A Non-Invasive Method for Estimating Cardiopulmonary Variables Using Breath-by-Breath Injection of Two Tracer Gases

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ABSTRACT Conventional methods for estimating cardiopulmonary variables usually require complex gas analyzers and the active co-operation of the patient. Therefore, they are not compatible with the crowded environment of the intensive care unit (ICU) or operating theatre, where patient co-operation is typically impossible. However, it is these patients that would benefit the most from accurate estimation of cardiopulmonary variables, because of their critical condition. This paper describes the results of a collaborative development between an anesthesiologists and biomedical engineers to create a compact and non-invasive system for the measurement of cardiopulmonary variables such as lung volume, airway dead space volume, and pulmonary blood flow. In contrast with conventional methods, the compact apparatus and non-invasive nature of the proposed method allow it to be used in the ICU, as well as in general clinical settings. We propose the use of a non-invasive method, in which tracer gases are injected into the patient’s inspired breath, and the concentration of the tracer gases is subsequently measured. A novel breath-by-breath tidal ventilation model is then used to estimate the value of a patient’s cardiopulmonary variables. Experimental results from an artificial lung demonstrate minimal error in the estimation of known parameters using the proposed method. Results from analysis of a cohort of 20 healthy volunteers (within the Oxford University Hospitals NHS Trust) show that the values of estimated cardiopulmonary variables from these subjects lies within the expected ranges. Advantages of this method are that it is non-invasive, compact, portable, and can perform analysis in real time with less than 1 min of acquired respiratory data.

INDEX TERMS Non-invasive, cardiopulmonary variables, breath-by-breath, tracer gas, tidal ventilation, model.

I. MOTIVATION

Patients are often admitted into the Intensive Care Unit (ICU) due to the need for mechanical ventilatory support using a ventilator [1]. Cardiopulmonary tests could benefit ICU patients significantly, because they could help to determine the most suitable ventilator settings, and help to avoid the common problem of Ventilator Induced Lung Injury (VILI). We aim to measure the following three cardiopulmonary variables:

1) $V_D$, airway dead space volume; i.e., the volume of the conducting airways. The airway is the path that the air follows to enter and exit the lung.
2) $V_A$, lung volume, or alveolar volume, at the end of an expiration.
3) $\dot{Q}_P$, pulmonary blood flow.

Measurement of cardiopulmonary variables typically requires the active co-operation of the patient. However, ICU patients depend on complex life support and monitoring equipment, and so are unable to co-operate with clinicians. Hence, ICU patients are the most difficult to assess using conventional cardiopulmonary tests, but their
critical condition makes them the most important patients to monitor.

Zwart et al. [2], [3] first introduced the non-invasive oscillating inspired gas-forcing technique to measure the average ventilation-perfusion relationship (V/Q) in the lung, in which a sinusoidally oscillating tracer gas is added to the patient’s inspired gas. They used halothane as the tracer gas, at very low concentrations (0.02 v/v). Hahn et al. further developed this method by using biologically non-toxic gases such as nitrous oxide (N₂O) and argon, instead of halothane, to measure V_D, V_A, and Q_P non-invasively [4]. However, their technique required a respiratory mass spectrometer that was difficult to use in the ICU due to its size, noise, complexity, high maintenance requirements, and lack of portability [5]. Moreover, their prototype gas mixer, which was used to supply the appropriate gases, is not compatible with modern ICU ventilators. A new method needs to be designed to deliver tracer gases according to the patient’s breathing flow rates in real time.

In this paper, we propose an on-line non-invasive gas-forcing technique that estimates the above three parameters, V_D, V_A, and Q_P. The apparatus is compact in size and is portable, consisting of a flow sensor, a gas concentration sensor, and a mass flow controller (MFC). Two types of tracer gases, N₂O and O₂, are injected into the patient’s airflow during inspiration. The on-line delivery of tracer gases is explained in Section II, and then a novel breath-by-breath tidal ventilation model is proposed in Section III. Conversion of tidal volume and response time enhancement are addressed in Section IV. An introduction to the datasets and other methodology is given in Section V. Experimental results are shown in Section VI for both an artificial lung and a cohort of healthy volunteers, acquired at the Oxford University Hospitals NHS Trust; finally, conclusions are discussed in Section VII.

II. ON-LINE TRACER GAS DELIVERY

Modern ICU ventilators deliver inspired air at variable and unpredictable flow rates. In order to deliver a pre-determined concentration of the tracer gas throughout a single inspiratory breath, the tracer gas must be injected in real time according to the inspired flow. In our previous study [5], only one type of tracer gas (N₂O) was injected into the patient’s inspiratory breathing flow and mixed immediately prior to entering the mouth. Here we improve the method by simultaneously injecting two types of tracer gases, O₂ and N₂O, into the patient’s airway during inspiration. The purpose of introducing O₂ as a second tracer gas is to achieve a more robust estimation of cardiopulmonary variables.

Two MFCs are used to deliver the two tracer gases at injection flow rates \( \dot{V}_{N_2O}(t) \) and \( \dot{V}_{O_2}(t) \), in L/min, respectively. This section will show how to determine the values of \( \dot{V}_{N_2O}(t) \) and \( \dot{V}_{O_2}(t) \), such that the resulting inspired concentration of each tracer gas is sinusoidal. We define

\[
F_{N_2O}(t) = M_{N_2O} + A_{N_2O} \sin(\omega t) \tag{1}
\]

\[
F_{O_2}(t) = M_{O_2} + A_{O_2} \sin(\omega t) \tag{2}
\]

where \( F_{N_2O}(t) \) is the concentration of the injected N₂O flow, in percentage (%); \( M_{N_2O} \) and \( A_{N_2O} \) are the mean and amplitude of the forcing N₂O sinusoid, respectively; \( F_{O_2}(t) \), \( M_{O_2} \), and \( A_{O_2} \) are similar quantities of O₂; \( \omega \) is the frequency of the forcing sinusoid in radians/sec (\( \omega = 2\pi/T \), where \( T \) is the forcing sinusoidal period). The sinusoidal concentration of the tracer gas is shown in Figure 1.

\[
F_{N_2O}(t) \text{ can be expressed as}
\]

\[
F_{N_2O}(t) = \frac{\dot{V}_{N_2O}(t) + F_{CON} \dot{V}(t)}{\dot{V}_{O_2}(t) + \dot{V}_{N_2O}(t) + \dot{V}(t)}, \tag{3}
\]

where \( F_{CON} \) is the existing N₂O concentration in the patient’s respiratory flow, measured as a percentage (%), and \( \dot{V}(t) \) is the patient respiratory flow rate, in L/min. The numerator is the total flow rate of N₂O, including the flow rate of both the injected N₂O and existing N₂O. The denominator is the total flow rate of all gases, consisting of the patient’s respiratory flow rate and the flow rates of injected tracer gases.

We assume that the patient’s respiratory flow contains no N₂O; i.e., N₂O is only present in the injected tracer gas N₂O. That is,

\[
F_{CON} = 0. \tag{4}
\]

Combining (1) and (3) gives

\[
\frac{\dot{V}_{N_2O}(t) + F_{CON} \dot{V}(t)}{\dot{V}_{O_2}(t) + \dot{V}_{N_2O}(t) + \dot{V}(t)} = M_{N_2O} + A_{N_2O} \sin(\omega t). \tag{5}
\]

Similarly for tracer gas O₂, we obtain

\[
\frac{\dot{V}_{O_2}(t) + F_{CON} \dot{V}(t)}{\dot{V}_{O_2}(t) + \dot{V}_{N_2O}(t) + \dot{V}(t)} = M_{O_2} + A_{O_2} \sin(\omega t). \tag{6}
\]
where $F_{cO_2}$ is the existing $O_2$ concentration in the patient’s inspiratory flow. $F_{cO_2} = 21\%$ for room air; $F_{cO_2}$ may alternatively take the value of $O_2$ concentration, if the patient has $O_2$ supplied.

Equations (4)–(6) may then be used to solve for $\dot{V}_{N_2O}(t)$ and $\dot{V}_{O_2}(t)$, resulting in

$$\dot{V}_{N_2O}(t) = \frac{(1 - F_{cO_2})F_{N_2O}(t)}{1 - F_{N_2O}(t) - F_{cO_2}} \dot{V}(t),$$

$$\dot{V}_{O_2}(t) = \frac{F_{N_2O}(t) - (1 - F_{N_2O}(t))F_{cO_2}}{1 - F_{N_2O}(t) - F_{O_2}} \dot{V}(t),$$

where $F_{N_2O}(t)$ and $F_{O_2}(t)$ are defined in equations (1) and (2).

In equations (7) and (8), the chosen parameters must satisfy the constraints $\dot{V}_{N_2O}(t) > 0$ and $\dot{V}_{O_2}(t) > 0$. This gives

$$F_{N_2O}(t) > 0$$

$$1 - F_{N_2O}(t) - F_{O_2}(t) > 0$$

$$F_{N_2O}(t) - (1 - F_{N_2O}(t))F_{cO_2} > 0$$

The above analysis shows how to set the values of $\dot{V}_{N_2O}(t)$ and $\dot{V}_{O_2}(t)$, delivered by the MFCs. In our experimental apparatus, a gas flow sensor was used to measure the inspired and expired gas flow rates. The tracer gas concentrations were measured by a concentration sensor. Data for sensor calibration can be found in [6]. Both the flow sensor and the concentration sensor are mounted in the breathing tube connected to the patient. Compared with the apparatus for previous models [4], the proposed setup is portable, simple to use, and is suitable for the ICU due to its non-invasive approach.

### III. A BREATH-BY-BREATH VENTILATION MODEL

In a traditional continuous ventilation lung model [2], [4], [7], the lung is treated as a rigid volume with a constant and continuous flow passing through it, shown in Figure 2(a). A tidal ventilation model for the forced inspired oscillation technique was introduced by Gavaghan and Hahn [8], and later modified by Whiteley et al. [9]. Compared with the rigid volume of the continuous ventilation model, a tidal ventilation model reflects the reality of breathing, where the lung expands during inspiration, and contracts during expiration. The proposed breath-by-breath tidal ventilation model employs a so-called “balloon-on-a-straw” model [10], shown in Figure 2(b). In the “balloon-on-a-straw” model, the inspired gas first enters the patient’s airway through the dead space which has volume $V_D$, and then enters the lung which has volume $V_A$. The lung expands during inspiration and eventually reaches volume $V_A + V_T$ at the end of inspiration, where $V_T$ is called “tidal volume,” and is defined to be the volume of gas inhaled and exhaled during a breath. The lung contracts during expiration and returns to $V_A$ at the end of expiration. The proposed model can be used with any tracer gas; hence the following analysis can be applied to either $O_2$ or $N_2O$.

The concentration sensor measures concentration before the tracer gas enters the mouth during inspiration, and after the tracer gas leaves the mouth during expiration. Let $F_{IA,n}(t)$ be the inspired concentration of the tracer gas that enters the lung during breath $n$; $F_{IA,n}(t)$ can be expressed as

$$F_{IA,n}(t) = \begin{cases} F_{A,n-1} & \text{if } t_{bd} \leq t < t_{bd} + T_{DI} \\ F_{I,n}(t) & \text{if } t_{bd} + T_{DI} \leq t < t_{el} \end{cases}$$

In the above, $t_{bd}$ is the time at the beginning of inspiration, $t_{el}$ is the time at the end of inspiration, and $T_{DI}$ is the time taken for the tracer gas to travel through the dead space during inspiration of breath $n$, $F_{A,n-1}$ is the tracer gas concentration in the lung during breath $n - 1$, and $F_{A,n}$ is the tracer gas concentration in the lung during breath $n$; we assume that $F_{A,n}$ is constant during breath $n$, and hence is not dependent on time $t$. $F_{I,n}(t)$ is the concentration of the tracer gas measured by the concentration sensor at the mouth during inspiration of breath $n$; $F_{I,n}(t)$ is a function of time $t$. Equation (12) shows that $F_{IA,n}(t)$ consists of two parts: in the first part of inspiration, the lung breathes the gas present in the dead space; in the second part of inspiration, the lung breathes in the injected tracer gas.

Let $V_I$ be the volume of tracer gas delivered into the lung during breath $n$,

$$V_I = \int_{t_{bd}}^{t_{el}} \dot{V}(t)F_{IA,n}(t) \, dt$$

where $\dot{V}(t)$ is the measured respiratory flow rate at time $t$. Substituting (12) into (13), we have

$$V_I = \int_{t_{bd}}^{t_{bd} + T_{DI}} \dot{V}(t)F_{A,n-1} \, dt + \int_{t_{bd} + T_{DI}}^{t_{el} - T_{DI}} \dot{V}(t)F_{I,n}(t) \, dt$$

$$= V_DF_{A,n-1} + \int_{t_{bd} + T_{DI}}^{t_{el} - T_{DI}} \dot{V}(t)F_{I,n}(t) \, dt$$

Let $V_{T,n}$ be the tidal volume (the volume of gas inhaled and exhaled) during breath $n$. Let $V_E$ be the expired volume of the tracer gas during breath $n$,

$$V_E = V_{T,n}F_{A,n}.$$  

Let $V_Q$ be the uptake of the tracer gas (i.e., the amount of tracer gas absorbed by the pulmonary capillary blood in the
lungs) during breath \( n \),
\[
V_Q = \dot{Q}_p \lambda_b (F_{A,n} - F_{\tilde{V},n}) T_n, \tag{16}
\]
where \( \dot{Q}_p \) is the pulmonary blood flow, \( \lambda_b \) is the blood solubility coefficient of the gas, and \( T_n \) is the duration of breath \( n \). \( F_{\tilde{V},n} \) is the average tracer gas concentration returned to the lung through venous recirculation in breath \( n \).

The volume of tracer gas in the lung is \( V_A F_{A,n} \) at the end of breath \( n - 1 \), and is \( V_A F_{A,n} \) at the end of breath \( n \). The conservation of mass before and after gas exchange implies that
\[
V_A F_{A,n} - V_A F_{A,n-1} = V_I - V_E - V_Q, \tag{17}
\]
where this is the volume change of tracer gas in the lung at the end of breath \( n \). Substituting (14), (15), and (16) into (17), we have
\[
V_A (F_{A,n-1} - F_{A,n}) + \dot{Q}_p \lambda_b (F_{\tilde{V},n} - F_{A,n}) T_n = V_{T,n} F_{A,n} - \left[ V_D F_{A,n-1} + \int_{t_{1d}}^{t_{1d} - T_{DI}} \dot{V}(t) F_{L,n}(t) dt \right]. \tag{18}
\]

We have assumed that \( F_{A,n} \) (the tracer gas concentration in the lung during breath \( n \)) is constant during breath \( n \); we hence note that
\[
F_{A,n} = F_{E',n}, \tag{19}
\]
where \( F_{E',n} \) is the measured tracer gas concentration at the end of expiration in breath \( n \). We introduce equation (19) because \( F_{E',n} \) is more readily measured than \( F_{A,n} \) using our apparatus. \( F_{E'} \) (\( F_{E',n} \) over all breaths) is the sine wave expressed in equations (1) and (2). Equation (19) implies that \( F_A \) (tracer gas concentration in the lung from all breaths) is also a sine wave.

The tracer gas is inhaled into the lung, where some is absorbed by the pulmonary capillary blood in the lung. It eventually returns to the lung via the venous blood. This process is known as “venous recirculation.” It has been previously shown that there exists a forcing sinusoidal frequency range of the tracer gas where venous recirculation effects are negligible [4], [11]. At a carefully chosen forcing frequency at which the recirculation effects can be ignored, the oscillatory component of \( F_{\tilde{V},n} \) diminishes, leaving
\[
F_{\tilde{V},n} = M_A, \tag{20}
\]
where \( M_A \) is the mean of the alveolar sinusoid \( F_A \). Equation (19) has shown that \( M_A \) is equal to the mean of the measured sinusoid \( F_{E'} \).

Substituting (19) and (20) into (18) gives
\[
V_A (F_{E',n-1} - F_{E',n}) + \dot{Q}_p \lambda_b (M_A - F_{E',n}) T_n = V_{T,n} F_{E',n} - \left[ V_D F_{E',n-1} + \int_{t_{1d}}^{t_{1d} - T_{DI}} \dot{V}(t) F_{L,n}(t) dt \right]. \tag{21}
\]

This is the mass balance equation for the cardiopulmonary variables that we aim to estimate, expressed in terms of breath-by-breath changes in gas volumes. Our goal is to determine the values of \( V_A \) and \( \dot{Q}_P \) in (21). For the chosen tracer gas, \( \lambda_b \) is a known constant. The measured variables are \( F_{E',n-1}, F_{E',n}, F_{L,n}(t), V_{T,n}, \) and \( M_A \). The Bohr equation is used to calculate \( V_D \) [5]. Every two successive breaths produce an equation using (21); therefore a total number of \( N \) breaths produce \( N - 1 \) equations of two unknown values \( V_A \) and \( \dot{Q}_P \). For this set of \( N - 1 \) linear equations, the least-squares technique is then used to determine \( V_A \) and \( \dot{Q}_P \).

**IV. CONSIDERATIONS**

A. **CONVERSION OF TIDAL VOLUME FOR TEMPERATURE AND HUMIDITY**

The measurement of gas volumes is affected by various parameters, such as ambient or environmental temperature and pressure, and whether gases are either “dry,” or “saturated” with water vapor. Gas volumes measured at different conditions need to be converted to a single standard condition. Two typical conditions are ambient temperature and pressure, saturated with water vapor (ATPS), and body temperature and pressure, saturated with water vapor (BTPS). Based on Charles’ and Boyle’s Laws, conversion from ATPS to BTPS is given by [12]
\[
V_{BTPS} = \left( \frac{273 + 37}{273 + d} \right) \left( \frac{P_B - P_{H_2O}}{P_B - 6.3} \right) V_{ATPS}, \tag{22}
\]
where \( V_{BTPS} \) is the volume measured at BTPS, \( V_{ATPS} \) is the volume measured at ATPS, \( P_B \) is barometric pressure in KPa, \( d \) is ambient temperature in degrees Celsius, and \( P_{H_2O} \) is the water vapor pressure of the sample in KPa at ambient temperature \( d \).

Let \( C \) be the constant of proportionality between ATPS and BTPS,
\[
C = \left( \frac{273 + 37}{273 + d} \right) \left( \frac{P_B - P_{H_2O}}{P_B - 6.3} \right). \tag{23}
\]

I.e.,
\[
V_{BTPS} = C \cdot V_{ATPS}. \tag{24}
\]

In our proposed method, the inspiratory tidal volume is obtained at the ambient temperature and pressure, using dry gases (ATPD), while the expiratory tidal volume is obtained at a certain measured temperature and pressure, using saturated gases (MTPS). Let \( d_a \) be the ambient temperature, \( d_m \) be the measured temperature, and \( d_b \) be the body temperature. Using a heat and moisture exchanger (HME) in the proposed experiment apparatus, our experiments have shown that
\[
d_a \leq d_m \leq d_b. \tag{25}
\]

Here we must convert inspiratory tidal volume in ATPD to expiratory tidal volume in MTPS
\[
V_{MTPS} = D \cdot V_{ATPD}. \tag{26}
\]

The advantage of using (26) is that we only need to determine the constant of proportionality, \( D \), without having to know \( d_m \) (which is difficult to measure). \( D \) can be measured
using an artificial lung at a known tidal volume. Our experiments have demonstrated that a suitable value for $D$ is

$$D = 1.171.$$  

(27)

This value of $D$ is appropriate for use of our apparatus under its expected operating conditions.

**B. RESPONSE TIME ENHANCEMENT**

“Response time” is typically defined to be the time required for a sensor output to rise from 10% to 90% of its maximum [5]. We have described how two types of signals, flow rates and gas concentrations, are measured by the flow sensor and concentration sensor, respectively.

At the beginning of normal inspiration, flow rates rise very quickly and may exceed 30 L/min within a few milliseconds. Unfortunately, this period coincides with a rapid change in the concentration signals, which causes the concentration signals to experience its response time before reaching the correct measurement. Consequentially, the error in the integration of the flow and concentration signals is exaggerated during the beginning of inspiration. It is therefore essential to enhance the response time of the concentration signals in the breath-by-breath tidal ventilation model. Various methods for the enhancement of response time have been discussed. Here we applied the first-order exponential model [13]. Letting $c(t)$ be the original signal, the response time enhanced signal $c'(t)$ is given by

$$c'(t) = c(t) + \alpha \frac{dc(t)}{dt},$$  

(28)

where $\alpha$ is a parameter decided by the response time of the sensor. For the concentration sensor used in our experiments, $\alpha = 0.1$ was shown through experiments to be a suitable value for enhancement of the measured concentration signal $c(t)$ without introducing large oscillations in $c'(t)$.

We note that prior to response time enhancement, the correct time alignment of flow and concentration signals is required for their integration in our breath-by-breath tidal ventilation model [5]. The response of the concentration sensor typically lags behind the measured flow signal by approximately 60 ms; these two signals are aligned accordingly.

**C. CHOOSING APPROPRIATE SINUSOIDAL PERIODS**

The proposed breath-by-breath model assumes that venous recirculation of the oscillatory component in the concentration signal is negligible; therefore care has to be taken when choosing the forcing sinusoidal periods $T$. Gavaghan et al. found that the venous recirculation effects are negligible in the range of $0.5 \leq T \leq 4$ mins for the soluble gases halothane, acetylene, and N\textsubscript{2}O [11], and become more pronounced at longer forcing periods [4]. In Section VI, we will present results obtained in the range $2 \leq T \leq 5$ mins using tracer gases N\textsubscript{2}O and O\textsubscript{2}, in order to determine the appropriate sinusoidal periods of the tracer gas.

### V. METHODOLOGY

#### A. VALIDATION USING AN ARTIFICIAL LUNG

The benefit of using an artificial lung is that the values of $V_D$ and $V_A$ are known, and $Q_p$ is always zero; therefore, it can be used to perform initial verification of a ventilation model.

The apparatus of the artificial lung in our experiments and its detailed description can be found in [14]. Data from the artificial lung were partitioned into twenty consecutive windows, each of 30s duration.

The results of application of the method to this initial validation task are described in the next section, where we can report the mean absolute error from this “gold standard” comparator.

#### B. PARAMETER ESTIMATION IN HUMAN SUBJECTS

Compared with the artificial lung, there is no comparable “gold standard” for the estimation of cardiopulmonary variables in humans. A cohort of 20 healthy human volunteers was studied, comprising 13 males and 7 females, in the age-ranges 20-60 and 20-40 years, respectively. Body mass indices for all patients were in the “normal” range. The current stage of the project has ethical approval for acquisition of data from healthy volunteers. A follow-up study, in which data from unhealthy patients is acquired for comparison, is planned.

We note that results presented in Section VI are not derived from partitioning the data into “training” and “test” sets, because there are no free parameters of the proposed model that need to be estimated from “training data.” Rather, the physiological model is directly applicable to patient respiratory waveforms, and therefore essentially treats all data as “test data.”

#### C. MODEL APPLICATION

While previous work has demonstrated that (non-breath-by-breath) models of tidal ventilation can estimate cardiopulmonary variables using single tracer gases, we here demonstrate the use of our novel breath-by-breath model, using a combination of N\textsubscript{2}O and O\textsubscript{2} tracer gases. N\textsubscript{2}O amplitude is dampened by both the alveolar compartment and the pulmonary blood flow. Since the influence of the variables $V_A$ and $Q_p$ on N\textsubscript{2}O amplitude are independent, the mass balance equations are theoretically soluble for N\textsubscript{2}O alone [5]. However, we test the hypothesis that, in practice, it is likely that a more robust solution would be obtained by combining data from a second gas whose plasma solubility is negligible (i.e., oxygen) since this provides a solution for $V_A$ which is independent of, and uninfluenced by, $Q_p$.

In the case of two tracer gases, the value of $V_A$ is determined by averaging the solutions for N\textsubscript{2}O and O\textsubscript{2}. These values are used, as described previously, to estimate $Q_p$, using least-squares to solve equation (21), noting that $Q_p = 0$ for O\textsubscript{2}.
VI. RESULTS
A. RESULTS USING ARTIFICIAL LUNG
All tidal volumes reported hereafter have been converted to MTPD using (26) and (27) in Section IV-A.

Figure 3 shows the results obtained using the proposed breath-by-breath method using data acquired from the artificial lung. For comparison, equivalent plots of results obtained for an exemplar healthy volunteer are also shown. The parameters of the artificial lung were set to be $\dot{Q}_P = 0$ L min$^{-1}$, $V_A = 2.36$ L, and $V_D = 0.23$ L. In equation (1), we have chosen tracer gas parameters $M_{N_2O} = 0.06$ and $A_{N_2O} = 0.03$, which is a non-toxic concentration level for $N_2O$.

The figure shows that $V_D$ estimation is consistently close to the actual value, where the estimated values of $V_D$ are close to the actual value $V_D = 0.23$ L.

The proposed method underestimates $V_A$ in the case of the artificial lung, at all four forcing sinusoidal periods $T = 2, 3, 4,$ and $5$ min. The mean absolute error between results obtained using all 20 windows of data from the artificial lung and the reference value was $0.13$ L, corresponding to an absolute percentage error of $5\%$. The estimated value of $V_A$ becomes closer to the actual value of $V_A$ as the forcing period increases, and is most accurate at the highest forcing period $T = 5$ min. It is likely that this error is in part due to incomplete gas mixing (which is assumed in the model) in the artificial lung.

At all four forcing sinusoidal periods $T = 2, 3, 4,$ and $5$ mins, both artificial lung measurements result in consistent estimates of $\dot{Q}_P$, suggesting that the proposed parameter recovery algorithms are robust. The estimated values of $\dot{Q}_P$ are zero in the artificial lung.

B. RESULTS USING HEALTHY VOLUNTEERS
For the human volunteers, standard population-based formulae exist for estimating the values of the cardiopulmonary variables described in this paper, based on factors such as age, sex, and body mass index. We have used these standard methods to determine the “physiologically plausible” ranges of values that our proposed breath-by-breath tidal method should output.

We firstly note that, for the exemplar patient shown in Figure 3, the estimated values of $V_D$ are appropriate for the values expected from the standard method. Our estimates have small standard deviations and are highly repeatable, indicating that the Bohr equation is an appropriate method for estimation of $V_D$.

A similar trend for the estimated $V_A$ can be observed for the human lung at $T = 2, 3,$ and $4$ min. The estimated values of $V_A$ are appropriate for the individual’s size and weight in whom the value of ($V_A + V_D$) would be expected to be approximately $1.8$ L, in the semi-recumbent sitting position. Although the estimated $V_A$ decreases to $1.77$ L at $T = 5$ min, the value is still within the expected range, and consistent with estimated $V_A$ at the remaining forcing periods $T$.

However, it should be noted that the estimated values of $\dot{Q}_P$ in the exemplar human volunteer are somewhat smaller than the expected value of $4$ L/min for this volunteer. A possible explanation for this potential discrepancy is that the sinusoidal signal is “recirculating” via the venous blood returning to the heart and lungs, whereas the model assumes no venous recirculation, as described in Section IV-C. However, previous experimental and theoretical work [4], [11], has suggested that this is unlikely to be a problem at periods of 2 minutes or less. Another possibility is that in the human volunteer study, an equilibrium between the arterial and venous blood had not been fully established. Although nitrous oxide has low blood and tissue solubility and therefore equilibrates quickly, further work is needed to establish what would be an adequate wash-in period before data collection is begun.
The proposed model is able to estimate cardiopulmonary variables using a small number of successive breaths. In practice, it is desirable to use five to ten breaths for robust estimation. This is much faster than using the traditional continuous model, which requires a relatively long time for collection of patient data.

We have shown that a potentially suitable range of the forcing sinusoidal periods is $2 \leq T \leq 5$ min, in order to avoid both large measurement errors and “venous recirculation” effects, for the purpose of estimating cardiopulmonary variables. Estimates of $V_D$, $V_A$, and $\bar{Q}_P$ obtained from using the proposed method are consistent and stable, using both the artificial lung and the human lung. The next stage of this research will include the validation of the model using data from patients in ICUs and operating theaters, acquired in collaboration with the Oxford University Hospitals NHS Trust.

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**REFERENCES**

[1] J. J. Rouby, J. M. Constantin, C. de A. Girardi, M. Zhang, and Q. Lu, “Mechanical ventilation in patients with acute respiratory distress syndrome,” *Anesthesiology*, vol. 101, no. 1, pp. 228–234, 2004.

[2] A. Zwart, R. C. Seagrave, and A. van Dieren, “Ventilation-perfusion ratio obtained by a noninvasive frequency response technique,” *J. Appl. Physiol.*, vol. 41, no. 3, pp. 419–424, 1976.

[3] A. Zwart, J. M. Bogaard, J. R. C. Jansen, and A. Versprille, “A non-invasive determination of lung perfusion compared with the direct Fick method,” *Pflügers Archiv*, vol. 375, no. 2, pp. 213–217, 1978.

[4] C. E. W. Hahn, A. M. Black, S. A. Barton, and I. Scott, “Gas exchange in a three-compartment lung model analyzed by forcing sinusoids of $N_2O$,” *J. Appl. Physiol.*, vol. 75, no. 4, pp. 1863–1876, 1993.

[5] L. A. Clifton, A. D. Farmery, and C. E. W. Hahn, “A non-invasive method for estimating lung function,” in *Proc. 6th Int. Conf. Condition Monitor: Mach. Failure Prevent. Technol.*, Dublin, Ireland, 2009, pp. 509–518.

[6] S. W. Van der Hoeven, “Modelling and control of gas flow in anaesthesia,” Ph.D. dissertation, Dept. Eng. Sci., Univ. Oxford, Oxford, U.K., 2007.

[7] C. E. W. Hahn, “Oxygen respiratory gas analysis by sine-wave measurement: A theoretical model.” *J. Appl. Physiol.*, vol. 81, no. 2, pp. 985–997, 1996.

[8] D. J. Gavaghan and C. E. W. Hahn, “A tidal breathing model of the forced inspired inert gas sinewave technique,” *Respir. Physiol.*, vol. 106, no. 2, pp. 209–221, 1996.

[9] I. P. Whiteley, A. D. Farmery, D. J. Gavaghan, and C. E. W. Hahn, “A tidal ventilation model for oxygenation in respiratory failure,” *Respirat. Physiol.*, vol. 136, no. 1, pp. 77–88, 2003.

[10] C. E. W. Hahn and A. D. Farmery, “Gas exchange modelling: No more gills, please,” *Brit. J. Anaesth.*, vol. 91, no. 1, pp. 2–15, 2003.

[11] D. J. Gavaghan and C. E. W. Hahn, “A mathematical evaluation of the alveolar amplitude response technique,” *Respirat. Physiol.*, vol. 102, no. 1, pp. 105–120, 1995.

[12] A. Lumb, *Nunn’s Applied Respiratory Physiology*, 5th ed. Oxford, U.K.: Butterworth-Heinemann, 2000.

[13] R. R. Mitchell, “Incorporating the gas analyser response time in gas exchange computations,” *J. Appl. Physiol.*, vol. 47, no. 5, pp. 1118–1122, 1979.

[14] E. M. Williams, L. B. Gale, P. A. Oakley, M. C. Sainsbury, and C. E. W. Hahn, “Development of a concentric water-displacement model lung,” *J. Biomed. Eng.*, vol. 15, no. 5, pp. 420–424, 1993.

**TABLE I.** Results obtained using $N_2O$ only, across all 20 healthy volunteers, with males and females separated. $T$ is the forcing sinusoidal period of tracer gas $N_2O$ in minutes. The standard deviation of the estimates is shown across all 20 volunteers. Across all patients (13 males, age 20-60 years; 7 females, age 20-40 years), the expected parameter ranges are $0.2 \leq V_D \leq 0.4$ L, $1.2 \leq V_A \leq 3$ L, and $1.5 \leq \bar{Q}_P \leq 5$ L min$^{-1}$.

| $T$ (min) | Sex | $V_D$ (L) | $V_A$ (L) | $\bar{Q}_P$ (L min$^{-1}$) |
|----------|-----|-----------|-----------|--------------------------|
| 2        | m   | 0.27 ± 0.01 | 2.17 ± 0.71 | 3.11 ± 0.98 |
| 2        | f   | 0.27 ± 0.01 | 2.05 ± 0.66 | 3.00 ± 0.99 |
| 3        | m   | 0.28 ± 0.01 | 2.23 ± 0.63 | 3.23 ± 0.95 |
| 3        | f   | 0.26 ± 0.01 | 1.96 ± 0.57 | 2.94 ± 0.94 |
| 4        | m   | 0.28 ± 0.01 | 2.19 ± 0.68 | 3.89 ± 0.98 |
| 4        | f   | 0.27 ± 0.01 | 1.84 ± 0.57 | 2.96 ± 0.92 |
| 5        | m   | 0.28 ± 0.01 | 2.36 ± 0.62 | 3.88 ± 0.91 |
| 5        | f   | 0.26 ± 0.01 | 1.88 ± 0.56 | 2.82 ± 0.91 |

**TABLE II.** As Table I, with results obtained using $N_2O$ combined with $O_2$, across all 20 healthy volunteers.

| $T$ (min) | Sex | $V_D$ (L) | $V_A$ (L) | $\bar{Q}_P$ (L min$^{-1}$) |
|----------|-----|-----------|-----------|--------------------------|
| 2        | m   | 0.27 ± 0.01 | 2.16 ± 0.51 | 3.14 ± 0.97 |
| 2        | f   | 0.27 ± 0.01 | 2.05 ± 0.52 | 3.02 ± 0.98 |
| 3        | m   | 0.28 ± 0.01 | 2.24 ± 0.49 | 3.16 ± 0.95 |
| 3        | f   | 0.26 ± 0.01 | 1.92 ± 0.42 | 3.06 ± 0.92 |
| 4        | m   | 0.28 ± 0.01 | 2.21 ± 0.52 | 3.79 ± 0.91 |
| 4        | f   | 0.27 ± 0.01 | 1.86 ± 0.49 | 2.99 ± 0.88 |
| 5        | m   | 0.28 ± 0.01 | 2.34 ± 0.53 | 3.80 ± 0.89 |
| 5        | f   | 0.26 ± 0.01 | 1.86 ± 0.48 | 2.80 ± 0.84 |
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