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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 ($\dot{V}/\dot{Q}$) 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 (N_2O) and argon, instead of halothane, to measure V_D, V_A, and $\dot{Q}_P$ 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 $\dot{Q}_P$. 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, N_2O and O_2, 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 (N_2O) 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, O_2 and N_2O, into the patient's airway during inspiration. The purpose of introducing O_2 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

$$F_{N_2O}(t) = M_{N_2O} + A_{N_2O}\sin(\omega t) \quad (1)$$

$$F_{O_2}(t) = M_{O_2} + A_{O_2}\sin(\omega t), \quad (2)$$

where $F_{N_2O}(t)$ is the concentration of the injected N_2O flow, in percentage (%); M_{N_2O} and A_{N_2O} are the mean and amplitude of the forcing N_2O sinusoid, respectively; $F_{O_2}(t)$, M_{O_2} and A_{O_2} are similar quantities of O_2; ω 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.

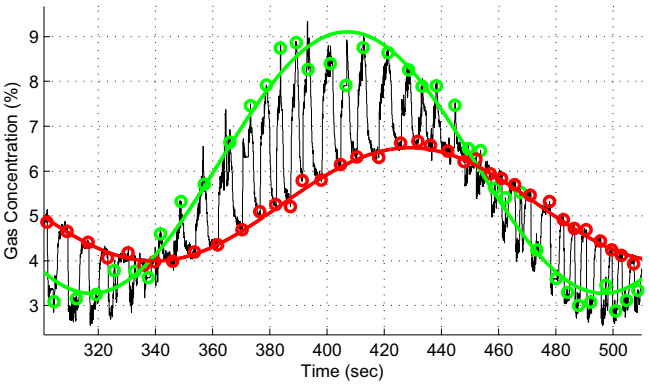


FIGURE 1. Concentration of tracer gas N_2O in the airway flow of a healthy female volunteer. The forcing sinusoidal period $T = 3$ mins for both $F_{N_2O}(t)$ and $F_{O_2}(t)$. The green and red circles are placed at the turning points of the patient respiratory flow rate $\dot{V}(t)$, indicating the end of inspiration and expiration, respectively. The green and red sinusoids are fitted to the green and red circles, respectively. The sinusoids show that the concentration of the tracer gas varies sinusoidally, with the chosen value of T.

$F_{N_2O}(t)$ can be expressed as

$$F_{N_2O}(t) = \frac{\dot{V}_{N_2O}(t) + F_{eN_2O}\dot{V}(t)}{\dot{V}_{O_2}(t) + \dot{V}_{N_2O}(t) + \dot{V}(t)}, \quad (3)$$

where F_{eN_2O} is the existing N_2O 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 N_2O, including the flow rate of both the injected N_2O and existing N_2O. 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 N_2O; i.e., N_2O is only present in the injected tracer gas N_2O. That is,

$$F_{eN_2O} = 0. \quad (4)$$

Combining (1) and (3) gives

$$\frac{\dot{V}_{N_2O}(t) + F_{eN_2O}\dot{V}(t)}{\dot{V}_{O_2}(t) + \dot{V}_{N_2O}(t) + \dot{V}(t)} = M_{N_2O} + A_{N_2O}\sin(\omega t). \quad (5)$$

Similarly for tracer gas O_2, we obtain

$$\frac{\dot{V}_{O_2}(t) + F_{eO_2}\dot{V}(t)}{\dot{V}_{O_2}(t) + \dot{V}_{N_2O}(t) + \dot{V}(t)} = M_{O_2} + A_{O_2}\sin(\omega t), \quad (6)$$

IEEE Journal of Translational Engineering in Health and Medicine

where F_{eO_2} is the existing O_2 concentration in the patient's inspiratory flow. $F_{eO_2} = 21\%$ for room air; F_{eO_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

$$\dot{V}_{N_2O}(t) = \frac{(1 - F_{eO_2})F_{N_2O}(t)}{1 - F_{N_2O}(t) - F_{O_2}(t)}\dot{V}(t), \tag{7}$$

$$\dot{V}_{O_2}(t) = \frac{F_{N_2O}(t) - (1 - F_{N_2O}(t))F_{eO_2}}{1 - F_{N_2O}(t) - F_{O_2}(t)}\dot{V}(t), \tag{8}$$

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

$$F_{N_2O}(t) > 0 \tag{9}$$

$$1 - F_{N_2O}(t) - F_{O_2}(t) > 0 \tag{10}$$

$$F_{N_2O}(t) - \big(1 - F_{N_2O}(t)\big)F_{eO_2} > 0 \tag{11}$$

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

$$F_{IA,n}(t) = \begin{cases} F_{A,n-1} & \text{if } t_{bI} \le t < t_{bI} + T_{DI} \\ F_{I,n}(t) & \text{if } t_{bI} + T_{DI} \le t < t_{eI}. \end{cases} \tag{12}$$

In the above, t_{bI} is the time at the beginning of inspiration, t_{eI} 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 $\mathcal{V}_I$ be the volume of tracer gas delivered into the lung during breath n,

$$\mathcal{V}_I = \int_{t_{bI}}^{t_{eI}} \dot{V}(t)F_{IA,n}(t) \tag{13}$$

where $\dot{V}(t)$ is the measured respiratory flow rate at time t.

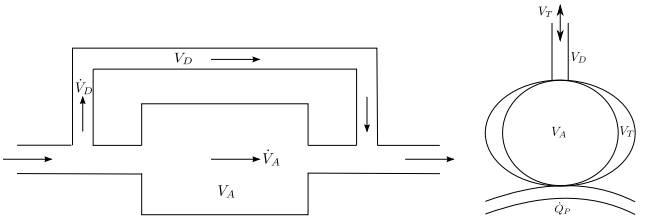
Substituting (12) into (13), we have

$$\begin{aligned}\mathcal{V}_I &= \int_{t_{bI}}^{t_{bI}+T_{DI}} \dot{V}(t)F_{A,n-1}dt + \int_{t_{bI}}^{t_{eI}-T_{DI}} \dot{V}(t)F_{I,n}(t)dt \\ &= V_D F_{A,n-1} + \int_{t_{bI}}^{t_{eI}-T_{DI}} \dot{V}(t)F_{I,n}(t)dt \end{aligned} \tag{14}$$

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

$$\mathcal{V}_E = V_{T,n}F_{A,n}. \tag{15}$$

Let $\mathcal{V}_Q$ be the uptake of the tracer gas (i.e., the amount of tracer gas absorbed by the pulmonary capillary blood in the



(a) A continuous ventilation model

(b) A "balloon-on-a-straw" tidal ventilation model

FIGURE 2. In a continuous ventilation model shown in (a), the lung has a fixed lung volume V_A and a parallel dead space of volume V_D, with constant and continuous gas flow $\dot{V}_A$ and $\dot{V}_D$, respectively. In comparison, the breath-by-breath tidal ventilation "balloon-on-a-straw" model shown in (b) has distinct inspiration and expiration phases, where the lung expands during inspiration and contracts during expiration.

lung) during breath n,

$$\mathcal{V}_Q = \dot{Q}_P \lambda_b (F_{A,n} - F_{\bar{V},n}) T_n, \tag{16}$$

where $\dot{Q}_P$ is the pulmonary blood flow, λ_b is the blood solubility coefficient of the gas, and T_n is the duration of breath n. $F_{\bar{V},n}$ 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 $V_A F_{A,n-1}$ 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

$$V_A F_{A,n} - V_A F_{A,n-1} = \mathcal{V}_I - \mathcal{V}_E - \mathcal{V}_Q, \tag{17}$$

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

$$V_A \left(F_{A,n-1} - F_{A,n}\right) + \dot{Q}_P \lambda_b \left(F_{\bar{V},n} - F_{A,n}\right) T_n = V_{T,n} F_{A,n} - \left[V_D F_{A,n-1} + \int_{t_{bI}}^{t_{eI}-T_{DI}} \dot{V}(t) F_{I,n}(t) dt\right]. \tag{18}$$

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 $F_{\bar{V},n}$ diminishes, leaving

$$F_{\bar{V},n} = M_A, \tag{20}$$

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

$$V_A \left(F_{E',n-1} - F_{E',n}\right) + \dot{Q}_P \lambda_b \left(M_A - F_{E',n}\right) T_n = V_{T,n} F_{E',n} - \left[V_D F_{E',n-1} + \int_{t_{bI}}^{t_{eI}-T_{DI}} \dot{V}(t) F_{I,n}(t) dt\right]. \tag{21}$$

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, λ_b is a known constant. The measured variables are $F_{E',n-1}$, $F_{E',n}$, $F_{I,n}(t)$, $V_{T,n}$, 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

$$d_a \le d_m \le d_b. \tag{25}$$

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

IEEE Journal of Translational Engineering in Health and Medicine

using an artificial lung at a known tidal volume. Our experiments have demonstrated that a suitable value for D is

$$D = 1.171. \tag{27}$$

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 mode. 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

$$c'(t) = c(t) + \alpha \frac{dc(t)}{dt}, \tag{28}$$

where α 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_2O [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_2O and O_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 $\dot{Q}_P$ 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 cardiopulminary variables using single tracer gases, we here demonstrate the use of our novel breath-by-breath model, using a combination of N_2O and O_2 tracer gases. N_2O amplitude is dampened by both the alveolar compartment and the pulmonary blood flow. Since the influence of the variables V_A and $\dot{Q}_p$ on N_2O amplitude are independent, the mass balance equations are theoretically soluble for N_2O 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, $\dot{Q}_p$. In the case of two tracer gases, the value of V_A is determined by averaging the solutions for N_2O and O_2. These values are used, as described previously, to estimate $\dot{Q}_p$, using least-squares to solve equation (21), noting that $\dot{Q}_p = 0$ for O_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 0.13L, 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 cardiopulminary 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.

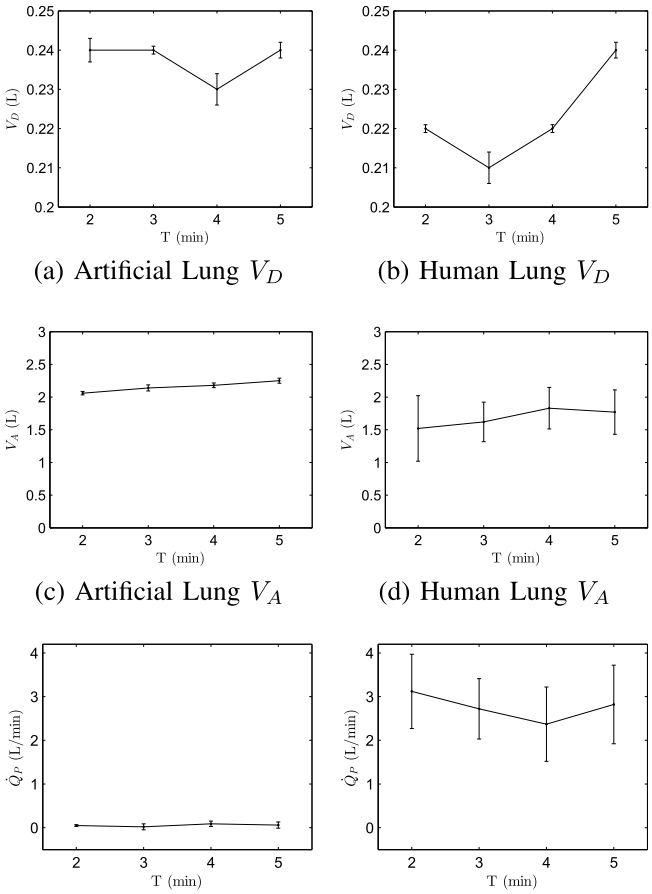


FIGURE 3. Estimates of V_D, V_A, and $\dot{Q}_P$ at five sinusoidal periods $T = 2$, 3, 4, and 5 mins, obtained from an artificial lung and an exemplar healthy volunteer, respectively. For both the artificial lung and the human lung, 20 consecutive 30s windows of data were used to obtain the results at each forcing period T. Each of these windows was used to obtain estimates of V_D, V_A, and $\dot{Q}$, for each value of T (i.e., $4 \times 20 = 80$ windows were used in total in this illustration). At each value of T, average values are plotted, with standard deviations shown as the error bar. The actual parameter values for the artificial lung are $V_D = 0.23$ L, $V_A = 2.36$ L, and $\dot{Q}_P = 0$ L min^{-1}. Expected parameter ranges for the exemplar human subject (female, 25 years, height 169cm, weight 60kg) are $0.2 \leq V_D \leq 0.3$ L, $1.5 \leq V_A \leq 3$ L, and $2 \leq \dot{Q}_P \leq 5$ L min^{-1}.

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.

IEEE Journal of Translational Engineering in Health and Medicine

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 $1.5 \leq \dot{Q}_P \leq 5$ L min^{-1}.

T (min)	Sex	V_D (L)	V_A (L)	$\dot{Q}_P$ (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)	$\dot{Q}_P$ (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

Tables I and II compare results across all 20 patients, partitioned according to sex, for the use of N_2O only, and N_2O with O_2, respectively. It may be seen that, as the Bohr equation is used in both cases to determine the value of V_D, there is no difference between the tracer gas injection methods. However, estimates of V_A obtained when using two tracer gases have lower variability than the estimates obtained using a single tracer gas, while taking similar mean values, as hypothesised in Section V. The variances of the estimates of $\dot{Q}_p$ follow a similar pattern.

VII. CONCLUSION

The purpose of this study was to establish whether the gas delivery device and the algorithms used for data analysis were capable of recovering stable data. In the artificial lung, the alveolar volume V_A and pulmonary blood flow $\dot{Q}_P$ are accurately recovered. In the human volunteer study, a finite value of pulmonary blood flow $\dot{Q}_P$ is recovered. We did not use an alternative comparator for this variable in this early stage pilot study; however, it seems that the recovered value probably under-represents the true value. Future studies should be undertaken against a known comparator for cardiac output/pulmonary blood flow, and complete equilibration of nitrous oxide should be ensured so that the analysis algorithms can be refined and appropriately calibrated. Later stages of validation will seek ethical approval to acquire data from unhealthy patients.

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 $2 \leq T \leq 5$ mins, 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 $\dot{Q}_P$ 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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