_{D-Alv}/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. The relationships of V_{D-Ana}/kg and V_{D-Alv}/kg with birth weight, gestational age, weight, postmenstrual age, day of life and days of ventilation were examined with the Kendall-tau rank correlation coefficient (r). The factor with the highest correlation coefficient with V_{D-Ana}/kg was analysed with bivariate regression analysis and the corresponding curve was constructed. The type of non-linearity was tested by visual inspection of the residuals. 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 had congenital anomalies or were extubated before the SBT could be performed and were excluded from the study. In two infants the quality of the traces did not allow for construction of a volumetric capnogram and were excluded from the study. In three infants there was no arterial CO₂ value in the 30 minutes preceding the SBT and were excluded from the study. Fifty-six 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 PaCO₂ levels. Prematurely born infants had higher V_{D-Ana}/kg and V_{D-Alv}/kg compared to term infants. Multivariate regression analysis revealed that V_{D-Ana}/kg was significantly higher in premature compared to term infants (p=0.001) independently of respiratory rate and days of ventilation. Multivariate regression analysis revealed that V_{D-Alv}/kg was not significantly different in premature compared to term infants (p=0.482) after correcting for respiratory rate and days of ventilation.

V_{D-Ana}/kg was negatively related to gestational age (r=-0.274, p=0.003), postmenstrual age (r=-0.388, p<0.001), birth weight (r=-0.397, p<0.001) and weight at measurement (r=-0.476, p<0.001) but not related to days of ventilation (r=0.118, p=0.215), F_IO₂ at measurement (r=0.076, p=0.426) and respiratory rate (r=0.109, p=0.242). The relation of V_{D-Ana}/kg with weight at measurement was best accommodated by the quadratic model (Figure 2).

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3 V_{D-AIV}/kg was negatively related to gestational age ($r=-0.304$, $p=0.001$), postmenstrual age
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5 ($r=-0.254$, $p<0.001$), birth weight ($r=-0.291$, $p=0.002$ and weight at measurement ($r=-0.281$,
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7 $p=0.003$) and positively related to days of ventilation ($r=0.194$, $p=0.044$) but not related to
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9 respiratory rate ($r=0.129$, $p=0.158$) and $F_{I}O_2$ at measurement ($r=0.120$, $p=0.213$).
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DISCUSSION

This study has demonstrated that anatomical dead space is higher in prematurely born ventilated infants compared to their term counterparts. Anatomical and alveolar dead space were significantly related to gestational age and weight at birth and at measurement. Alveolar dead space was also significantly related to the duration of mechanical ventilation.

Values of pulmonary dead space in newborn infants have been reported in previous studies. Numa et al used the water displacement technique to calculate the extrathoracic anatomical dead space in seven full term ventilated infants and reported a mean dead space of 2.33 ml/kg¹¹. Wenzel et al, similar to our study, applied the Fowler method of volumetric capnography in twenty-two ventilated infants with a mean gestational age of 34 weeks and reported a mean anatomical dead space of 1.6 ml/kg⁶. Minocchieri et al constructed an upper airway model corresponding to a premature infant of 32 weeks of gestational age by three-dimensional reconstruction of a magnetic resonance imaging scan and subsequent 3D-printing and reported a dead space of 1.27 ml in an infant of 1.75 kg (0.7 ml/kg)²⁰. Neumann et al used an ultrasonic flowmeter and reported a mean anatomical dead space of 2.51 ml/kg in a cohort of forty-three ventilated infants of a mean gestational age of 28 weeks¹⁹. We report higher median anatomical dead spaces of 2.4 ml/kg in term and 3.7 ml/kg in prematurely born infants. This might be explained by equipment differences. We used a low dead space capnograph, which results in less apparatus dead space rebreathing, a lower expired CO₂ and a higher arterial to exhaled CO₂ gradient and hence a calculation of a higher anatomical dead space.

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3 To our knowledge, only one recent previous study has reported values of alveolar dead space.
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5 Wenzel et al ⁶, in infants of a median gestational age of 34 weeks, reported a mean V_{D-Alv} of
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7 0.96 ml/kg in infants weighing less than 2.5 kg and 0.49 ml/kg in infants weighing more than
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9 2.5kg. We report a smaller mean V_{D-Alv} of 0.1-0.3 ml/kg. The difference in findings might be
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11 explained by differences in respiratory status as our cohort's respiratory status was
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13 sufficiently improved that they were considered ready for extubation, whereas in Wenzel's
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15 cohort half of the infants were still ventilated two days after the initial measurement.
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20 Our study has a number of strengths and some limitations. The CO₂ sensor had a low
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22 apparatus dead space and its mainstream position in the respiratory circuit allowed for a faster
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24 response time even at high respiratory rates ²¹. Another strength is that we studied a cohort
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26 that consisted of both term and extremely prematurely born infants. In addition, we routinely
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28 use shouldered endotracheal tubes that minimise leak ²², high leak would introduce
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30 significant error to the measurements via shortening of the plateau phase of the expired CO₂
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32 ²³. A limitation is that we only included infants well enough to be considered ready for
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34 extubation. In a future study it would be interesting to determine the V_{D-Alv} in infants with
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36 acute respiratory distress. We did not deduct the endotracheal tube dead space in our
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38 calculation of anatomical dead space as in clinical practice real-time values of tidal volume
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40 include the apparatus dead space. However, this would be a fixed volume and changes of
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42 anatomical dead space over time would not be affected by this method if each patient is
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44 acting as their own control.
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52 V_{D-Alv} was significantly related to the duration of mechanical ventilation. This might be
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54 explained by either that alveolar dead space progressively increases due to over distension
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3 and ventilator induced lung injury²⁴ and/or that infants with more severe lung disease remain
4 ventilated for longer periods and the duration of mechanical ventilation is a reflection of the
5 severity of the underlying lung disease.
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13 It has been postulated that the higher anatomical dead space in infants compared to older
14 children might be a predisposing condition that places infants at higher risk of sudden infant
15 death syndrome (SIDS) due to rebreathing of dead space and the ensuing hypercapnia¹¹.

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17 From our results, it is plausible that the relatively higher V_{D-Ana} in premature infants
18 compared to their term counterparts might explain the higher risk of SIDS in that population
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Our study has the potential clinical application that the calculation of dead space could be included in medical devices software and integrated in treatment algorithms as it could assist the selection of the optimal targeted tidal volume in volume targeted ventilation. For example, in our study we report a median anatomical dead space of 3.7 ml/kg in prematurely born infants: this might explain why the work of breathing is higher in premature infants when ventilated with low targeted tidal volumes²⁶.

In conclusion, weight-adjusted anatomical dead space is higher in premature infants compared to term infants and weight-adjusted anatomical and alveolar dead space increase with decreasing weight and gestation. Alveolar dead space is increased in infants that have undergone prolonged mechanical ventilation.

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Conflict of interest statement: Professor Greenough has held grants from various manufacturers (Abbot Laboratories, MedImmune) and ventilator manufacturers (SLE). Professor Greenough has received honoraria for giving lectures and advising various manufacturers (Abbot Laboratories, MedImmune) and ventilator manufacturers (SLE). Professor Greenough is currently receiving a non conditional educational grant from SLE.

Author contributions: TD conceived the study, collected the data, participated in the analysis of the data and drafted the first version of the article. PD designed the software for the study, synchronised the signals and constructed the volumetric capnograms, AH contributed to data collection and critically appraised the manuscript. SF contributed in conceiving the study and critically appraised the manuscript. AG supervised the project, contributed to the study design and interpretation of the results and critically revised the manuscript. All authors were involved in the preparation of the manuscript and approved the final manuscript as submitted.

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Table 1: Demographics and respiratory parameters. Data are presented as median (IQR) or n (%)

	Term	Premature	
	N=11	N=45	P value
GA (weeks)	40 (38 – 41)	25 (26-30)	<0.001
PMA (weeks)	40 (38 – 42)	30 (27 – 33)	<0.001
BW (kg)	3.30 (2.81 – 3.71)	0.88 (0.72 – 1.09)	<0.001
Male gender	5 (45)	23 (51)	0.113*
Weight (kg)	3.30 (2.81 – 3.85)	1.18 (0.93 – 1.62)	<0.001
Postnatal age (days)	2 (1 – 5)	11 (3 – 40)	0.001
Days of ventilation	1 (1 – 5)	8 (3 – 33)	0.001
FiO ₂	0.23 (0.21 – 0.32)	0.27 (0.23 – 0.34)	0.290
MAP (cm H ₂ O)	8 (7 – 9)	8 (7 – 9)	0.852
PEEP (cm H ₂ O)	5.3 (4.9 – 5.8)	5.6 (4.8 – 6.2)	0.757
Backup rate	35 (30 – 40)	40 (35 – 40)	0.046
Respiratory rate	55 (40 – 68)	71 (58 – 83)	0.027
PaCO ₂ (mmHg)	40 (35 – 43)	47 (40 – 53)	0.007
ET CO ₂ (mmHg)	26 (22 – 29)	27 (21 - 33)	0.452
P _E CO ₂ (mmHg)	14 (10 – 21)	10 (7 – 14)	0.035
V _T (ml)	16.0 (14.0 – 22.5)	6.7 (5.4 – 8.9)	<0.001
V _T /kg (ml)	5.3 (4.0 – 5.8)	5.6 (4.2 – 7.6)	0.348
V _{D-Phys} (ml)	8.6 (6.9 – 9.8)	5.0 (3.9 – 6.0)	<0.001
V _{D-Ana} (ml)	5.1 (4.0 – 5.4)	4.6 (3.7 – 5.5)	<0.001
V _{D-Ana} /kg (ml)	2.4 (1.9 - 2.9)	3.7 (3.0 – 4.5)	<0.001
V _{D-Alv} (ml)	0.1 (0.0 – 0.7)	0.4 (0.1 – 0.5)	0.293
V _{D-Alv} /kg (ml)	0.1 (0.0 – 0.2)	0.3 (0.1 – 0.5)	0.015

Mann Whitney U 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, PaCO₂: arterial partial pressure of carbon dioxide, ET CO₂ end-tidal carbon dioxide, P_ECO₂: volume-averaged expired carbon dioxide, VT: inspiratory tidal volume, V_{D-Phys}: physiological dead space, V_{D-Ana}: anatomic dead space, V_{D-Alv}: alveolar dead space.

*Chi square test.

FIGURE LEGENDS

Fig. 1. The Fowler method of volumetric capnography for calculating anatomical dead space (V_{D-Ana}). The expiratory curve of PCO_2 versus volume is comprised of three phases: an initial phase where no CO_2 is expired, a second phase, where expired CO_2 rises rapidly and a final plateau phase. A tangent line can be constructed at the alveolar plateau and a vertical line is set in the middle of the second phase so that two equal triangles are created. V_{D-Ana} is measured from the beginning of expiration to the point where the vertical line crosses the volume axis. Arterial ($PaCO_2$) and end tidal ($ETCO_2$) are also schematically presented.

Fig. 2. Regression analysis of V_{D-Ana}/kg with weight at measurement. 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.

▲ Male

○ Female

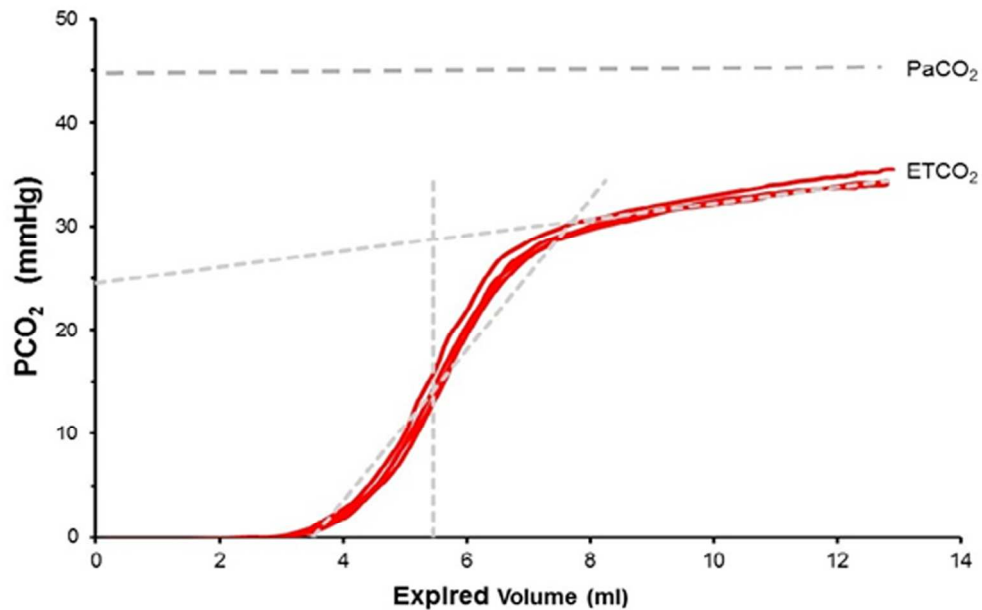


Fig. 1. The Fowler method of volumetric capnography for calculating anatomical dead space (VD-Ana). The expiratory curve of PCO₂ versus volume is comprised of three phases: an initial phase where no CO₂ is expired, a second phase, where expired CO₂ rises rapidly and a final plateau phase. A tangent line can be constructed at the alveolar plateau and a vertical line is set in the middle of the second phase so that two equal triangles are created. VD-Ana is measured from the beginning of expiration to the point where the vertical line crosses the volume axis. Arterial (PaCO₂) and end tidal (ETCO₂) are also schematically presented.

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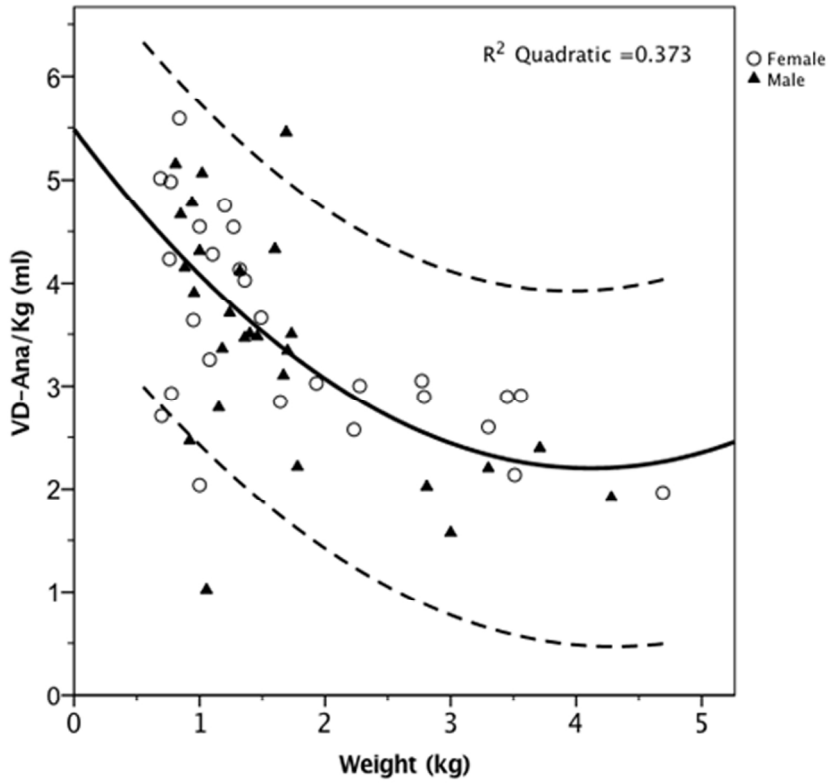


Fig. 2. Regression analysis of VD-Ana/kg with weight at measurement. The regression line and 95% confidence intervals are presented. The type of non-linearity was tested by visual inspection of the residuals and the quadratic model was found to accommodate the best non-linear fit.

▲ Male
○ Female

159x127mm (300 x 300 DPI)

