Systematic errors and susceptibility to noise of four methods for calculating anatomical dead space from the CO₂ expirogram

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Background. Anatomical dead space is usually measured using the Fowler equal area method. Alternative methods include the Hatch, Cumming, and Bowes methods, in which first, second, and third order polynomials, respectively, fitted to an expired CO₂ volume vs expired volume curve, intercept the x-axis at the anatomical dead space. This study assessed systematic errors and susceptibility to noise of the Fowler, Hatch, Cumming, and Bowes dead spaces calculated over 40–80% of the CO₂ expirogram.

Methods. Simulated CO₂ expirograms with 220 ml anatomical dead space and varying alveolar plateau slopes were generated digitally and zero-mean Gaussian noise added. CO₂ expirograms were recorded in 10 anaesthetized human subjects. Anatomical dead space was calculated by the Fowler, Hatch, Cumming, and Bowes methods.

Results. The Fowler, Hatch, Cumming, and Bowes methods displayed systematic biases of −1.8%, 13.2%, 2.4%, and −1.3%, respectively, at a normalized simulated alveolar plateau slope of 1.6 litre⁻¹. At a noise level of 0.0066 vol/vol, the standard deviations of recovered simulated dead spaces were 70.6, 1.8, 2.4, and 3.7 ml, respectively. The Hatch, Cumming, and Bowes methods applied to human expirograms differed significantly from that of Fowler by 13, −4, and −11 ml, respectively. In the human study, the Hatch and Cumming methods yielded the lowest intra-individual dead space variability.

Conclusions. The Fowler method shows greatest susceptibility to measurement noise and the Hatch method exhibits the largest systematic error. The Cumming method, which exhibits both low bias and low noise susceptibility, is preferred for estimating anatomical dead space from CO₂ expirograms.


Keywords: airway, dead space; carbon dioxide, measurement; lung, dead space

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The measurement of respiratory dead space, which provides important insight into the efficiency of gas exchange, has found wide application in respiratory physiology, clinical anaesthesia, and critical care medicine. Classically, respiratory dead space is divided into two parts: anatomical dead space (VDₐ) and alveolar dead space. Alveolar dead space is calculated as the difference between physiological dead space (VDₚₚₚ) and anatomical dead space, and can be affected by changes in the distribution of ventilation to perfusion ratio in the lungs. Anatomical dead space is thus important because the measurement of alveolar dead space depends on the accurate measurement of anatomical dead space.

Anatomical dead space is commonly calculated by the Fowler equal area method, which uses the expired CO₂ concentration or partial pressure vs expired volume curve. An alternative is the Hatch or Langley method in which a straight line is fitted to the most linear part of the expired CO₂ volume (VECO₂) vs expired volume (VE) curve by linear regression. The intersection of this regression line and the x-axis is an estimate of the anatomical dead space. Recognizing that a non-zero slope in the alveolar
plateau (phase III) of the CO₂ expirogram causes a quadratic phase II \( V_{ECO2}^2 - V_E \) relationship, Cumming and Guyatt\(^\text{10}\) and Wolff and colleagues\(^\text{11}\) fitted a second order polynomial to the \( V_{ECO2}^2 - V_E \) data to calculate anatomical dead space. Bowes and colleagues\(^\text{12}\) used a third order polynomial which allows a changing slope in phase III. Because capnograms are always contaminated with noise,\(^\text{13}\) and the integration required to calculate \( V_{ECO2} \) reduces noise, the Hatch, Cumming, and Bowes methods may yield results of greater precision than the Fowler equal area method.

Since the recommendation of the Hatch method by Fletcher,\(^\text{14,}\text{15}\) numerous authors have used this method to calculate anatomical dead space in various physiological and clinical settings.\(^ \text{1–3 14–16–19}\) The Cumming and Bowes methods, however, have not been used extensively. In this study, we investigated the systematic errors and susceptibilities to measurement noise of the Fowler, Hatch, and modified forms of the Cumming and Bowes methods, using simulated CO₂ expirograms and CO₂ expirograms recorded in anaesthetized patients without clinically significant lung disease.

**Theoretical considerations**

A CO₂ expirogram (Fig. 1A) comprises three distinct phases. In phase I, CO₂-free gas is exhaled from the airway dead space. Phase II is a sigmoidal curve with a rapidly increasing CO₂ fraction caused by asymmetry in the airway structure and mixing of fresh gas in the airways with CO₂-rich gas from the alveoli. Phase III represents alveolar gas and usually has an increasing CO₂ concentration. If the lungs are normal, a straight line can be fitted to a selected part of phase III of the curve by linear regression (Fig. 1A):

\[
F_{ECO2} = aV_E + b
\]

where \( F_{ECO2} \) is the fraction of CO₂ in expired gas and \( V_E \) is a variable representing expired volume. The Fowler dead space is estimated by extrapolating the regression line fitted to phase III backwards and constructing a vertical line such that areas \( p \) and \( q \) are equal (Fig. 1A). A corresponding expired CO₂ volume vs expired volume curve is obtained by cumulatively integrating expired CO₂ concentration with respect to expired volume (solid line, Fig. 1B). The dotted line in Figure 1A can be considered to be an idealized CO₂ expirogram in which there is no mixing of alveolar and anatomical dead space gas and no asymmetry in the respiratory airways. The dotted line in Figure 1B is the cumulative integral of this idealized expirogram, given by:

\[
V_{ECO2}(V_E) = \int_0^V F_{ECO2} dV_E
\]

\[
= \begin{cases} 
0 & (0 \leq V_E < V_D) \\
\int_0^V (aV_E + b) dV_E & (V_D \leq V_E < V_T) \\
0 & (V_T \leq V_E)
\end{cases}
\]

\[
= \frac{1}{2} aV_E^2 + bV_E - c & (V_D \leq V_E < V_T)
\]

where:

\[
c = \frac{1}{2} V_D^2 + bV_D
\]

and \( V_T \) is the tidal volume.

Thus, the part of the idealized \( V_{ECO2} - V_E \) curve corresponding to phase III of the CO₂ expirogram is a second
order polynomial that intersects the x-axis at \( V_Dm \). This analysis suggests that the part of the \( V_{eco2} - V_E \) curve corresponding to phase III of the CO₂ expirogram should preferably be approximated by a second order polynomial rather than by a straight line or a third order polynomial curve, and that the x-axis intercept of a second order polynomial fitted to an appropriately selected part of the \( V_{eco2} - V_E \) curve may be a good estimate of the Fowler dead space.

**Methods**

**Simulation study: systematic errors**

Idealized CO₂ expirograms, \( F'_{CO2}(V_E) \), were generated by defining

\[
F'_{CO2}(V_E) = \begin{cases} 
0 & (0 \leq V_E < V_{DP}) \\
\alpha V_E + b & (V_{DP} \leq V_E < V_T)
\end{cases}
\]

In all idealized expirograms, the simulated anatomical dead space (\( V_{DP} \)) and tidal volume were 220 and 750 ml, respectively, and the volume of CO₂ expired in one breath was 25.2 ml. The normalized slope of phase III, \( a \) (absolute slope divided by mean phase III \( F'_{CO2} \)), was varied from 0 to 1.6 litre⁻¹ in steps of 0.4 litre⁻¹. The constant \( b \) was selected such that all the idealized expirograms passed through the point \( [(V_T + V_{DP})/2, 0.05] \) to obtain an average alveolar \( F_{CO2} \) of 0.05. Idealized numerical expirograms were calculated with 0.35 ml increments in expired volume. Each expirogram comprised 2000 points. The effects of airway asymmetry and gas mixing in the airways were simulated by smoothing the idealized expirogram with a weighted moving average filter. Weighting factors comprised a 701 order Blackman window. The smoothed curves were used for estimation of the anatomical dead space by the Fowler equal area, Hatch (first order polynomial), Cumming (second order polynomial), and Bowes (third order polynomial) methods.

**Dead space calculation methods**

Fowler dead space was calculated by the equal area method (Fig. 1A), assuming that the linear section of the alveolar plateau extended from 40% to 80% of expired volume. In the Hatch method, a first order polynomial was fitted to the \( V_{eco2} - V_E \) curve between 40% and 80% of the expired volumes by linear regression. The Cumming and Bowes methods were modified by fitting second and third order polynomials, respectively, to the \( V_{eco2} - V_E \) curve between 40% and 80% of the expired volumes. The intersections of the polynomials with the x-axis formed the respective estimates of anatomical dead space. The resulting anatomical dead spaces are referred to as \( V_{DH1} \), \( V_{DC2} \), and \( V_{DB3} \) for the first order polynomial curve method (Hatch method), second order polynomial curve method (modified Cumming method), and third order polynomial curve method (modified Bowes method), respectively. All calculations were performed using computer programs written in Matlab (Mathworks, Natick, MA, USA).

**Monte Carlo simulation study: effect of noise in the CO₂ measurement**

A Monte Carlo simulation study of the effect of CO₂ analyser noise on dead space calculation was performed as follows. A smoothed CO₂ expirogram was generated using the same parameters described earlier and a normalized phase III slope of 1.2 litre⁻¹. Zero-mean normally distributed random noise (σ 0.0013, 0.0026, 0.0039, 0.0053, and 0.0066 vol/vol, corresponding to CO₂ partial pressures of 1, 2, 3, 4, and 5 mm Hg, respectively, at a barometric pressure of 760 mm Hg) representing measurement noise, the effects of the limited resolution of the CO₂ analyser, and variability in airway CO₂ fraction, was added to the expirogram. The four dead spaces, \( V_{DH1} \), \( V_{DH2} \), \( V_{DC2} \), and \( V_{DB3} \), were estimated using the methods described earlier. This procedure was repeated 1000 times, and the means and standard deviations of the four dead space values were calculated.

**Clinical study**

After approval by the local ethics committee of the Royal Prince Alfred Hospital and with written informed patient consent, 10 American Society of Anesthesiologists physical status II–III patients aged 52–76 presenting for vascular surgery were enrolled in this study. All patients received a radial artery cannula for haemodynamic monitoring. Routine monitoring included pulse oximetry, ECG, pharyngeal temperature, and capnometry. Anaesthesia was induced with propofol 2 mg kg⁻¹, fentanyl 2 μg kg⁻¹, and rocuronium 0.8 mg kg⁻¹ given i.v. and auffed endotracheal tube was inserted. Anaesthesia was maintained with inhalation isoflurane 1–1.5%, bolus rocuronium 0.3 mg kg⁻¹ and fentanyl 1–2 μg kg⁻¹. The lungs were mechanically ventilated with a volume-controlled mechanical ventilator (Cato, Dräger, Germany). Arterial blood pressure was maintained within 20% of baseline with a low-dose infusion of metamizol (0–0.05 mg min⁻¹). Baseline ventilation parameters were as follows: tidal volume, 10 ml kg⁻¹; respiratory frequency, 10 bpm; inspiration to expiration ratio (I:E ratio), 1:1.7; end-inspiratory hold, 10%; end-expiratory pressure, 0 cm H₂O; and inspired O₂ concentration, 35%.

Airway gas flow, CO₂, and pressure were measured by a NICO monitor (Novametrix Medical Systems Inc., New Haven, CT, USA). The response time of the mainstream CO₂ analyser was less than 60 ms and the resolution was 2 mm Hg. The standard deviation of noise in the \( P_CO2 \) data logging system (including the analogue-to-digital converter) was approximately 0.3 mm Hg when the input
$P_{CO_2}$ was constant. The airway configuration from proximal to distal was endotracheal tube, catheter mount, airway filter, mainstream infrared CO$_2$ analyser, pneumotachograph, pressure monitor, sidestream O$_2$ analyser, and Y piece of the anaesthetic circuit. Partial pressure of CO$_2$, O$_2$, gas flow and pressure signals in the airway were digitized at a frequency of 300 Hz using a 12-bit analogue-to-digital converter (DAQPad-1200, National Instruments Corporation, TX, USA) and recorded by a computer running Matlab. The CO$_2$ analyser was calibrated with known concentrations of CO$_2$ and the flowmeter was calibrated using a second order polynomial method with a calibrated 3 litre syringe. All signals were digitally filtered with a 51st order low pass filter ($-3$ dB frequency 5.0 Hz).

To vary the dead space in each patient, the respiratory parameters were randomly adjusted one at a time to the following settings: tidal volume: 64%, 80%, 100%, 120%, and 144% of baseline; end-expiratory pressure: 0, 5, and 10 cm H$_2$O; I:E ratio: 1:1.7, 1:1, and 2:1; end-inspiratory hold: 10%, 30%, and 50% of the inspiratory time. Under each condition, 46–53 breaths were recorded for off-line analysis. When one parameter was adjusted the other ventilatory parameters were kept at baseline values. A total of 11 different ventilatory settings were used in this study. To reduce variations in the CO$_2$ expirogram caused by external interference, only undisturbed breaths were included in the study. Surgical activity and manual interference with the respiratory circuit caused airway pressure and $P_{CO_2}$ perturbations. When airway pressure increased to more than half the average peak inspiratory pressure and corresponding $FE_{CO_2}$ was more than half the average $FE_{CO_2}$ for that ventilatory condition, a valid breath was identified and analysed. For each breath, the four dead spaces ($V_{DF}$, $V_{DH1}$, $V_{DC2}$, and $V_{DB3}$) were calculated using the methods described earlier. Data are reported as mean (SD) where applicable. Mean values were compared by single factor ANOVA with Bonferroni post hoc test for multiple comparisons. F-tests were used to compare variances. We used non-parametric tests (Friedman and Dunn’s multiple comparison tests) to analyse the data which were not normally distributed. Statistical analysis was performed using Prism V3.0 (GraphPad Software, San Diego, CA, USA). $P<0.05$ was considered to be statistically significant.

**Results**

**Simulation study**

Simulated CO$_2$ expirograms with and without added noise (0.0026 vol/vol corresponding to 5% of indicated $F_{CO_2}$ at an $FCO_2$ of 0.05) and corresponding $V_{eco2} - V_E$ curves are shown in Figure 2A and B. The high slope of phase III caused a high curvature in the $V_{eco2} - V_E$ curve (dotted curves in Fig. 2A and B). Integration visibly reduced noise in the $V_{eco2} - V_E$ curve (solid line in Fig. 2B).

**Simulation study: systematic errors**

When the slope of phase III was zero, all four methods recovered anatomical dead spaces within 2.5% of the model dead space (Fig. 3). As the normalized phase III slope increased from 0 to 1.6 litre$^{-1}$, calculated $V_{DH1}$ increased from 220 to 249 ml, corresponding to a bias of $-0.1\%$ to $13.2\%$ compared with the true anatomical dead space of 220 ml. Over the same range of phase III slope, $V_{DF}$ decreased from 220 to 216 ml ($0\%$ to $-1.8\%$ bias) and $V_{DC2}$ increased from 218 to 225 ml ($-0.8\%$ to $2.4\%$ bias). $V_{DB3}$ slightly underestimated anatomical dead space when the phase III slope was 1.6 litre$^{-1}$ (217 ml, bias $-1.3\%$). In the normal range of normalized phase III slope ($0.4$–$1.2$ litre$^{-1}$), the systematic errors of $V_{DF}$ and $V_{DC2}$ were low ($-0.9\%$ to $0.8\%$).
Monte Carlo simulation study: effect of noise in the CO₂ measurement

Noise in the CO₂ measurement caused a significant change in the mean dead space calculated by the Fowler method ($V_{DF}$), the Hatch linear regression method ($V_{DH1}$), the modified Cumming second order polynomial regression method ($V_{DC2}$), and the modified Bowes third order polynomial regression method ($V_{DB3}$).

Clinical study

All patients had oxygen saturations higher than 95% throughout the study. A total of 6903 expirograms were obtained from 10 patients with various ventilator settings. From calculations based on monitoring times and ventilator rates, we estimate that approximately 100 ventilator cycles were not identified as valid breaths and therefore not analysed. The initial non-parametric ANOVA shows that there are significant differences among the dead spaces measured by the four methods ($P<0.0001$). Differences between $V_{DH1}$ and $V_{DF}$ ranged from $-240$ to $171$ ml (mean 13 ml, limits of agreement $-37$ to $63$ ml). Differences between $V_{DC2}$ and $V_{DF}$ ranged from $-75$ to $112$ ml (mean $-4$ ml, limits of agreement $-36$ to $28$ ml). Differences between $V_{DB3}$ and $V_{DF}$ were significantly smaller than those of $V_{DF}$ for all non-zero noise levels ($0.01<P<0.05$).
**Systematic error and dead space measurement**

$V_D$ ranged from $-158$ to $174$ ml (mean $-11$ ml, limits of agreement $-60$ to $39$ ml). All the mean differences were significantly different from zero ($0.0001<P<0.001$, Dunn’s multiple comparison test). Mean intra-individual standard deviations (95% confidence intervals) of dead space calculated from expirograms acquired during baseline ventilation were: $V_{DC2}: 11$ (7.9–14.1) ml, $V_{DH1}: 3.3$ (2.3–4.3) ml, $V_{DC2}: 4.3$ (3.2–5.4) ml, and $V_{DH3}: 8.3$ (5.9–10.7) ml (Fig. 5). In the 10 patients studied, the intra-individual standard deviations of $V_{DH1}$ and $V_{DC2}$ were significantly smaller than those of both $V_{DC}$ and $V_{DH3}$ ($0.001<P<0.05$).

The difference between $V_{DH1}$ and $V_{DC2}$ was positively correlated with the normalized slope of phase III ($R=0.6667$, $0.01<P<0.05$) (Fig. 6). The difference was similar in magnitude to the bias in our simulation study and had a similar dependence on normalized phase III slope. At a normalized phase III slope of zero, the difference between $V_{DC2}$ and $V_{DH1}$ predicted by the regression equation was $3.4$ ml (95% confidence intervals 2.9–3.9 ml), which agreed well with our simulation results.

**Discussion**

This study using simulated data and clinical measurements shows that anatomical dead space calculated by the Hatch method, in which a straight line is fitted to the phase III portion of the $V_{ECO2} - V_E$ curve, systematically overestimates anatomical dead space when phase III of the expirogram has a positive slope. The bias of the Hatch method increases with increasing phase III slope and reaches clinically significant values (more than 10%) when the phase III slope is greater than approximately 1 litre$^{-1}$. The $x$-axis intercepts of second and third order polynomials fitted to the phase III portion of the $V_{ECO2} - V_E$ curve (modified Cumming and Bowes methods, respectively) show negligible mean bias compared with the classical Fowler method in both simulation and clinical studies. Our simulation and clinical studies show similar relationships between the bias of the Hatch method and the phase III slope (Figs 3 and 6, respectively). The Hatch ($V_{DH1}$) and modified Cumming ($V_{DC2}$) and Bowes ($V_{DH3}$) methods are significantly less sensitive to noise than the Fowler method in the simulation study and yield significantly lower intra-individual variance in the clinical study. If the $P_{CO2}$ measurement contains noise with a standard deviation greater than approximately 1 mm Hg, the random errors in anatomical dead space calculated by the Fowler method may be clinically significant (>10%) in 5% or more of measurements. The modified Cumming method in which anatomical dead space is estimated as the $x$-intercept of a second order polynomial fitted to the $V_{ECO2} - V_E$ curve between 40% and 80% of expired volume yields both low mean bias (4 ml compared with Fowler equal area method in the clinical study) and low noise susceptibility.

In the original Cumming method, a second order polynomial is fitted to the $V_{ECO2} - V_E$ data by adding data points to the regression sequentially from the top of the curve downwards, until the addition of further points produces no change in these parameters. We modified the Cumming method using $V_{ECO2} - V_E$ data only between 40% and 80% of the expired volume in the polynomial regressions. This part of the expirogram includes only the approximately linear part of phase III of the $CO_2$ expirogram and does not include the increase in $V_{ECO2}$ associated with closing volume (phase IV) that occasionally occurs. The more pronounced cardiogenic oscillations that are occasionally seen at the end of an expirogram are also omitted. These modifications reduce bias and may explain why this study found good agreement between the Fowler and the modified Cumming methods (4 ml mean difference), whereas Cumming and Guyatt found a larger (20 ml) mean difference. We used the same section of the $V_{ECO2}$ vs $V_E$ curves in the linear and third order polynomial regressions for the same reasons and for comparative purposes.

Integration reduces noise in a signal; hence, anatomical dead space, estimated from the $V_{ECO2} - V_E$ curve, is expected to exhibit lower variability than the Fowler dead space. A non-zero phase III slope, however, leads to a quadratic relationship between $V_{ECO2}$ and $V_E$, which results in systematic errors in dead space estimates when a straight line is fitted to the $V_{ECO2} - V_E$ curve (Hatch method). This mechanism is also the reason for the bias of the Hatch method in the noise simulation study. If phase III of the expirogram is not a straight line then a third order polynomial should fit the $V_{ECO2} - V_E$ curve between 40% and 80% of expired volume better than a second order polynomial. Our clinical study suggests that the third order polynomial results in small but statistically significant under-estimation of Fowler dead space, and the additional degree of freedom increases its susceptibility to noise.

The $x$-axis intercept of a straight line fitted to a $V_{ECO2} - V_E$ curve, as an estimate of anatomical dead space, was first reported by Hatch and colleagues in 1953 and apparently independently developed by Langley and colleagues in 1975. Fletcher recommended and used this method in a series of studies on respiratory dead space in 1984. The Hatch method has been widely used and referred to in most citations as the Langley method. Among the available methods for calculating anatomical dead space (Fowler method, Hatch method, a pre-interface expirate method, a threshold method, the Romero method, substitution of end-tidal $P_{CO2}$ in the Bohr equation), the Hatch method is possibly the second most commonly used after the Fowler method. The results and conclusions of studies that used the Hatch method should be interpreted with caution, as this study suggests that the Hatch method introduces a positive bias in anatomical dead space estimates when phase III of the expirogram has a positive slope.

Our theoretical analysis shows that the Cumming second order polynomial method produces lowest errors independent of the ventilator setting. In the clinical study,
we obtained different dead spaces by varying ventilator setting. It is possible that dead space measurement errors might depend slightly on the ventilator setting. As the four methods were applied to the same CO₂ expirograms for comparative purposes, we expect the effect of ventilator setting on dead space errors to be negligible. Although the finite resolution of the CO₂ analyser and gas flowmeter affects the accuracy of dead space estimates, these errors are very small and are random rather than systematic.

In conclusion, the Fowler equal area method for the calculation of anatomical dead space is susceptible to noise and the Hatch method yields results with systematic errors. This study suggests that of the four methods assessed, the modified Cumming method is preferred for estimating anatomical dead space from CO₂ expirograms.

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