Assessment of lung function using a non-invasive oscillating gas-forcing technique

Lei Clifton, David A. Clifton, Clive E.W. Hahn, Andrew D. Farmery

Nuffield Division of Anaesthetics, Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK
Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Old Road Campus, Roosevelt Drive, Oxford OX3 7DQ, UK

A R T I C L E   I N F O
Article history:
Accepted 13 May 2013

Keywords:
Lung function
Non-invasive
Alveolar volume
Airway dead space
Pulmonary blood flow
Tidal ventilation
Model
Oscillating
Gas-forcing
Nitrous oxide
Oxygen
Indicator gas

A B S T R A C T
Conventional methods for monitoring lung function can require complex, or special, gas analysers, and may therefore not be practical in clinical areas such as the intensive care unit (ICU) or operating theatre. The system proposed in this article is a compact and non-invasive system for the measurement and monitoring of lung variables, such as alveolar volume, airway dead space, and pulmonary blood flow. In contrast with conventional methods, the compact apparatus and non-invasive nature of the proposed method could eventually allow it to be used in the ICU, as well as in general clinical settings. We also propose a novel tidal ventilation model using a non-invasive oscillating gas-forcing technique, where both nitrous oxide and oxygen are used as indicator gases. Experimental results are obtained from healthy volunteers, and are compared with those obtained using a conventional continuous ventilation model. Our findings show that the proposed technique can be used to assess lung function, and has several advantages over conventional methods such as compact and portable apparatus, easy usage, and quick estimation of cardiopulmonary variables.

© 2013 The Authors. Published by Elsevier B.V. All rights reserved.

1. Introduction
Patients in the intensive care unit (ICU) often require mechanical ventilatory support using positive pressure ventilation (Rouby et al., 2004). Estimation of lung variables benefits these patients because they help the clinician to determine the most suitable values in therapeutic measures such as positive end-expired pressure (PEEP). They could also help to avoid the common problem of ventilator induced lung injury (VILI). Three key lung variables are:

1. alveolar volume at the end of an expiration, $V_A$
2. airway dead space volume, $V_D$
3. pulmonary blood flow, $Q_P$

Current techniques for measuring these variables can require the cooperation of the patient, or a modification of the patient's ventilator system. ICU patients depend on complex life support and monitoring equipment, and thus are usually unable to cooperate with the physician. These patients are therefore some of the most difficult to assess using conventional lung function tests.

Zwart et al. pioneered the non-invasive oscillating gas-forcing technique (Zwart et al., 1976, 1978), and used halothane as the forcing gas at a very low concentration (around 0.02, $v/v$) to measure the average ventilation-perfusion ratio ($V/Q$) in the lung. Hahn et al. further developed this method by using biologically inert gases such as nitrous oxide ($N_2O$) and argon (instead of halothane) to measure $V_A$, $V_D$, and $Q_P$ non-invasively (Hahn et al., 1993; Williams et al., 1994). They later proposed that oxygen ($O_2$) can be used to measure $V_A$ and $V_D$ (Hahn, 1996; Hamilton, 1998). When $O_2$ was used together with $N_2O$, their model can also be used to measure $Q_P$. However, their initial technique required a respiratory mass spectrometer that presented considerable difficulty when used in the ICU due to its size, noise, complexity, high maintenance requirements, and lack of portability (Farmery, 2008). Moreover, their prototype gas mixer is not compatible with modern ICU ventilators. There was therefore a clinical need to design a new system to deliver indicator gases according to the patient’s breathing flow rates in real time.

A conventional existing model based on continuous ventilation is described in Section 2; we propose a novel non-invasive method for estimating the cardiopulmonary variables, $V_A$, $V_D$, and $Q_P$ in Section 3. Indicator gases $O_2$ and $N_2O$ are injected into the patient’s...
airway breath-by-breath "on the fly" to make the concentration of
these gases vary sinusoidally in the inspired gas. The apparatus
is compact in size and is portable, consisting of a flow rate
sensor, a gas concentration sensor, and two mass flow controllers (MFCs).
We improve the original Bohr equation for dead space calculation in
Section 4. Results obtained using the proposed single alveolar com-
partment tidal ventilation model are compared with those obtained
using the continuous ventilation model in Section 5. A discussion
is presented in Section 6, and conclusions are drawn in Section 7. A
list of abbreviations can be found in the appendix.

2. The continuous ventilation model

The continuous ventilation model (Zwart et al., 1976; Hahn et al.,
1993; Hahn, 1996; Williams et al., 1994), as shown in Fig. 1(a), treats
the lung as a rigid volume with a constant flow rate of gas passing
through it. Dead space is regarded as a tube of negligible volume
parallel to the lung, with another constant flow rate passing through it.
The inspired concentration of an indicator gas $F_i(t)$ is controlled by a
gas mixing apparatus, and is forced to vary sinusoidally at a chosen
frequency.

$$ F_i(t) = M_i + \Delta F_i \sin(2\pi ft + \phi), \tag{1} $$

where $M_i$ and $\Delta F_i$ are the mean and amplitude of the forcing
indicator gas sinusoid, respectively, $f$ is the forcing frequency in min$^{-1}$,
and $\phi$ is the phase of the sine wave.

In the absence of venous recirculation, and assuming that the
inspired indicator gas concentration is in equilibrium in all tissues
throughout the respiratory and cardiovascular systems, the mixed-expired
and end-expired (i.e., alveolar) indicator gas concentrations are also
forced to be sinusoidal (Zwart et al., 1976; Hahn et al., 1993; Williams et al., 1994).

Let $F_A$ be the indicator gas concentration in the alveolar compart-
ments of the lung, and $\Delta F_A$ be the amplitude of $F_A$ measured
from its mean; we therefore have (Hahn et al., 1993)

$$ \frac{\Delta F_A}{\Delta F_i} = \frac{1}{\sqrt{(1 + \lambda_b (\dot{Q}_b/V_A))^2 + \omega^2 \tau^2}} \tag{2} $$
in which $\lambda_b$ is the blood-gas solubility coefficient; note that
$\lambda_b = 0.03$ for $O_2$, and $\lambda_b = 0.47$ for $N_2O$. $\omega$ is the forcing
frequency in radians; i.e., $\omega = 2\pi f$. $\tau$ is the lung ventilatory time constant,

$$ \tau = \frac{V_A'}{V_A}, \tag{3} $$

where $V_A'$ is the effective lung volume given by (4) below, and $V_A$
is the ventilation rate in L/min (Gavaghan and Hahn, 1995). The relationship is given by

$$ V_A = V_A + \lambda_B V_B + \lambda_D V_D, \tag{4} $$

where $V_D$ is the volume of blood in the lung, $V_A$ is the volume of lung
tissue, and $\lambda_D$ is the lung tissue-gas partition coefficient. Indicator
gas $O_2$ can be approximately regarded as a non-soluble gas with
$\lambda_b \approx 0$ and $\lambda_D \approx 0$, hence $V_A' = V_A$. Therefore, $\tau$ for $O_2$ is

$$ \tau_{O_2} = \frac{V_A}{V_A'}, \tag{5} $$

For the soluble gas $N_2O$, using the values of the above variables
given in Gavaghan and Hahn (1995), (4) can be re-written as $V_A' = V_A + 0.43$. Therefore $\tau$ for $N_2O$ is

$$ \tau_{N_2O} = \frac{V_A + 0.43}{V_A'}, \tag{6} $$

We can express the ventilation rate $V_A$ by (Williams et al., 1994)

$$ V_A = R(V_T - V_D), \tag{7} $$

where $R$ is the respiration rate in breaths/min, $V_T$ is the tidal volume,
and $V_D$ is the airway dead space volume.

At high frequencies $\omega$, the term $\omega^2 \tau^2$ dominates the denomina-
tor in (2), therefore allowing $\tau$ to be estimated using

$$ \frac{\Delta F_A}{\Delta F_i} \rightarrow \frac{1}{\omega^2 \tau^2} \tag{8} $$

where $\Delta F_A$, $\Delta F_i$, and $\omega$ are known values. The estimated $\tau$ is then
subsequently used to determine lung volume $V_A$ using (3) and (4).

Conversely, at low values of $\omega$, the term $\lambda_b (\dot{Q}_b/V_A)$ dominates the denominator in (2), and therefore reveals information concerning $\dot{Q}_b$. This indicates that careful selection of $\omega$ allows the variable
determination of both lung volume $V_A$ and lung perfusion $\dot{Q}_b$.

Hahn et al. (1993) found that the forcing sinusoidal frequency
should be $f > 1$ min, when $N_2O$ is used as the forcing gas.

Lung volume $V_A$ derived from a continuous ventilation model is
greater than the actual $V_A$, due to the assumption that $V_A$ is constant. In reality, the lung volume including dead space volume $V_D$
tidies between $(V_A + V_D)$ at the beginning of inspiration
and $(V_A + V_B + V_T)$ at the end of inspiration. Sainsbury et al. (1997)
showed that subtracting a correction term $V_T$ from the lung volume
determined by the continuous ventilation model produces a more
realistic estimate of the lung volume,

$$ V_L = \frac{1}{2}(V_T + V_D) \tag{9} $$
In our proposed new system, we have used both O2 and N2O to estimate \( V_A \) and \( Q_p \). With the indicator gas O2 regarded as a non-soluble gas with \( \lambda \approx 0, \) (2) therefore becomes
\[
\left( \frac{\Delta F_A}{\Delta F_I} \right)_{O_2} = \frac{1}{\sqrt{1 + \omega^2 t_{O_2}^2}},
\]
(10)
where \( \left( \frac{\Delta F_A}{\Delta F_I} \right)_{O_2} \) indicates \( \Delta F_A/\Delta F_I \) obtained using O2 data.

From (5) and (10), we have
\[
V_A = \frac{V_{IT}}{2\pi} \left[ \left( \frac{\Delta F_A}{\Delta F_I} \right)_{O_2}^2 - 1 \right]^{1/2}
\]
(11)
where \( V_A \) is given by (7), and \( T \) is the forcing sinusoidal period in minutes; i.e., \( T = f^{-1} = 2\pi(\omega)^{-1} \). Here we have reached the estimate of lung volume \( V_A \), using (11).

For the soluble indicator gas N2O, (2) can be re-written as
\[
\left( \frac{\Delta F_A}{\Delta F_I} \right)_{N_2O} = \frac{1}{\sqrt{1 + 0.47(Q_{p}/V_A)}}^{2} + \omega^2 t_{N_2O}^2
\]
(12)
From (5), (6), (10) and (12), we have
\[
Q_p = \frac{V_A}{0.47} \left[ \left( \frac{\Delta F_A}{\Delta F_I} \right)_{N_2O}^2 - \left( \frac{VA + 0.43}{VA} \right)^2 . \left( \frac{\Delta F_A}{\Delta F_I} \right)_{O_2}^2 + \left( \frac{VA + 0.43}{VA} \right)^2 \right]^{1/2},
\]
where \( V_A \) is given by (7), and \( V_A \) is given by (11).

A set of \( V_A \) and \( Q_p \) can be produced at any sinusoidal period \( T \), using (11) and (12) where both O2 and N2O contribute to the estimation.

In previous work concerning the continuous ventilation model (Hahn, 1996; Hamilton, 1998), only one type of indicator gas was used, hence \( V_A \) and \( Q_p \) had to be estimated separately. One of the proposed system is that, for the first time, \( V_A \) and \( Q_p \) can be estimated at the same time using the continuous ventilation model, and this therefore reduces the time to obtain estimates \( V_A \) and \( Q_p \). This is achieved by injecting two types of indicator gases O2 and N2O simultaneously, where O2 data are used to estimate \( V_A \), and N2O data are used to estimate \( Q_p \), when the continuous ventilation model is applied.

A drawback of the continuous ventilation model is that it requires a relatively long period of time to obtain its measurements, mainly because obtaining \( \Delta F_A/\Delta F_I \) requires the duration of signals to be at least one period \( T \) (and is typically taken to be several periods). In the ICU or operating theatre where prompt response to changes in patient conditions is required, it is essential to estimate patient lung function in a short time. In Section 3, we propose a breath-by-breath tidal ventilation model (assuming a single alveolar compartment), which allows fast estimation of patient lung function in a non-invasive manner.

3. The tidal ventilation model

3.1. A breath-by-breath model

In contrast with the continuous ventilation model discussed in Section 2, a tidal ventilation model was introduced by Gavaghan and Hahn (1996), and later modified by Williams et al. (Williams et al., 1998; Whiteley et al., 2000, 2003; Farmery, 2008). We employ a “balloon-on-a-straw” tidal ventilation model (Hahn and Farmery, 2003), shown in Fig. (1b).

In a “balloon-on-a-straw” tidal ventilation model, the gases enter and leave the lung via a common dead space (the straw) of volume \( V_D \). Compared with the rigid volume of the continuous ventilation model, the lung volume (the balloon) in the “balloon-on-a-straw” model reflects the reality of breathing, where the lung expands during inspiration and empties during expiration. A detailed description of the “balloon-on-a-straw” tidal ventilation model can be found in Hahn and Farmery (2003).

Let \( F_{A,n} \) be the indicator gas concentration in the lung during breath \( n \); we assume that \( F_{A,n} \) is constant during any breath \( n \), and hence is not dependent on time \( t \). The volumes of the indicator gas at the end of breath \( (n - 1) \) and \( n \) are \( V_A F_{A,n-1} \) and \( V_A F_{A,n} \), respectively. Let \( V_I \) be the volume of indicator gas delivered into the lung during breath \( n \), let \( V_Q \) be the expired volume of the indicator gas during breath \( n \), and let \( V_Q \) be the uptake of the indicator gas (i.e., the amount of indicator gas absorbed by the pulmonary capillary blood in the lung) during breath \( n \). Conservation of mass requires that at the end of breath \( n \), the volume change of indicator gas in the alveolar compartments is equal to the inspired indicator gas less the sum of expired volume and the pulmonary uptake. Hence,
\[
V_A F_{A,n} - V_A F_{A,n-1} = V_I - V_E - V_Q.
\]

In the remainder of this section, we will further explore the mathematical expression of \( V_I, V_Q \), and \( V_Q \).

The inspired indicator gas volume \( V_I \) can be expressed as
\[
V_I = \int_{t_{SI}}^{t_{EI}} V(t) F_{IA,n}(t) dt
\]
(15)
where \( t_{SI} \) is the time at the beginning of inspiration, \( t_{EI} \) is the time at the end of inspiration, \( V(t) \) is the measured respiratory flow rate at time \( t \), and \( F_{IA,n}(t) \) is the inspired concentration of the indicator gas that enters the alveolar compartment during breath \( n \).

The gas inspired into the alveolar compartment in is two parts: the first comes from the dead space compartment, and the second is fresh inspired gas. \( F_{IA,n}(t) \) also therefore consists of two parts: the first part has a value of \( F_{A,n-1} \), since this was the alveolar concentration of indicator gas from the previous breath which now resides in the dead space; the second part has a value of \( F_{I,n}(t) \), the concentration of the indicator gas measured by the concentration sensor at the mouth during inspiration of breath \( n \). Here we have made the distinction between indicator gas concentration in the lung and that at the mouth, and therefore \( F_{IA,n}(t) \) can be expressed as
\[
F_{IA,n}(t) = \begin{cases} 
F_{A,n-1} & \text{if } t_{SI} \leq t < t_{SI} + T_{DI} \\
F_{I,n}(t) & \text{if } t_{SI} + T_{DI} \leq t < t_{EI}.
\end{cases}
\]
(16)
where \( T_{DI} \) is the time taken for the indicator gas to travel through the dead space during inspiration of breath \( n \).

Substituting (16) into (15), we have
\[
V_I = \int_{t_{SI}}^{t_{SI} + T_{DI}} V(t) F_{A,n-1} dt + \int_{t_{SI} + T_{DI}}^{t_{EI} - T_{DI}} V(t) F_{I,n}(t) dt
\]
\[
= V_D F_{A,n-1} + \int_{t_{SI}}^{t_{EI} - T_{DI}} V(t) F_{I,n}(t) dt
\]
(17)

Here we have arrived at an expression for \( V_I \). Now we seek to find an expression for \( V_Q \) and \( V_Q \), to complete the conservation of mass equation (14).

In the above analysis of the first part of \( F_{IA,n}(t) \) in (16), we have assumed that \( F_{A,n} \) (the indicator gas concentration in the lung during breath \( n \)) is constant during any breath \( n \); this means that \( F_{A,n} \) is
equal to $F_{E,n}$ (the measured indicator gas concentration at the end of expiration in breath $n$). That is,

$$F_{A,n} = F_{E,n}$$ \hspace{1cm} (18)

The reason for using $F_{E,n}$ here is that it is more readily measured than $F_{A,n}$. $F_e$ (the function of $F_{E,n}$ over all breaths) is a sine wave expressed in Eqs. (25) and (26), using our indicator gas injection method in Section 3.2. Eq. (18) implies that $F_{A}$ (the function of the indicator gas concentration in the lung from all breaths) is also a sine wave.

The expired indicator gas volume $V_i$ can be expressed as

$$V_i = V_{T,n} F_{A,n},$$ \hspace{1cm} (19)

where $V_{T,n}$ is the tidal volume (the volume of gas inhaled and exhaled) during breath $n$.

Substituting (18) into (19) gives the final expression for $V_i$

$$V_i = V_{T,n} F_{E,n}.$$ \hspace{1cm} (20)

The uptake of the indicator gas $V_Q$ is

$$V_Q = Q_p \lambda_b (F_{A,n} - F_{T,n}) T_n,$$ \hspace{1cm} (21)

where $Q_p$ is the pulmonary blood flow, $\lambda_b$ is blood solubility coefficient of the indicator gas, and $T_n$ is the duration of breath $n$. $F_{T,n}$ is the average indicator gas concentration returned to the lung through venous recirculation in breath $n$.

Some of the inspired indicator gas is taken up by the pulmonary capillary blood in the lung, and eventually returns to the lung via venous recirculation. Previous research has shown that at carefully chosen forcing frequencies, the venous recirculation effects can be ignored (Hahn et al., 1993; Gavaghan and Hahn, 1995) because the oscillatory component of the venous concentration signal is negligible at these forcing frequencies, leaving

$$F_{T,n} = M_{A},$$ \hspace{1cm} (22)

where $M_{A}$ is the mean of the alveolar sinusoid $F_A$. We have stated in (18) that $M_{A}$ is equal to the mean of the measured sinusoid $F_E$.

Substituting (22) and (18) into (21), we have an expression for $V_Q$

$$V_Q = Q_p \lambda_b (F_{E,n} - M_{A}) T_n.$$ \hspace{1cm} (23)

Here we have reached expressions for $V_i$, $V_E$, and $V_Q$ in Eqs. (17), (20) and (23), respectively. Substituting them into the right-hand-side of (14), and substituting (18) into the left-hand-side of (14), we have

$$V_A \left( F_{E,n-1} - F_{E,n} \right) + Q_p \lambda_b \left( M_A - F_{E,n} \right) T_n$$

$$= V_{T,n} F_{E,n} - \left[ V_D F_{E,n-1} + \int_{t_n}^{t_n+T_n} \dot{V}(t) F_{E,n}(t) dt \right].$$ \hspace{1cm} (24)

This is the conservation of mass equation for the lung variables that we aim to estimate, expressed in terms of volume change of the indicator gas in a breath-by-breath manner. Our goal is to determine the values of $V_A$ and $Q_P$ in (24). The measured variables are $F_{E,n-1}, F_{E,n}, F_{T,n}, V_{T,n}$, and $M_{A}$; the blood solubility coefficient $\lambda_b$ is a known constant for the chosen indicator gas. We have previously used the Bohr equation to calculate $V_Q$ (Clifton et al., 2009); here $V_D$ is calculated using the method proposed in Section 4 where both CO2 and the indicator gas were used to achieve a robust estimate of $V_D$. Using (24), every two successive breaths produce an equation; therefore a total of $N$ breaths results in $N-1$ equations of two unknown values, $V_A$ and $Q_P$. For this set of $N-1$ linear equations, we used the least-squares technique to determine the values of $V_A$ and $Q_P$.

3.2. "On the fly" indicator gas delivery

Early ventilators such as the Servo 900 (Siemens) were capable of being driven by an auxiliary low pressure gas supply, and so could be fed by a gas mixer generating sinusoidal indicator concentrations. However, modern ICU ventilators cannot be adapted easily to allow premixed gases to be delivered. Consequently, the indicator gas must be injected into the inspiratory limb of the ventilator “on the fly”. We adapted a novel on-line indicator gas delivery method (Farmery, 2008), where the indicator gas is injected into the patient’s inspiratory breathing flow and mixed in real time immediately before entering the mouth. Two types of indicator gases, O2 and N2O, are injected simultaneously into the patient’s airway flow during inspiration. Two mass flow controllers (MFC, Alicat Scientific, Inc., USA) were used to deliver the two indicator gases at rates proportional to the subject’s inspiratory flow rate at any instant such that the indicator concentration remained constant within the breath, but could be forced to vary between breaths according to

$$F_{N_2O}(t) = M_{N_2O} + \Delta F_{N_2O} \sin(2\pi ft)$$ \hspace{1cm} (25)

$$F_{O_2}(t) = M_{O_2} + \Delta F_{O_2} \sin(2\pi ft),$$ \hspace{1cm} (26)

where $F_{N_2O}(t)$ is the concentration of the injected N2O flow; $M_{N_2O}$ and $\Delta F_{N_2O}$ are the mean and amplitude of the forcing N2O sinusoid,
respectively; \( F_O(t), M_O, \) and \( \Delta F_O \) are similar denotations for \( O_2 \).

A D-lite™ flow sensor (GE Healthcare, Finland) and a differential pressure transducer (Validyne Engineering, USA) were used to measure breathing flow rates. The indicator gas concentration was measured by an IRMA™ multi-gas analyser (PHASEIN AB, Sweden) that measures \( O_2, N_2O, CO_2, \) and other anaesthetic gases simultaneously. Detailed measuring principles and sensor calibration data can be found in Farmery (2008) and Van der Hoeven (2007). Both the flow sensor and the concentration sensor can be mounted on the breathing tube connected to the patient. Compared with the apparatus for previous continuous (Hahn et al., 1993; Williams et al., 1994) and tidal models (Williams et al., 1998), the proposed setup is portable, simple to use, and is suitable for the ICU because of its non-invasive nature.

It is essential to enhance the “response time” (the time taken for the signal to rise to 90% of its value after a step response) of the concentration signals in the proposed breath-by-breath tidal ventilation model (Farmery and Hahn, 2000) in order to avoid errors in estimation of the mass flux of gases. A first-order exponential model (Clifton et al., 2009) has been applied to reduce the response time to around 100 ms.

3.3. Venous recirculation

Both the continuous model (Zwart et al., 1976, 1978) and the tidal model (Gavaghan and Hahn, 1996; Williams et al., 1998; Whiteley et al., 2000, 2003) have regarded the oscillatory component of the venous recirculation signals as being sufficiently small to be neglected. Gavaghan et al. constructed a mathematical model including recirculation times (Gavaghan and Hahn, 1995) and concluded that the recirculation effects are negligible in the forcing period range of 0.5 min \( \leq T \leq 4 \) min for the soluble gases halothane, acetylene, and \( N_2O \) (Gavaghan and Hahn, 1995), and become more pronounced at long forcing periods \( T > 4 \) min. Williams et al. recommended forcing sine periods of 2 min \( \leq T \leq 3 \) min for solving airway dead space \( V_D \) and lung volume \( V_A \) (Williams et al., 1994, 1998). In Section 5 we show that 2 min \( \leq T \leq 4 \) min is a potentially appropriate range for forcing sinusoidal periods \( T \).

4. Dead space calculation

4.1. Original Bohr equation

Various methods for calculating the volume of airway dead space \( V_D \) are discussed in Farmery (2008), among which two classical methods are Fowler’s method (Fowler, 1948; Fletcher et al., 1981) and the Bohr equation (Hlastala and Berger, 1996). The latter is used in the proposed method as follows:

\[
V_D = V_T \frac{F_A - F_F}{F_F - F_T},
\]

where \( F_F \) is the mixed expired indicator gas concentration, and \( F_T \) is the indicator gas concentration at the end of inspiration.

We have assumed that \( F_{A,n} \) is constant during breath \( n \), and is equal to \( F_{E,n} \) in (18). Substituting (18) into (27) gives

\[
V_D = V_T \frac{F_E - F_F}{F_F - F_T},
\]

where \( F_E \) is the indicator gas concentration at the end of expiration. In the tidal ventilation model, each breath \( n \) produces data which allows a separate solution of the Bohr equation using (28).

However, one potential problem when (28) is used to produce an estimate of the value of \( V_D \) at each breath is that at breaths where the values of the numerator or the denominator in (28) are close to zero, the estimates of \( V_D \) become sensitive to small measurement errors, and so the solution becomes unstable.

Another problem is the choice of gases when using (28): both \( CO_2 \) and the indicator gas produce a set of Bohr equations. The estimated values of \( V_D \) obtained using different gases are usually different from one another, and it is difficult to know which gas produces the more reliable results. A simple average of all the various estimates for each indicator gas may not be sufficiently stable, if some estimates are erroneous.

4.2. Improved Bohr equation

To overcome the problems described above, we propose a regression approach to improve the stability of the original Bohr equation. We re-write (28) as

\[
(F_E - F_F) = V_D \frac{V_D}{V_T} (F_E - F_T).
\]

Each breath produces a set of values for \( x \) and \( y \), corresponding to a point on a straight line

\[
y = ax,
\]

where \( y = (F_E - F_F), x = (F_E - F_T) \), and \( a \) is the slope of the line, \( a = V_D/V_T \). The optimal value of \( V_D \) can be determined by finding the value of \( a \) that best describes the straight line using linear regression.

Values \((x, y)\) of both \( CO_2 \) and the indicator gas from all breaths are used in the linear regression, in order to achieve a robust estimate that incorporates results obtained using both gases. The proposed method uses all breaths without suffering from the instabilities induced by near-zero values in the original Bohr equation.

The results shown in Section 5.2 indicate that using both gases achieves a more robust estimate than using a single gas, and that the proposed linear regression approach is more stable than using a simple average of estimates obtained using the original Bohr equation.

5. Results and comparisons

Twenty data sessions from healthy human volunteers were studied, with results obtained from one volunteer studied in detail in this paper, for illustration of the prototype system. Results obtained from all volunteers are then summarised in Fig. 4 and Table 3. Both \( N_2O \) and \( O_2 \) are injected as indicator gases.

For each of \( T = 2, 3, 4, \) and 5 min, data were collected for 10 min duration. For the tidal ventilation model, the data were divided into 20 data windows (i.e., each window contained 30 s of data); each of these windows of data was used to estimate \( V_D, V_A, \) and \( Q_0 \). The mean and standard deviation of these estimates are shown in Fig. 3(a)-(c). The continuous ventilation model requires measurements of \( \Delta F_A \) and \( \Delta F_T \), and hence the total duration of data was used to produce a single set of estimates for this method, against which our breath-by-breath tidal ventilation model will be compared.

5.1. Comparison of the continuous ventilation model with the tidal ventilation model

As described in Section 2, for the continuous ventilation model, a set of \( V_D \) and \( Q_0 \) estimates can be produced at any sinusoidal period \( T \), using (11) and (13), where both \( O_2 \) and \( N_2O \) estimates contribute to the overall estimates.

For the tidal ventilation model, the results obtained using \( N_2O \) are presented. The results obtained using \( O_2 \) are similar to those obtained using \( N_2O \), and are not shown here. In (25), we have chosen indicator gas parameters \( M_{N_2O} = 0.06 \) l/min, \( A_{N_2O} = 0.03 \) l/min, which is a non-toxic concentration level for \( N_2O \).
Fig. 3. (a)–(c) Comparison of results for the continuous ventilation model with those of the tidal ventilation model, at forcing sinusoidal periods \( T = 2, 3, 4, 5 \) min for one individual. Results for the continuous and the tidal ventilation model are shown by dashed and solid lines, respectively. Note that results obtained using the continuous ventilation model do not have the error bars, because it uses all of the data to perform a single estimation. (d) Dead space results obtained using a healthy male volunteer. (x, y) pairs obtained using CO\(_2\) and N\(_2\)O are shown using ( , +), respectively. Regression lines obtained using only N\(_2\)O and using both CO\(_2\) and N\(_2\)O are shown by solid and dashed lines, respectively. The regression line obtained using N\(_2\)O is approximately the same as the regression line obtained using both CO\(_2\) and N\(_2\)O.

Fig. 4. Comparison of results obtained using the continuous ventilation model with those of the tidal ventilation model, at forcing sinusoidal periods \( T = 3 \) min. Results of \( V_A \) and \( Q_F \) are shown in (a) and (b), respectively, as Bland–Altman plots. The mean and differences (continuous − tidal) of estimates obtained using the two models are shown on the x- and y-axis, respectively. Mean difference and the limit of agreement (mean difference ± 1.96\( \sigma \), where \( \sigma \) is the standard deviation of the differences) are plotted as horizontal dashed lines.

Table 1 compares the continuous ventilation model with the tidal ventilation model, using data obtained from a healthy male volunteer. The results in Table 1 are also plotted in Fig. 3(a)–(c), where standard deviations of the results obtained using the proposed tidal ventilation model are shown as error bars. Fig. 3(a)–(c) compares the estimate obtained using the continuous ventilation model with the average values of the estimates produced by the tidal ventilation model at different forcing frequencies in one individual.

5.2. Results of estimating \( V_D \)

Estimated values of \( V_D \) using the mean and linear regression approaches are shown in Table 2. Three types of results are

| T (min) | \( V_D \) (L) | \( V_A \) (L) | \( Q_F \) (L/min) |
|--------|---------------|---------------|-----------------|
|        | CV | TV | CV | TV | CV | TV | CV | TV |
| 2      | 0.26 | 0.26 | 1.77 | 1.56 | 2.78 | 2.11 |
| 3      | 0.26 | 0.26 | 1.72 | 1.66 | 3.22 | 3.25 |
| 4      | 0.25 | 0.25 | 1.67 | 1.84 | 3.54 | 2.90 |
| 5      | 0.26 | 0.26 | 2.55 | 2.37 | 2.66 | 2.25 |

Table 2

| T (min) | \( V_D \) only | \( N_2O \) only | \( CO_2 + N_2O \) |
|--------|----------------|-----------------|-------------------|
|        | \( V_{D_{BOHR}} \) | \( V_{D_{BOHR}} \) | \( V_{D_{BOHR}} \) |
| 2      | 0.27 | 0.75 | 0.40 | 0.26 | 0.33 | 0.26 |
| 3      | 0.27 | 0.65 | 0.19 | 0.23 | 0.23 | 0.26 |
| 4      | 0.27 | 0.73 | 0.26 | 0.24 | 0.27 | 0.25 |
| 5      | 0.27 | 0.85 | 0.35 | 0.24 | 0.31 | 0.26 |
Table 3
Comparison of the continuous ventilation (CV) model with the tidal ventilation (TV) model. Results are obtained from healthy volunteers; the first 13 data sessions are from male volunteers of age 20–60 years, and the remaining 3 data sessions are from female volunteers of age 20–40 years. The standard deviation on the estimates of the TV model are shown as “estimate ± standard deviation”. Both N2O and O2 are used as indicator gases, and results obtained using N2O are shown here. Results obtained using O2 are similar to those obtained using N2O, and hence are not shown here. The forcing sinusoidal period T = 3 min; Vp, estimates are equal to V
\text{space} using both CO2 and N2O.

| Session | V0 (L) | CV | TV | V0 (L) | CV | TV | Qp (L/min) | CV | TV |
|---------|-------|----|----|-------|----|----|------------|----|----|
| 1       | 0.26  | 0.26 ± 0.002 | 1.72 | 1.66 ± 0.32 | 3.22 | 3.25 ± 0.85 |
| 2       | 0.28  | 0.28 ± 0.001 | 2.92 | 2.98 ± 0.59 | 3.56 | 3.46 ± 0.67 |
| 3       | 0.26  | 0.26 ± 0.002 | 2.69 | 2.47 ± 0.43 | 4.91 | 4.68 ± 0.64 |
| 4       | 0.37  | 0.37 ± 0.001 | 1.34 | 1.57 ± 0.52 | 2.38 | 2.69 ± 0.62 |
| 5       | 0.33  | 0.33 ± 0.001 | 1.70 | 2.27 ± 0.49 | 3.00 | 3.29 ± 0.65 |
| 6       | 0.28  | 0.28 ± 0.001 | 2.99 | 2.53 ± 0.31 | 2.70 | 2.16 ± 0.93 |
| 7       | 0.30  | 0.30 ± 0.002 | 1.90 | 2.26 ± 0.52 | 4.09 | 3.68 ± 0.69 |
| 8       | 0.32  | 0.32 ± 0.002 | 2.13 | 2.25 ± 0.42 | 4.19 | 3.43 ± 0.79 |
| 9       | 0.24  | 0.24 ± 0.001 | 2.35 | 2.45 ± 0.38 | 3.60 | 2.96 ± 0.44 |
| 10      | 0.29  | 0.29 ± 0.001 | 2.17 | 2.18 ± 0.54 | 3.91 | 3.23 ± 0.72 |
| 11      | 0.23  | 0.23 ± 0.001 | 2.61 | 2.38 ± 0.75 | 3.77 | 2.95 ± 0.81 |
| 12      | 0.21  | 0.21 ± 0.003 | 2.24 | 2.41 ± 0.36 | 3.40 | 3.74 ± 0.64 |
| 13      | 0.35  | 0.35 ± 0.001 | 2.06 | 1.69 ± 0.53 | 3.19 | 2.57 ± 0.42 |
| 14      | 0.25  | 0.25 ± 0.002 | 1.99 | 2.02 ± 0.60 | 3.01 | 2.84 ± 0.72 |
| 15      | 0.23  | 0.23 ± 0.001 | 1.72 | 1.39 ± 0.47 | 2.81 | 2.47 ± 0.82 |
| 16      | 0.29  | 0.29 ± 0.001 | 2.20 | 1.98 ± 0.34 | 2.44 | 2.62 ± 0.52 |
| 17      | 0.27  | 0.27 ± 0.002 | 1.86 | 1.53 ± 0.46 | 2.71 | 2.07 ± 0.71 |
| 18      | 0.23  | 0.23 ± 0.001 | 1.20 | 1.35 ± 0.51 | 3.35 | 2.27 ± 0.73 |
| 19      | 0.22  | 0.22 ± 0.003 | 1.79 | 2.12 ± 0.61 | 3.61 | 2.89 ± 0.59 |
| 20      | 0.27  | 0.27 ± 0.001 | 1.71 | 1.75 ± 0.34 | 3.59 | 2.88 ± 0.75 |

presented: results obtained using CO2, results obtained using N2O, and results obtained using both CO2 and N2O. Results obtained using indicator gas O2 are similar to those using N2O, and are not shown here.

5.3. Results from all human volunteers

Fig. 4 shows Va and Qp results from all human volunteers. Table 3 compares the results derived from the continuous model with the tidal ventilation model. Results of V0, shown in Table 3, obtained using the continuous model are, with experimental error, the same as those obtained using the tidal model. Hence, they are not plotted in Fig. 4.

6. Discussion

It is acknowledged that the two models described in this work have only a single alveolar compartment and a single dead space compartment. The great advantage of these models is that they can be “inverted” when real physiological data is inserted in them to reveal estimates of physiological variables which have meaning to the clinician or physiologist. Due to their simplicity, they can only be used to describe relatively healthy lungs. However, as Whiteley et al. (Whiteley et al., 2000) demonstrated, the use of mathematical models with more than one lung compartment can lead to great difficulty in reaching an inverse solution for the respiratory variables of dead space, alveolar volume, and pulmonary blood flow when the subject’s lung is inhomogeneous. Also, such models do not lend themselves readily to physiological interpretation. This is why simple one-alveolar lung compartment models have survived the succeeding decades after they were first proposed (Hahn and Farmery, 2003). Our techniques are likely to be valid in exercise testing in subjects or patients without overt lung disease, and could be applied to the field of human exercise physiology, as pioneered by Luijendijk et al. (Luijendijk et al., 1981) for the forced inspired sine wave technique.

We have not yet evaluated the techniques for patients with severe lung disease. However, we note that for our single compartment model, the solutions for VA, Qp, and Qp should be the same regardless of the period of the sinusoid. Our preliminary modelling and experimental work reveals that where ventilatory inhomogeneity exists, the determined variables appear to be dependent on the period. The degree of period dependency is likely to provide a robust index of ventilatory heterogeneity, and this will be developed in future work.

Oxygen is used as an indicator gas in these studies. It is assumed that oxygen behaves much like an insoluble inert gas with respect to the diminution of the amplitude of its sinusoidal inspired concentration within the alveolar compartment. This is because in this analysis it is only the oscillatory components of the indicator concentration signal which is required for the analysis. The static or “DC” component of the signal can then be neglected. This was described in detail by Hahn (1996). The effect is independent of arterial oxyhaemoglobin saturation and concentration and there is no recirculation of the oscillatory signal in the venous blood.

6.1. Comparison of the continuous ventilation model with the tidal ventilation model

Fig. 3(a)–(c) shows the estimates for VA, Qp, and Vp obtained using the continuous ventilation and the tidal ventilation model at different forcing periods. It can be seen that the estimates of Qp obtained using both the continuous ventilation model and the tidal ventilation model are similar for all forcing sinusoidal periods T = 2, 3, 4, 5 min. Similar behaviour can be observed in the estimates of VA at T = 2, 3, 4 min where the estimates of Vp are close to the expected value, but Vp estimates differ from expected values when T = 5 min. This may be due either to potential artifact from “venous recirculation”, or to the fact that the recovered values become frequency dependent if real data from inhomogeneously ventilated lungs are analysed in a single compartment model. The consistency of the results using both the continuous ventilation model and the tidal ventilation model for 2 ≤ T ≤ 4 suggests that this range is suitable for the forcing sinusoid. For both the continuous ventilation model and the tidal ventilation model, V0 is calculated by the proposed regression method using both CO2 and N2O as described in Section 4. The results of V0 estimation are the same for both models, and are close to the expected value (0.25 L), indicating that the proposed improved Bohr equation method produces stable estimation of V0.

However, we note that the estimated values of Qp appear smaller than the expected value of Qp of the volunteer (4.5 L/min). One possible reason is that the effect of “venous recirculation” of the N2O still exists to some degree, whereas both the continuous ventilation model and the tidal ventilation model assume that it is negligible. Another possible reason is that the equilibrium between the arterial and venous blood had not yet been established during the data collection, although nitrous oxide has low blood and tissue solubility. In this early stage of the pilot study on human volunteers, we did not use a comparator for Qp, but our results have shown that the proposed tidal ventilation model is able to produce consistent and repeatable results. In the next stage of the study, we will incorporate a comparator algorithm, further investigate “venous recirculation” and ventilatory inhomogeneity, and ensure that the complete equilibrium of nitrous oxide is established for data collection.

6.2. Results of Vp

Estimated values of Vp using the mean and linear regression approaches are shown in Table 2. Using only CO2, the mean approach produces more consistent estimates of Vp than regression
at all forcing sinusoidal periods $T$. By contrast, when using only N$_2$O, estimates of $V_D$ using regression are more stable than those obtained using the mean. The reason for such behaviour is demonstrated in Fig. 3(d), where the $(x, y)$ pairs in (3) for CO$_2$ form a dense cluster, while the $(x, y)$ pairs for N$_2$O resemble a straight line.

### 6.3. Results from all human volunteers

Fig. 4(a) shows that the differences in $V_A$ estimates obtained from the tidal and continuous ventilation models have a mean difference of approximately zero, and differences about this mean are not correlated with the mean of the estimates.

While differences in the estimates of $Q_D$ obtained from both models are similarly uncorrelated to the means of the estimates, Fig. 4(b) shows that the mean difference is approximately $-0.35$ L/min; i.e., the estimate obtained from the continuous model is an average of $0.35$ L/min lower than that obtained from the tidal model.

Table 3 shows the results of using each model for estimating $V_D$, $V_A$ and $Q_D$. As described earlier, the tidal ventilation model takes an approach whereby the data acquired in a session are divided into a set of 20 windows, with an estimate of lung variables provided for each window. The table reports the mean and standard deviation of this set of 20 estimates for the tidal ventilation model, for each session. The continuous ventilation model, however, uses all of the data from a session to produce a single estimate of each lung variable; therefore, the table reports only these single estimates (i.e., without standard deviation) for the continuous ventilation model.

### 7. Conclusion

The continuous ventilation model uses only the amplitude of indicator gas concentration, without incorporating other variables, hence the underlying physiological information may not be sufficiently characterised. In comparison, a tidal ventilation model allows the examination of the effect of $V_D$, $V_A$, respiratory rates, etc. (Hahn and Farmery, 2003); therefore variations in variables can be more accurately investigated.

The proposed tidal ventilation model is able in theory, with noise-free data, to estimate lung variables using two successive breaths. In practice, it is desirable to use a few more than two breaths for robust estimation for on-line patient monitoring. This procedure is much faster than using the traditional continuous ventilation model, which requires a relatively long data collection time (at least two forcing periods). On the other hand, the tidal ventilation model is marginally more sensitive to measurement error. However, the output of the continuous ventilation model produces a stable single set of estimates for a certain duration, and this could be used as a check against the output of the tidal ventilation model.

The proposed improved Bohr equation method produces stable estimates of $V_D$. Results using both the continuous ventilation model and the tidal ventilation model have shown that $2 < T < 4$ is a potentially suitable range for the forcing sinusoid, in order to achieve reliable variable determination and to avoid recirculation effects. The proposed experimental gas delivery technique is suitable for use in assessing lung function in patients with healthy lungs in the clinical setting, and in exercise physiology, but further testing is needed to further validate the algorithm that we have used.

### Acknowledgements

The authors gratefully acknowledge funding by EPSRC (grant number EP/E028950/1). LC was supported by the Overseas Research Students Award Scheme, provided by the UK Government, and is currently supported by the NIHR Biomedical Research Centre Programme, Oxford. DAC was supported by the Wellcome Trust/EPSRC Centre of Excellence in Personalised Healthcare (grant number WT 0888777/2/09/Z). The authors give sincere thanks to Roger Belcher and Lionel Gale for their valuable technical assistance.

### Appendix A. List of abbreviations

The abbreviations used in this paper are summarised as follows:

- $V_A$: lung volume at the end of expiration
- $V_D$: airway dead space volume
- $V_I$: volume of the indicator gas delivered into the lung during a breath
- $V_Q$: expired volume of the indicator gas during a breath
- $V(t)$: uptake of the indicator gas during a breath
- $V(t)$: respiratory flow rate at time $t$
- $F_{IA,n}(t)$: inspired indicator gas concentration in the lung during breath $n$
- $F_{IA,n}$: indicator gas concentration in the lung during breath $n$
- $F_{IA,n}(t)$: indicator gas concentration during inspiration of breath $n$
- $F_{IA,n}$: indicator gas concentration at the end of expiration in breath $n$
- $F_{IV,n}$: tidal volume of breath $n$
- $V_{II}$: tissue-gas partition coefficient of a gas
- $F_A$: pulmonary blood flow through the lung
- $F_T$: indicator gas concentration in the lung
- $F_{T}$: average measured indicator gas concentration during expiration
- $F_T$: indicator gas concentration at the end of inspiration
- $F_{E}$: indicator gas concentration at the end of expiration

### References

Clifton, L.A., Farmery, A.D., Hahn, C.E.W., 2009. A non-invasive method for estimating lung function. In: IET Condition Monitoring, Dublin, Ireland, pp. 509–518.

Farmery, A.D., 2008. Interrogation of the Cardiopulmonary System with Inspired Gas Tension Sinusoids.

Farmery, A.D., Hahn, C.E.W., 2000. Response-time enhancement of a clinical gas analyzer facilitates measurement of breath-by-breath gas. Journal of Applied Physiology 89 (2), 581–589.

Fletcher, R., Jonson, B., Cumming, G.S.B.J., 1981. The concept of deadspace with reference to the single breath test for carbon dioxide. British Journal of Anaesthesia 53, 77–81.

Fowler, W.S., 1948. Lung function studies II. American Journal of Physiology 154, 405–416.

Gavaghan, D.J., Hahn, C.E.W., 1995. A mathematical evaluation of the alveolar amplitude response technique. Respiration Physiology 102 (1), 105–120.

Gavaghan, D.J., Hahn, C.E.W., 1996. A tidal breathing model of the forced inspired inert gas sinewave technique. Respiration Physiology 106 (2), 209–221.

Hahn, C.E.W., 1996. Oxygen respiratory gas analysis by sine-wave measurement: a theoretical model. Journal of Applied Physiology 81 (2), 985–997.

Hahn, C.E.W., Black, A.M., Barton, S.A., Scott, L., 1993. Gas exchange in a three-compartment lung model analyzed by forcing sinusoids of A0. Journal of Applied Physiology 75 (4), 1863–1876.

Hahn, C.E.W., Farmery, A.D., 2003. Gas exchange modelling: no more gills, please. British Journal of Anaesthesia 91 (1), 1–25.

Hamilton, R.M., 1998. Cardiorespiratory Measurements Using Inspired Oxygen Sinewaves. Hlastala, M.P., Berger, A.J., 1996. Physiology of Respiration, 1st ed. Oxford University Press, Oxford.

Luijendijk, S.C.M., Zwart, A., van der Kooij, A.M., de Vries, W.R., 1981. Evaluation of alveolar amplitude response technique for determination of lung perfusion in exercise. Journal of Applied Physiology 50 (5), 1071–1078.

Rouby, J.J., Constantin, J.M., Girard, C.d.A., Zhang, M., Lu, Q., 2004. Mechanical ventilation in patients with acute respiratory distress syndrome. Anesthesiology 101, 228–234.

Sainsbury, M.C.A.L., Williams, E.M., Hahn, C.E.W., 1997. A reconciliation of continuous and tidal ventilation gas exchange models. Respiration Physiology 108 (1), 89–99.

Van der Hoeven, S.W., 2007. Modelling and Control of Gas Flow in Anaesthesia. Whiteley, J.P., Farmery, A.D., Gavaghan, D.J., Hahn, C.E.W., 2003. A tidal ventilation model for oxygenation in respiratory failure. Respiration Physiology 136 (1), 77–88.
Whiteley, J.P., Gavaghan, D.J., Hahn, C.E.W., 2000. A tidal breathing model of the inert gas sinewave technique for inhomogeneous lungs. Respiration Physiology 124 (1), 65–83.

Williams, E.M., Aspel, J.B., Burrough, S.M., Ryder, W.A., Sainsbury, M.C., Sutton, L.L.X., Black, A.M., Hahn, C.E.W., 1994. Assessment of cardiorespiratory function using oscillating inert gas forcing signals. Journal of Applied Physiology 76 (5), 2130–2139.

Williams, E.M., Sainsbury, M.C., Sutton, L., Xiong, L., Black, A.M.S., Whiteley, J.P., Gavaghan, D.C., Hahn, C.E.W., 1998. Pulmonary blood flow measured by inspiratory inert gas concentration forcing oscillations. Respiration Physiology 113 (1), 47–56.

Zwart, A., Bogaard, J.M., Jansen, J.R.C., Versprille, A., 1978. A non-invasive determination of lung perfusion compared with the direct Fick method. Pflugers Archiv European Journal of Physiology 375 (2), 213–217.

Zwart, A., Seagrave, R.C., van Dieren, A., 1976. Ventilation-perfusion ratio obtained by a noninvasive frequency response technique. Journal of Applied Physiology 41 (3), 419–424.