Physiological and anatomical dead space in mechanically ventilated newborn infants

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Complete List of Authors: Dassios, Theodore; King's College Hospital, Neonatal Intensive Care Centre
Dixon, Paul; Individual Consultant
Hickey, Ann; King's College Hospital, Neonatal Intensive Care Centre
Fouzas, Sotirios; University Hospital of Patras, Greece, Respiratory Unit, Department of Pediatrics
Greenough, Anne; King's College London School of Medicine at Guy's, King's College and St Thomas' Hospitals

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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.

Working hypothesis: VD-Ana and VD-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.

45 preterm) were studied at a median age of 8 (IQR 2-33) days.

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.

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).

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.
Physiological and anatomical dead space in mechanically ventilated newborn infants

Theodore Dassios PhD¹, Paul Dixon PhD², Ann Hickey MB BCh¹, Sotirios Fouzas PhD³, Anne Greenough MD⁴,⁵

¹ Neonatal Intensive Care Centre, King’s College Hospital NHS Foundation Trust, London, United Kingdom; ² Individual Consultant, London, United Kingdom; ³ Paediatric Respiratory Unit, University Hospital of Patras, Patras, Greece; ⁴ Division of Asthma, Allergy and Lung Biology, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, King’s College London, London, United Kingdom; ⁵ NIHR Biomedical Centre at Guy’s and St Thomas NHS Foundation Trust and King’s College London, United Kingdom

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Corresponding author: Theodore Dassios, NICU, 4th Floor Golden Jubilee Wing, King’s College Hospital, Denmark Hill, London, SE5 9RS, Tel: 0203 299 4644; fax: 0203 299 8284; email: theodore.dassios@kcl.ac.uk

Running head: Dead space in newborns

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

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

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

Results: The median $V_{D-A}$/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). $V_{D-A}$/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: $V_{D-A}$/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 inhomogeneity\(^1\). The physiological dead space (\(V_{D,\text{Phys}}\)) is the sum of the anatomical dead space (\(V_{D,\text{Ana}}\)) (the conducting non-gas exchanging airways) and the alveolar dead space (\(V_{D,\text{Alv}}\)) which corresponds to the ventilated alveoli that are not perfused by the pulmonary circulation\(^2\). The physiological dead space (\(V_{D,\text{Phys}}\)) is elevated in adults with chronic obstructive pulmonary disease\(^3\) and pulmonary embolism\(^4\) and it has been used to predict mortality in acute respiratory distress syndrome\(^5\).

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 space\(^10\). 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 \(V_{D,\text{Phys}}\) per kilogram of body weight increases with decreasing weight and gestation\(^7\) but it is not known...
whether this relationship is a reflection of lung disease severity or of anthropometric differences in anatomical dead space. The latter is plausible as it has been shown that term-born newborn infants have higher anatomical dead space per kilogram compared to older children. Furthermore, it is not known how $V_{D-Ana}$ and $V_{D-Alv}$ change with decreasing gestation and birth weight and with increasing severity of lung disease.

Our hypotheses were that weight-adjusted $V_{D-Alv}$ and $V_{D-Ana}$ would be higher in prematurely-born compared to term infants and that these indices will increase with decreasing body weight and gestation and with increasing duration of mechanical ventilation, used as a proxy for the severity of lung disease. Our aims were to test these hypotheses using a low-dead 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)\(^\text{12}\). Flow, volume and expired 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. 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 (PaCO\(_2\)) was assessed within 30 minutes prior to extubation. Infants that did not have an arterial CO\(_2\) 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\(_{\text{I}O_2}\)) was less than 0.4, the infant had a pH > 7.25 and a PaCO\(_2\) < 8.5 kPa and their breathing rate was above the set ventilator rate\(^\text{12}\). Sedation was discontinued at least...
12 hours before the SBT and all infants less than 34 weeks of postmenstrual age were receiving caffeine.

**Measuring equipment**

The NM3 respiratory profile monitor (RPM) (Philips Respironics, Connecticut, USA) was used to measure flow, volume and the concentration of expired CO$_2$. 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 CO$_2$ and flow sensor which was placed between the endotracheal tube and the ventilator circuit. Expired CO$_2$ 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).

**Calculation of V$_{D-Ana}$ and V$_{D-Alv}$**

The measured physiological dead space ($V_{D-Phys}$) was calculated from the Bohr/Enghoff equation: $V_D = V_T \times (1-P_{E}CO_2/PaCO_2)$ from patient-triggered mechanical breaths with a plateau, during mechanical ventilation where $V_T$ was the expired tidal volume and $P_{E}CO_2$ was the volume-averaged expired CO$_2$. The measured $V_{D-Ana}$ was calculated using the Fowler method of volumetric capnography where the expired CO$_2$ was plotted against the expired tidal volume. The resulting “volumetric capnogram” comprised of three phases: an initial phase where no CO$_2$ is expired, a second phase, where expired CO$_2$ rises rapidly (indicating the expiration of mixed air from the airways and from the alveoli) and a final plateau phase which represents pure alveolar gas. A tangent line was constructed at the alveolar plateau and a vertical line was inserted in the middle of the second phase so that two
equal triangles were created. $V_{D,Ana}$ was measured from the beginning of expiration to the point where the vertical line crosses the volume axis (Figure 1)\(^\text{16}\). The calculation of the $V_{D,Ana}$ was made by a researcher who was unaware of the demographics of the infants. As the endotracheal tube bypasses the upper airways, this modified index of dead space corresponds to the capnograph dead space (less than 1 ml), the endotracheal tube dead space (approximately 0.9 ml) and the part of the airways below the endotracheal tube. $V_{D-Alv}$ was calculated by subtracting the $V_{D,Ana}$ from the $V_{D-Phys}$. The CO\(_2\) and volume signals were synchronised by aligning the maximum of tidal CO\(_2\) with the end of expiration\(^\text{17}\). $V_{D,Ana}$ and $V_{D-Alv}$ were corrected for body weight at the time of measurement.

**Information from the medical records**

Gender, gestational age, birth weight, postmenstrual age, postnatal age and weight at the time of measurement were recorded. The $F_{I,O_2}$ and the PaCO\(_2\) within 30 minutes prior to the measurement were also recorded from the nursing observation charts.

**Sample size calculation**

The sample size calculation was based on the observation that a difference in tidal volume of 0.92 ml/kg was observed in premature infants between the first and twenty-first day after birth despite permissive hypercapnia\(^\text{18}\). The standard deviation of $V_D$/kg had been previously shown to be 0.61 ml/kg\(^\text{19}\). 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.
Statistics

Data were tested for normality with the Kolmogorov–Smirnoff 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 CO\textsubscript{2} 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 PaCO\textsubscript{2} levels. Prematurely born infants had higher V\textsubscript{D-Ana}/kg and V\textsubscript{D-Alv}/kg compared to term infants. Multivariate regression analysis revealed that V\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{I}O\textsubscript{2} at measurement (r=0.076, p=0.426) and respiratory rate (r=0.109, p=0.242). The relation of V\textsubscript{D-Ana}/kg with weight at measurement was best accommodated by the quadratic model (Figure 2).
V_{D,Alv}/kg was negatively related to gestational age (r=-0.304, p=0.001), 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 positively related to days of ventilation (r=0.194, p=0.044) but not related to respiratory rate (r=0.129, p=0.0158) and F_{I\O_2} at measurement (r=0.120, p=0.213).
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/kg. 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/kg. 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). 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 weeks. 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.
To our knowledge, only one recent previous study has reported values of alveolar dead space. Wenzel et al\textsuperscript{6}, in infants of a median gestational age of 34 weeks, reported a mean $V_{D-Alv}$ of 0.96 ml/kg in infants weighing less than 2.5 kg and 0.49 ml/kg in infants weighing more than 2.5 kg. We report a smaller mean $V_{D-Alv}$ of 0.1-0.3 ml/kg. The difference in findings might be explained by differences in respiratory status as our cohort’s respiratory status was sufficiently improved that they were considered ready for extubation, whereas in Wenzel’s cohort half of the infants were still ventilated two days after the initial measurement.

Our study has a number of strengths and some limitations. The CO\textsubscript{2} sensor had a low apparatus dead space and its mainstream position in the respiratory circuit allowed for a faster response time even at high respiratory rates\textsuperscript{21}. Another strength is that we studied a cohort that consisted of both term and extremely prematurely born infants. In addition, we routinely use shouldered endotracheal tubes that minimise leak\textsuperscript{22}, high leak would introduce significant error to the measurements via shortening of the plateau phase of the expired CO\textsubscript{2}\textsuperscript{23}. A limitation is that we only included infants well enough to be considered ready for extubation. In a future study it would be interesting to determine the $V_{D-Alv}$ in infants with acute respiratory distress. We did not deduct the endotracheal tube dead space in our calculation of anatomical dead space as in clinical practice real-time values of tidal volume include the apparatus dead space. However, this would be a fixed volume and changes of anatomical dead space over time would not be affected by this method if each patient is acting as their own control.

$V_{D-Alv}$ was significantly related to the duration of mechanical ventilation. This might be explained by either that alveolar dead space progressively increases due to over distension.
and ventilator induced lung injury and/or that infants with more severe lung disease remain ventilated for longer periods and the duration of mechanical ventilation is a reflection of the severity of the underlying lung disease.

It has been postulated that the higher anatomical dead space in infants compared to older children might be a predisposing condition that places infants at higher risk of sudden infant death syndrome (SIDS) due to rebreathing of dead space and the ensuing hypercapnia. From our results, it is plausible that the relatively higher V\textsubscript{D-Ana} in premature infants compared to their term counterparts might explain the higher risk of SIDS in that population.

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 volumes.

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.
ACKNOWLEDGEMENTS

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.
REFERENCES


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<td>40 (38 – 42)</td>
<td>30 (27 – 33)</td>
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<td>5 (45)</td>
<td>23 (51)</td>
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<td>Weight (kg)</td>
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<td>71 (58 – 83)</td>
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<td>V\textsubscript{D-Phys} (ml)</td>
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<td>V\textsubscript{D-Ana} (ml)</td>
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<td>V\textsubscript{D-Ana}/kg (ml)</td>
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<td>V\textsubscript{D-Alv} (ml)</td>
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<td>0.1 (0.0 – 0.2)</td>
<td>0.3 (0.1 – 0.5)</td>
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Mann Whitney U test. GA: gestational age, PMA: postmenstrual age, BW: birth weight, FiO\textsubscript{2}: fraction of inspired oxygen, MAP: mean airway pressure on mechanical ventilation, PEEP: positive end expiratory pressure, PaCO\textsubscript{2}: arterial partial pressure of carbon dioxide, ET CO\textsubscript{2}: end-tidal carbon dioxide, P\textsubscript{E}CO\textsubscript{2}: volume-averaged expired carbon dioxide, VT: inspiratory tidal volume, V\textsubscript{D-Phys}: physiological dead space, V\textsubscript{D-Ana}: anatomic dead space, V\textsubscript{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 (Pa$CO_2$) and end tidal (ET$CO_2$) 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.

148x98mm (300 x 300 DPI)
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)