Estimation of pulmonary blood flow from sinusoidal gas exchange during anaesthesia: a theoretical study

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We simulated the use of simultaneous sinusoidal changes of inspired O_2 and N_2O (Williams *et al.*, *J Appl Physiol*, 1994; **76**: 2130–9) at fractional concentrations up to 0.3 and 0.7, respectively, to estimate FRC and pulmonary blood flow (PBF) during anaesthesia, using O_2 as an insoluble indicator. Hahn's approximate equations, which neglect the effect of pulmonary uptake and excretion on expiratory flow, estimate dead space and alveolar volume (V_A) with systematic errors less than 10%, but yield systematic errors in PBF which are approximately proportional to $F_{I_{N_2O}}$ in magnitude. A correction factor $(1 - \bar{P})^{-1}$ for Hahn's equations for PBF (where $\bar{P}$ is the mean partial pressure of the soluble indicator) reduces the dependence of PBF estimates on $F_{I_{N_2O}}$, and the solution of equations describing the simultaneous mass balance of both indicators yields accurate results for a wide range of mean $F_{I_{N_2O}}$. However, PBF estimates are sensitive to measurement errors and a third gas must be present to ensure that the indicator gases behave independently.

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The sinusoidal frequency response technique for estimating pulmonary blood flow (PBF) was described by Zwart *et al.*[1] in 1976. The method has recently been extended by Williams *et al.*[2] in 1994 to allow simultaneous estimation of dead space, alveolar volume and PBF using insoluble (argon) and soluble (nitrous oxide: N_2O) indicator gases modulated in anti-phase at low mean inspired fractions. An important advantage of this technique is that the sinusoidal perturbation of the soluble indicator gas fraction in mixed venous blood is attenuated and can be ignored if the modulation frequency is high enough. In their analysis, Zwart *et al.*[1] imply that the sinusoidal forcing technique depends only on the modulation and is independent of the mean inspired fraction of the soluble indicator gas. Barton *et al.*[3 4] recognized the problem associated with large mean fractions of N_2O and suggested that the mean inspired fraction should be kept below 0.1 but did not assess the magnitude of the errors that result if the mean indicator fraction goes above 0.1.

Oxygen (O_2) has a very low blood–gas partition coefficient of 0.024 in fully saturated arterial blood. In healthy well oxygenated lungs, variations in alveolar P_{O_2} result in very small variations in pulmonary venous O_2 content when high haemoglobin saturation (P_{O_2}>100 mm Hg) is maintained. If $F_{I_{O_2}}$ is varied, then the O_2 flux from the airway into the alveolar compartment can be considered to consist of two components: a constant unidirectional flux which brings mixed venous blood to arterial saturation; and a varying bidirectional flux which changes the fraction of O_2 in the alveolar compartment. Hahn[5] showed that if arterial haemoglobin is well saturated and oxygen uptake is constant, the constant unidirectional flux may be ignored and O_2 can be used as an approximately insoluble indicator gas for the measurement of lung volumes. This technique has been verified experimentally in healthy adults.[6]

It would be convenient if N_2O and O_2 could be used as indicator gases in the same concentrations as they are commonly used during anaesthesia. We analysed the sinusoidal technique theoretically and used detailed computer modelling of dynamic multi-component gas exchange to investigate the systematic errors in estimates of dead space, alveolar volume and PBF that result when the sinusoidal technique is used as published with mean inspired fractions of indicator gases (O_2 and N_2O) greater than 10% as is commonly the case during general anaesthesia.

Patients and methods

Theoretical analysis

Equation (A1) (see Appendix) gives the mass balance of a soluble indicator gas in a perfectly mixed, single-compartment lung subjected to continuous ventilation and perfusion (Fig. 1). If both the mean concentration and the sinusoidal amplitude of the indicator gas are small, then equation (A1) can be simplified to yield a linear first-order differential equation (equation (A4)), as previously shown.[2] Neglecting the effects of the mean indicator concentration is equivalent to assuming that inspiratory and expiratory flows are identical,[3] and causes PBF to be underestimated by the factor $(1 - \bar{P})$ where $\bar{P}$ is the mean fraction of the soluble gas. The complete mass balance equation also contains a non-linear term which can be neglected when the modulation amplitude is small. A steady-state sinusoidal solution to the complete mass balance equation is derived (equation (A10)) to estimate PBF when the fraction of the soluble indicator gas is high and alveolar volume is known exactly. Alveolar volume can be estimated simultaneously from measurements of the partial pressure of an insoluble indicator gas modulated in anti-phase to the soluble indicator using equation (A8). However, it is preferable to consider the mass balances of the two indicator gases simultaneously. Equation (A13) is a frequency domain steady-state sinusoidal solution to the simultaneous mass balance equations (A11) and (A12), which can be solved simultaneously with equation (A10) to yield estimates of both alveolar volume and PBF.

If a lung is ventilated with a binary mixture of a soluble and insoluble indicator gas, then the sum of the partial pressures of the two gases always equals barometric pressure, if the small effects of carbon dioxide (CO_2) and water vapour are ignored. Any excursion of the partial pressure of one component is matched by an equal and opposite excursion of the partial pressure of the other component. Hence, in the alveolar gas, the magnitude of the peak sinusoidal excursion of the partial pressure of the insoluble gas is equal to that of the partial pressure of the soluble gas, regardless of their mean concentrations. Only one independent measurement can be made from a sinusoidally oscillating binary gas mixture and it is not possible to estimate two unknown parameters. Therefore, a binary mixture of soluble and insoluble indicator gases (e.g. the commonly used mixture of O_2 and N_2O) cannot be used to monitor alveolar volume and PBF simultaneously.

Computer simulation

Computer simulation was used to investigate the systematic errors introduced by the following assumptions in the derivation of Hahn's equations: (i) the indicator gases are present at low concentrations; (ii) the absorption of the soluble indicator gas does not affect expiratory flow; (iii) each indicator gas behaves independently of all the other gases in the lung. The computer model (see Appendix) comprises four simultaneous differential equations describing the mass balance of four gases (O_2, CO_2, N_2 and N_2O) in a single perfectly mixed constant-volume alveolar compartment subjected to continuous inspiratory ventilation $\dot{V}_I$ with a mixture of O_2, N_2 and N_2O. These equations describe the complete mass balance of the four gases and do not rely on the above assumptions. N_2O is exchanged with a constant PBF ($\dot{Q}_p$) and the mixed venous partial pressure of N_2O is kept constant at the mean inspired value. Hence, once steady-state sinusoidal equilibrium is reached by the model, the mean N_2O flux becomes zero. The body compartment is assumed to be large enough to filter out all perturbations in gas concentrations.[7] A proportion (30%) of the total inspiratory gas flow bypasses the alveolar compartment and mixes continuously with expired gas to represent dead space ventilation, leaving a net inspiratory alveolar flow of $\dot{V}_{AI}$. Shunted blood flow, lung tissue absorption of N_2O and the effects of water vapour are not included in the model as they do not influence the validity of this study. Constant oxygen consumption is modelled by the removal of oxygen from the alveolar compartment at a rate of 250 ml min^{-1}. CO_2 is added to the alveolar compartment at a rate equal to the O_2 consumption (RQ=1). Both N_2 (blood–gas partition coefficient=0.012) and O_2 (blood–gas partition coefficient in saturated blood=0.024) are assumed to be insoluble, and the blood–gas partition coefficient of N_2O is assumed to be 0.47. The sum of gas partial pressures is equal to atmospheric pressure at all times.

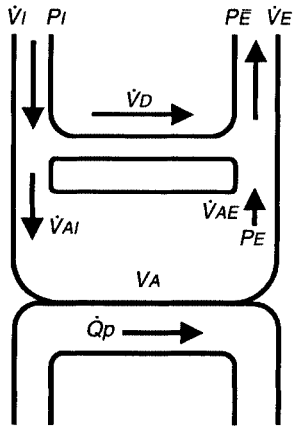

Fig 1 Diagrammatic representation of the computer model of the respiratory system. $\dot{V}_I$, $\dot{V}_E$: total inspiratory and expiratory flows, respectively; $\dot{V}_{AI}$, $\dot{V}_{AE}$: alveolar inspiratory and expiratory flows, respectively; P_I, P_E, $P_{\bar{E}}$: partial pressure of indicator in inspiratory, alveolar and mixed expired gases, respectively; $\dot{Q}_p$: PBF.

The model was implemented using Matlab and Simulink software (The MathWorks, Natick, MA, USA) and solved with the integration routine 'ode15' with variable step size and an absolute tolerance parameter of 1×10^{-6}.

The inspired gas composition was modulated sinusoidally with a peak-to-peak amplitude of 0.02 and a period of 120 s

which has been suggested to be the optimum period for this technique.[8] Alveolar volume was maintained constant at 2.5 litres by adjusting the alveolar expiratory flow $\dot{V}_{AE}$ at each time step. The initial values of the gas fractions in the lungs were set to the mean inspired values and the model run for 1200 s to achieve steady-state sinusoidal conditions. The relative amplitudes and phases of the sinusoidal components of the inspired, mixed expired and end-expired indicator gas fractions were estimated from the last 120 s of the simulation by fitting the expression $P\sin(\omega t + \Phi)$ to simulated partial pressure values using the Gauss–Newton method (Matlab, The MathWorks), and these values were used to recover dead space using equation (A9). Alveolar volume and PBF were estimated from the amplitudes of the sinusoids using the following sets of equations (see Appendix): (i) equations (A9), (A8) and (A6) evaluated sequentially; (ii) equations (A9), (A8) and (A10) evaluated sequentially; and (iii) evaluation of equation (A9) followed by simultaneous solution of equations (A10) and (A13) by an interval bisection technique (Matlab, The MathWorks).

The simulation study was conducted in two parts using inspired gas mixtures comprising N_2O, O_2 and N_2 under the following conditions.

(i) N_2O was oscillated in anti-phase with N_2 such that $F_{I_{N_2O}} + F_{I_{N_2}}$ was constant. $F_{I_{O_2}}$ was not modulated. The mean $F_{I_{N_2}}$ was kept constant at 0.01 while the mean $F_{I_{N_2O}}$ was first set to 0.01 and then varied from 0.1 to 0.7 in steps of 0.1. $F_{I_{O_2}}$ was selected to make up the balance. This condition represents the case in which an inert gas (in this case N_2) is used as an insoluble indicator gas at low concentration, and N_2O as a soluble indicator gas at concentrations ranging between those typical of an indicator gas and those typical of an anaesthetic agent. These conditions were used to evaluate the performance of equations (A9), (A8), (A6) and (A10) as a function of mean $F_{I_{N_2O}}$ when the mean inspired fraction of the insoluble gas was low.

(ii) N_2O was oscillated in anti-phase with O_2 such that $F_{I_{N_2O}} + F_{I_{O_2}}$ was constant. The mean $F_{I_{O_2}}$ took values of 0.2, 0.25 and 0.3, while mean $F_{I_{N_2O}}$ was first set to 0.01 and then varied from 0.1 to 0.7 in steps of 0.1. $F_{I_{N_2}}$ was selected to make up the balance and was not modulated. This condition represents the case in which O_2 is used as an insoluble indicator gas at physiological concentrations and N_2O as a soluble indicator gas at concentrations ranging between that of a typical indicator gas and that of an anaesthetic agent. The per unit sensitivities of PBF to errors in alveolar volume and gas partial pressure measurements, and of alveolar volume to errors in partial pressure measurements were calculated numerically using a forward difference numerical technique as follows. If $y_0 = y(x_0)$ and $y_1 = y(x_0 + \Delta x)$ where Δx is small compared with x_0, then the per unit sensitivity of y to errors in x is given by

$$\frac{(y_1 - y_0)/y_1}{\Delta x/x_0}.$$

Each condition was simulated with PBF at values of 1, 5 and 10 litre min^{-1} and the recovered PBF compared with the true value. Only systematic errors (referred to in this report simply as 'errors') related to approximations in the simplified equations were assessed.

Results

The amplitudes and phases of the inspiratory, alveolar and mixed expiratory sinusoids were recovered with standard error of regression less than 2.5×10^{-6} atmospheres in all cases. The results obtained in the two parts of this study are as follows.

(i) When N_2 at a mean inspired fraction of 0.01 was used as the insoluble indicator gas, the absolute values of the systematic errors in estimates of dead space (equation (A9)) and alveolar volume (equation (A8)) were less than 0.5% for $0.01 < \text{mean } F_{I_{N_2O}} < 0.70$. PBF calculated from simulation results by the approximate equation (equation (A6)) and plotted in Fig. 2 exhibited systematic errors which were negative and increased in magnitude in approximate proportion to increasing mean $F_{I_{N_2O}}$. The systematic errors in the corrected equation (equation (A10)) were substantially smaller (less than 3.5%).

(ii) When N_2O was oscillated in anti-phase with O_2, at mean $F_{I_{O_2}}$ of 0.2–0.3, systematic errors in dead space were less than 2% in all cases. However, systematic errors in alveolar volume (equation (A8)), shown in Fig. 3, increased strongly with increasing $F_{I_{O_2}}$ and with

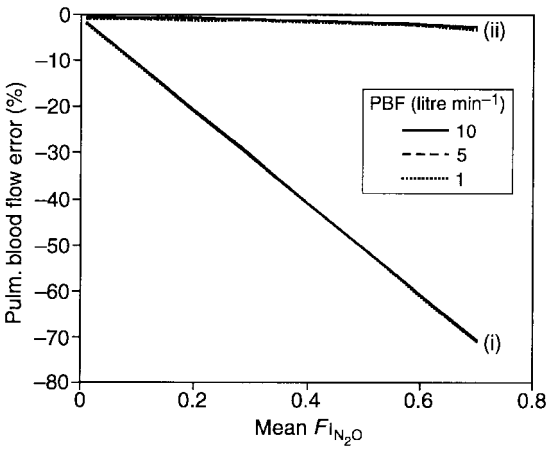

Fig 2 Systematic errors in PBF estimates when a low-concentration insoluble tracer gas (N_2) is used to monitor alveolar volume, and various mean concentrations of N_2O with O_2 as balance are used to monitor $\dot{Q}_p$. (i) Equations (A9), (A8) and (A6) evaluated sequentially. (ii) Equations (A9), (A8) and (A10) evaluated sequentially. PBF, pulmonary blood flow.

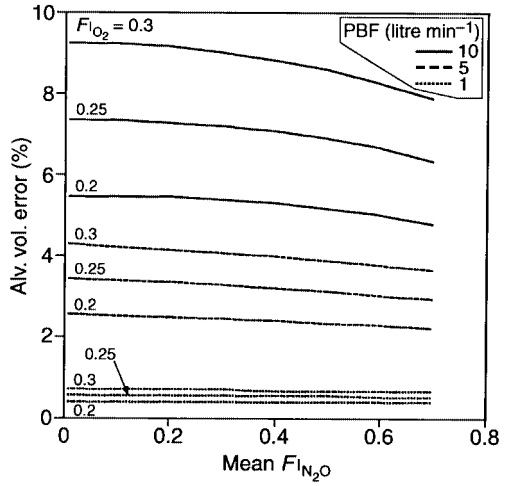

Fig 3 Systematic errors in estimated values of alveolar volume when the mean $F_{I_{O_2}}$ was 0.20, 0.25 and 0.30, and PBF was 1, 5 and 10 l min^{-1}. Equations (A9) and (A7) were evaluated sequentially to estimate V_A.

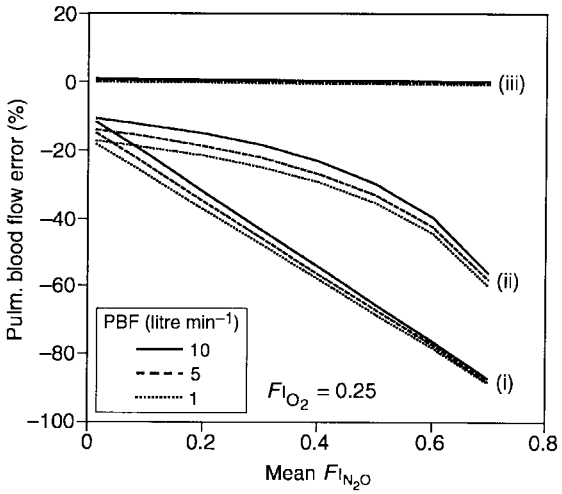

Fig 4 Systematic errors in PBF estimates when O_2 (mean $F_{I_{O_2}}$ 0.25) is used as the insoluble tracer gas and N_2O as the soluble gas with N_2 as balance using: (i) equations (A9), (A8) and (A6) evaluated sequentially; (ii) equations (A9), (A8) and (A10) evaluated sequentially; and (iii) evaluation of equation (A9) followed by simultaneous solution of equations (A10) and (A13) by interval bisection.

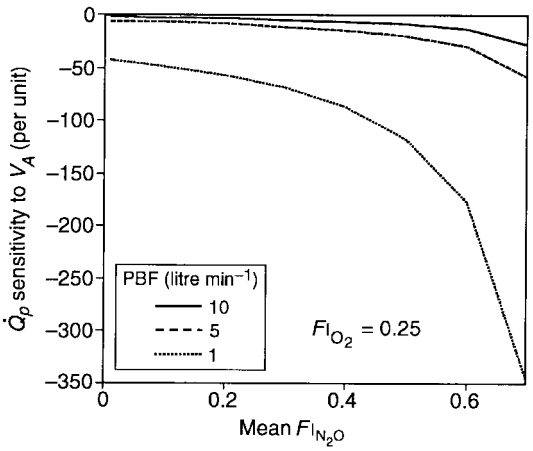

Fig 5 Per unit sensitivity of estimated PBF (using simultaneous equation (A10) to errors in alveolar volume calculated using a forward difference technique for $F_{I_{O_2}}$ = 0.25 and balance N_2).

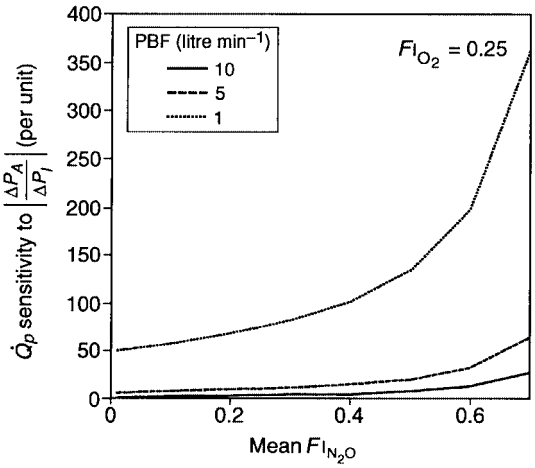

Fig 6 Per unit sensitivity of estimated PBF (using simultaneous equations (A10) and (A13)) to errors in the ratios of the magnitudes of the partial pressure of the indicator gases calculated using a forward difference technique for $F_{I_{O_2}}$ = 0.25 and balance N_2. The sensitivities to O_2 and N_2O are almost identical, therefore only one curve is plotted at each PBF.

increasing PBF. PBF error depended weakly on the mean $F_{I_{O_2}}$ and for clarity is shown in Fig. 4 for a mean $F_{I_{O_2}}$ of 0.25 only. Equation (A10) performed substantially better than the approximate equation (equation (A6)) at low $F_{I_{N_2O}}$ values, but deteriorated at high $F_{I_{N_2O}}$. Figure 5, in which the sensitivity of PBF to errors in alveolar volume is plotted, suggests that the errors in PBF in curves (ii) in Fig. 4 were related to errors in alveolar volume. Equations (A10) and (A13) solved simultaneously yielded estimates of alveolar volume and PBF (curves (iii) in Fig. 4) within 1% of the true values for all mean concentrations of indicators studied. However, the sensitivity of this technique to measurement error is large, particularly when the PBF is low (Fig. 6). The sensitivity to measurement error of alveolar volume estimates obtained by simultaneous solution of equations (A10) and (A13), shown in Fig. 7, is substantially smaller.

Discussion

We have shown that while approximate solutions to the steady-state sinusoidal mass balance of a soluble indicator gas yield acceptable estimates when the mean concentrations of the indicators are small, modified solutions allow a greater range of mean indicator concentrations to be used.

The difference between the performance of equations (A6) and (A10) in Fig. 2 can be explained as follows. When

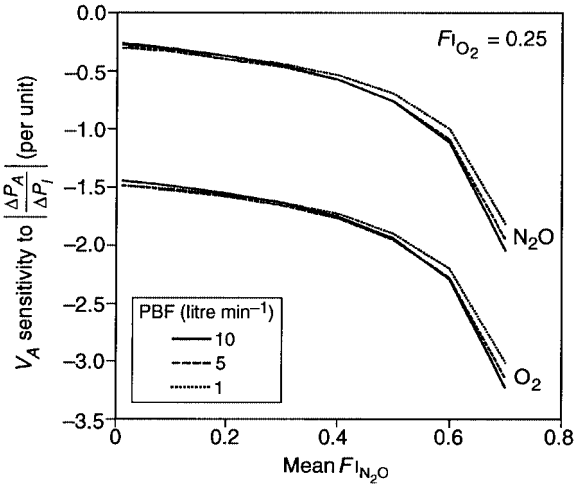

Fig 7 Per unit sensitivity of estimated alveolar volume (using simultaneous equations (A10) and (A13)) to errors in the ratios of the magnitudes of the partial pressures of the indicator gases calculated using a forward difference technique for $F_{I_{O_2}} = 0.25$ and balance N_2.

the alveolar N_2O concentration exceeds its mean value, N_2O flows from the alveolar gas into the blood, causing expiratory flow to decrease. Similarly, a decrease in alveolar N_2O concentration causes expiratory flow to increase. Hence, there is a sinusoidal component of alveolar expiratory flow superimposed on the mean flow. In a subject in whom FRC is determined by the balance of elastic and muscular forces, we would expect to observe an equivalent behaviour superimposed on tidal gas movements. Expiratory flow carries N_2O out of the alveoli at a rate proportional to the absolute alveolar N_2O concentration, hence the sinusoidal component of the expiratory flow causes a sinusoidal flux of N_2O to be superimposed on the mean expiratory flux, disturbing the mass balance of N_2O in the lung in proportion to the mean N_2O fraction. In equation (A10) this effect appears as the modifying term $(1 - \bar{P})^{-1}$. When the inspired fraction of N_2O approaches 1 ($\bar{P} = 1$), PBF causes no change in the alveolar partial pressure of N_2O and hence a 100% error results. The simplified mass balance equation (equation (A4)) is strictly true only when the indicator gas is present at negligibly low concentrations and modulated at very low amplitudes. Although the corrected equation apparently performs well under some conditions in the model study (curves (ii) in Fig. 2), the sensitivity to errors in measurements of the soluble gas concentration increases in inverse proportion to $(1 - \bar{P})$, hence this approach is impractical at high $\bar{P}$.

Equation (A13) is a complex (magnitude and phase) solution to the steady-state sinusoidal mass balance in the alveolar compartment when a soluble gas is modulated in anti-phase to an insoluble gas in the presence of at least one additional insoluble gas. If PBF is known, then equation (A13) can be solved for alveolar volume, or equations (A13) and (A10) can be solved simultaneously for alveolar volume and PBF when a third gas is present in the lungs.

When a non-respiring lung is ventilated with a modulated binary mixture of a soluble and insoluble indicator gas at constant barometric pressure, the modulation amplitudes of the indicators cannot be different. Hence, only one independent measurement can be made from which only one unknown can be estimated. In a respiring lung, the presence of CO_2 transforms the alveolar gas into a ternary mixture, and therefore in principle both volume and blood flow estimates are possible. However, the large sensitivity to measurement errors (Fig. 6) makes this approach impractical.

Figure 3 shows that when the insoluble indicator gas (in this case O_2) has a mean concentration greater than is typically used for indicator gases and is modulated at low amplitude in anti-phase with a soluble gas, then substantial but perhaps clinically acceptable (less than 10%) systematic errors in lung volume estimates result, even when the soluble gas is at a low mean concentration. These errors are approximately proportional to PBF and mean $F_{I_{O_2}}$ and are caused by the sinusoidal component of the expiratory flow. These observations are related to the last term in equation (A12) which is neglected in equation (A8). When the interdependence between the indicator gases is not neglected (equation (A13)) the systematic errors are less than 1%, although the magnitude of the sensitivity to errors in O_2 measurements is greater than unity (Fig. 7). The sensitivity to errors in soluble gas measurements exceeds unity only when $F_{I_{N_2O}} > 0.5$.

When the insoluble indicator gas is used at physiological inspired fractions (in this case O_2 at 0.20–0.30), the errors in PBF estimated by equation (A6) (Fig. 4) are similar in pattern but slightly larger in magnitude than those obtained with N_2 as insoluble indicator at an inspired fraction of 0.01 (Fig. 2). The negative bias of the corrected equation (A10) (curves (ii) in Fig. 4) results from errors in alveolar volume estimates (Fig. 3). Figure 5 shows that estimates obtained with equation (A10) are extremely sensitive to errors in alveolar volume under the conditions of this study, particularly at high $F_{I_{N_2O}}$ and low cardiac output. When alveolar volume and PBF are estimated simultaneously from noise-free measurements of soluble and insoluble gases modulated in anti-phase, then the systematic errors in PBF are small. However, the sensitivity analysis (Fig. 6) suggests that this technique is extremely sensitive to measurement error, particularly at low values of PBF.

This study has identified an upper limit on the performance of the sinusoidal forcing technique under idealized conditions, but has not examined all possible causes of error. Effects that were ignored, including non-equilibrium of the soluble indicator gas throughout the body, the solubility of the indicators in lung tissue, pulmonary shunt and variations in O_2 consumption and in RQ, are likely to increase the uncertainty in estimates of cardiopulmonary variables. Pulmonary disease leading to maldistribution of ventilation and $\dot{V}/\dot{Q}$ mismatch, and variations in FRC during anaesthesia are also likely to cause additional systematic

and random errors. Tidal breathing, the limited dynamic response of gas analysers and measurement noise limit the accuracy with which mixed expired and alveolar gas composition can be measured, and hence also adversely affect the uncertainty in the estimates, particularly when the alveolar plateau slopes steeply.

Conclusions

If soluble (N_2O) and insoluble indicator gases are used at low concentrations, and modulated at low amplitudes, then dead space, alveolar volume and PBF can be monitored simultaneously using simple closed-form equations and the magnitude of the per unit error in the PBF estimate is approximately equal to the inspired fraction of the soluble indicator. The $(1 - \bar{P})^{-1}$ correction factor allows the closed-form equations to be used with mean alveolar N_2O fractions up to ~0.7 if the mean inspired fraction of the insoluble gas is low. If the mean inspired fraction of the insoluble gas is high (0.2–0.3), then estimates of PBF are biased low by ~20% when the mean inspired fraction of N_2O is low. In this case the dependence of estimates of PBF on mean $F_{I_{N_2O}}$ is reduced by the $(1 - \bar{P})^{-1}$ correction factor for mean $F_{I_{N_2O}}$ less than ~0.3 and simple correction for the bias is possible. Simultaneous solutions to the mass balance of the two indicator gases allow alveolar volume and PBF to be estimated from noise-free measurements when the indicator gases are used at any mean concentrations in a ternary gas mixture, but the results are sensitive to measurement error, particularly at low PBF and high N_2O concentrations.

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References

1 Zwart A, Seagrave RC, van Dieren A. Ventilation-perfusion ratio obtained by a noninvasive frequency response technique. *J Appl Physiol* 1976; **41**: 419–24

2 Williams EM, Aspel JB, Burrough SML, *et al.* Assessment of cardiorespiratory function using oscillating inert gas forcing signals. *J Appl Physiol* 1994; **76**: 2130–9

3 Barton SA, Black AMS, Hahn CEW. Dynamic models and solutions for evaluating ventilation, perfusion, and mass transfer in the lung – Part I: the models. *IEEE Trans Biomed Eng* 1988; **35**: 450–7

4 Barton SA, Black AMS, Hahn CEW. Dynamic models and solutions for evaluating ventilation, perfusion, and mass transfer in the lung – Part II: analog solutions. *IEEE Trans Biomed Eng* 1988; **35**: 458–65

5 Hahn CEW. Oxygen respiratory gas analysis by sine-wave measurement: a theoretical model. *J Appl Physiol* 1996; **81**: 985–97

6 Williams EM, Hammilton R, Sutton L, Viale JP, Hahn CEW. Alveolar and dead space volume measured by oscillations of inspired oxygen in awake adults. *Am J Respir Crit Care Med* 1997; **156**: 1834–9

7 Hahn CEW, Black AMS, Barton SA, Scott I. Gas exchange in a three-compartment lung model analyzed by forcing sinusoids of N_2O. *J Appl Physiol* 1993; **75**: 1863–76

8 Williams EM, Hahn CEW. Measurements of cardiorespiratory function using single frequency gas concentration forcing signals. *Adv Exp Med Biol* 1994; **361**: 187–95

Appendix

Glossary of symbols

Symbol	Description	Unit
s	Laplace variable	s^{-1}
t	Time	s
F	Fraction	—
$\bar{P}$	Mean partial pressure	Atmospheres
$P(t)$	Partial pressure (time variable)	Atmospheres
$\dot{Q}$	Pulmonary blood flow	litres s^{-1}
V	Volume	litres
$\dot{V}$	Volumetric gas flow	litres s^{-1}
Φ	Phase angle	radians
τ	Time constant of gas turnover in lungs	s
λ	Ostwald blood–gas partition coefficient	—
ω	Frequency	rad s^{-1}

Subscripts

atm	Atmospheric	E	Expiratory
m	Metabolic gas consumption or production	I	Inspiratory
p	Pulmonary	$\bar{V}$	Mixed venous
A	Alveolar	1	Soluble indicator gas
D	Dead space	2	Insoluble indicator gas

Equations for recovering lung volumes and pulmonary blood flow

With reference to the model in Fig. 1, the mass balance of a single indicator gas with blood–gas partition coefficient λ in a perfectly mixed single-compartment lung is given by:

$$V_A \frac{d}{dt} P_A(t) = \dot{V}_{AI} P_I(t) - \dot{V}_{AE}(t) P_A(t) + \lambda \dot{Q}_p [P_{\bar{V}}(t) - P_A(t)] \quad \text{(A1)}$$

where $P_I(t)$, $P_A(t)$ and $P_{\bar{V}}(t)$ are the time varying inspired, alveolar and mixed venous partial pressures of the indicator gas. Alveolar volume V_A and continuous inspiratory alveolar ventilation ($\dot{V}_{AI}$) are assumed to be constant. $\dot{V}_{AE}(t)$ is expiratory ventilation. Storage of indicator gas in lung tissue and pulmonary capillary blood is ignored.

In the absence of metabolic gas exchange, or if the respiratory quotient is unity, the alveolar expiratory flow can be written as:

$$\dot{V}_{AE}(t) = \dot{V}_{AI} - \lambda \dot{Q}_p (P_A(t) - P_{\bar{V}}(t)) \quad \text{(A2)}$$

where $\lambda \dot{Q}_p (P_A(t) - P_{\bar{V}}(t))$ is the volumetric rate of uptake of the soluble indicator gas (in this case N_2O) by the pulmonary blood.

Under steady-state sinusoidal conditions when the indicator gas is equilibrated throughout the instrumentation and all the tissues of the subject, then $P_I(t)$ and $P_A(t)$ can be written as $P_I(t) = \bar{P} + \Delta P_I(t)$, $P_A(t) = \bar{P} + \Delta P_A(t)$, respectively, where $\bar{P}$ is the mean partial pressure which is equal in

all compartments, and $\Delta P(t)$ indicates the time-varying perturbation about the mean in each compartment. If the frequency of the sinusoid is high, the perturbations are strongly attenuated in the systemic circulation, and mixed venous content of the indicator gas is constant and $\Delta P_{\bar{V}}(t) \approx 0$.

Substituting for $\dot{V}_{AI}$, P_I, P_A and $P_{\bar{V}}$ in equation (A1) and introducing the alveolar time constant $\tau = V_A/\dot{V}_{AI}$ yields:

$$\tau \frac{d}{dt}\Delta P_A(t) = \Delta P_I(t) - \Delta P_A(t) - \frac{\dot{Q}_P}{\dot{V}_{AI}}\lambda \Delta P_A(t)(1-\overline{P}) + \frac{\dot{Q}_P}{\dot{V}_{AI}}\lambda(\Delta P_A(t))^2 \quad \text{(A3)}$$

If the perturbation amplitude is small and $\bar{P} << 1$, then equation (A3) reduces to:

$$\tau \frac{d}{dt}P_A(t) = P_I(t) - P_A(t)\left(1 + \frac{\lambda \dot{Q}_P}{\dot{V}_A}\right) \quad \text{(A4)}$$

Equation (A4) is a linear first-order differential equation. Steady-state sinusoidal modulation of $P_I(t)$ at a frequency ω rad s^{-1} results in sinusoidal perturbation of P_A with amplitude given by:

$$\frac{P_A}{P_I} = \left(\left(1 + \frac{\lambda \dot{Q}_P}{\dot{V}_A}\right)^2 + \omega^2 \tau_L^2\right)^{-\frac{1}{2}} \quad \text{(A5)}$$

Solving for $\dot{Q}_P$ yields:

$$\dot{Q}_P = \frac{\dot{V}_A}{\lambda}\left(\left(\left|\frac{P_I}{P_A}\right|^2 - \omega^2\tau_L^2\right)^{\frac{1}{2}} - 1\right) \quad \text{(A6)}$$

If the inspired indicator is insoluble ($\lambda = 0$) and the concentration of the soluble gas is negligible, then equation (A5) reduces to:

$$\frac{P_A}{P_I} = (1 + \omega^2\tau_L^2)^{-\frac{1}{2}} \quad \text{(A7)}$$

Solving equation (A7) for alveolar volume yields:

$$V_A = \frac{\dot{V}_A}{\omega}\left(\left(\frac{P_I}{P_A}\right)^2 - 1\right)^{\frac{1}{2}} \quad \text{(A8)}$$

Alveolar ventilation $\dot{V}_A$ is estimated by subtracting dead space ventilation $\dot{V}_D$ from the total ventilation $\dot{V}_E$. Dead space ventilation is given by:[2]

$$\frac{\dot{V}_D}{\dot{V}_E} = \frac{|P_{\bar{E}}|\cos\Phi_{\bar{E}} - |P_A|\cos\Phi_A}{P_I - |P_A|\cos\Phi_A} \quad \text{(A9)}$$

where Φ_A and $\Phi_{\bar{E}}$ are the phase differences between the inspiratory and alveolar, and inspiratory and mixed expiratory sinusoids, respectively, and $P_{\bar{E}}$ is the amplitude of the sinusoidally modulated mixed expired partial pressure of the indicator gas. Equation (A9) is a form of the standard Bohr dead space equation.

Therefore, if the inspiratory concentration of an insoluble indicator gas is modulated sinusoidally about an arbitrary mean value and measurements of the amplitude and phase of the alveolar and mixed expiratory concentrations are made, dead space ventilation can be recovered using equation (A9) and alveolar ventilation estimated. Alveolar volume is estimated with equation (A8) and, if a soluble gas is oscillated simultaneously at low mean concentration, pulmonary blood flow can be estimated using equation (A6).

If $\bar{P}$ is not small then equation (A6) becomes:

$$\dot{Q}_P = \frac{\dot{V}_A}{\lambda(1-\overline{P})}\left(\left(\left|\frac{P_I}{P_A}\right|^2 - \omega^2\tau_L^2\right)^{\frac{1}{2}} - 1\right) \quad \text{(A10)}$$

Most of the Oxford work[2 6–8] subsequent to Barton's papers[3 4] is based on equations (A4)–(A9).

Simultaneous solution

Equation (A10) allows the estimation of pulmonary blood flow from measurements of inspired and alveolar partial pressures of a sinusoidally modulated soluble gas at any mean partial pressure less than one atmosphere, if τ is known. If we wish to estimate V_A simultaneously from measurements of an insoluble indicator gas modulated in anti-phase with the soluble gas, then the mass balances of the two gases must be considered simultaneously. Using the subscripts 1 and 2 to denote the soluble and insoluble gases, respectively, and neglecting second-order small terms, equation (A3) can be written as:

$$\tau \frac{d}{dt}\Delta P_{A1}(t) = \left(\Delta P_{I1}(t) - \Delta P_{A1}(t)\right) - \frac{\dot{Q}_p}{\dot{V}_{AI}}\lambda \Delta P_{A1}(t)(1-\overline{P}_1) \quad \text{(A11)}$$

for the soluble gas and

$$\tau \frac{d}{dt}\Delta P_{A2}(t) = \left(\Delta P_{I2}(t) - \Delta P_{A2}(t)\right) + \frac{\dot{Q}_p}{\dot{V}_{AI}}\lambda \Delta P_{A1}(t)\overline{P}_2 \quad \text{(A12)}$$

for the insoluble gas. Equations (A11) and (A12) must be satisfied simultaneously. Transforming to the Laplace domain under steady-state sinusoidal conditions and noting that $\Delta P_{I1}(t) = -\Delta P_{I2}(t)$ when the soluble and insoluble gases are modulated in anti-phase, equations (A10) and (A11) can be solved simultaneously to yield:

$$\frac{\Delta P^*_{A2}(s)}{\Delta P^*_{I2}(s)} = \left(\frac{\dot{V}_{AI}}{sV_A + \dot{V}_{AI}}\right)\left(\frac{sV_A + \dot{V}_{AI} + \lambda\dot{Q}_p(1-\overline{P}_1-\overline{P}_2)}{sV_A + \dot{V}_{AI} + \lambda\dot{Q}_p(1-\overline{P}_1)}\right) \quad \text{(A13)}$$

where s is the Laplace variable and the superscript * indicates a transformed variable. Under steady-state sinusoidal conditions $s = i\omega$, where $i = \sqrt{-1}$. Equation (A13)

allows V_A to be estimated from the magnitude of the ratio $\Delta P_{A2}/\Delta P_{I2}$ if $\dot{Q}_p$ is known. Both V_A and $\dot{Q}_p$ can be estimated if magnitude and phase components of equation (A13) are solved simultaneously. Alternatively, V_A and $\dot{Q}_p$ can be estimated by solving equation (A10) and the magnitude component of equation (A13) simultaneously.

The model

The model is based on four simultaneous equations describing the complete mass balance of O_2, CO_2, N_2O and N_2 in a constant-volume, single-compartment well mixed lung at constant temperature and pressure. No approximations are made other than to assume that all the gases obey the perfect gas law.

$$\frac{d}{dt}V_{A_{O_2}} = P_{I_{O_2}}(t)\dot{V}_{AI} - P_{A_{O_2}}(t)\dot{V}_{AE} - \dot{V}m_{O_2}$$

$$\frac{d}{dt}V_{A_{CO_2}} = P_{I_{CO_2}}(t)\dot{V}_{AI} - P_{A_{CO_2}}(t)\dot{V}_{AE} - \dot{V}m_{CO_2}$$

$$\frac{d}{dt}V_{A_{N_2O}} = P_{I_{N_2O}}(t)\dot{V}_{AI} - P_{A_{N_2O}}(t)\dot{V}_{AE} + \lambda\dot{Q}_p\left(P\bar{v}_{N_2O} - P_{A_{N_2O}}(t)\right)$$

$$\frac{d}{dt}V_{A_{N_2}} = P_{I_{N_2}}(t)\dot{V}_{AI} - P_{A_{N_2}}(t)\dot{V}_{AE}$$

N_2 is assumed to be insoluble. $P\bar{v}_{N_2O}$ is assumed to be constant and equal to the mean inspired partial pressure of N_2. The total pressure in the alveolar compartment is always equal to atmospheric pressure:

$$P_{A_{O_2}}(t) + P_{A_{N_2}}(t) + P_{A_{N_2O}}(t) + P_{A_{CO_2}}(t) = P_{atm}$$

All gases are assumed to be ideal. For the jth gas:

$$P_{Aj}(t) = \frac{V_{Aj}(t)P_{atm}}{\sum_k V_{Ak}}$$

Inspiratory alveolar ventilation is given by:

$$\dot{V}_{AI} = (1 - F_D)\dot{V}_I$$

Expiratory alveolar ventilation ($\dot{V}_{AE}$) is adjusted in each time step to maintain constant alveolar volume.

Total expiratory ventilation is given by:

$$\dot{V}_E(t) = \dot{V}_{AE}(t) + F_D\dot{V}_I$$

In the mixed expired gas the partial pressure of the jth component is given by:

$$P_{\bar{E}j}(t) = \frac{P_{Aj}(t)\dot{V}_{AE}(t) + P_{Ij}(t)F_D\dot{V}_I(t)}{\dot{V}_E(t)}$$