Inspired Sinewave Technique to Non-invasive Lung Function Testing
An Introduction and Update of Recent Developments

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Abstract: Inspired Sinewave is a novel technique to measure dead space, alveolar volume, and pulmonary blood flow noninvasively. In this paper, we describe a brief introduction to the principle of the technique, which involves forcing inspired concentrations to oscillate sinusoidally and measuring responding expired concentrations. Then, we give some updates to the recent developments of the device. These include accuracy and robustness studies of the device on bench lungs and volunteers, and study of lung volume change from sitting to supine. The success of these studies is a big step forward to make this novel device a useful clinical tool. The paper concludes with a description of future work.

1 INTRODUCTION

Lung function testing is essential to the diagnosis of how the lung works in health and disease. Even though the use of spirometry with simple volume and flow measurements remains the cornerstone, respiratory function testing has now advanced to involve sophisticated analyses of volume, flow, airway pressure and expired breath (King, 2011). Predominantly in the research domain, these techniques include forced oscillation technique, multiple breath nitrogen washout, optical coherence tomography, surface tomography methods (King, 2011), and inspired sinewave technique, etc. These new techniques will likely improve the understanding of airways disease and benefit the development of new treatments.

The inspired sinewave is such a technique, aiming at providing measurements of dead space, alveolar volume, pulmonary blood flow, and lung inhomogeneity simultaneously, non-invasively, and without patients' cooperation. By forcing the inspired concentrations of O_2 and N_2O to oscillate sinusoidally with very low amplitudes (3-5%) and low mean for N_2O (3%), lung parameters can be estimated from the responding amplitudes and phases of the expired concentrations. The larger the lung parameters, the greater are the attenuations of the expired oscillations.

Historically, the technique was originated from Zwart's idea of using forced inspired sinusoids of halothane and acetylene in the 1970s, to measure the average ventilation-to-blood flow ratio $\left(\dot{V}_A / \dot{Q}_P\right)$ and the pulmonary blood flow $\left(\dot{Q}_P\right)$ (Zwart et al., 1976); (Aart Zwart et al., 1978).

Hahn and collegues extended this idea to the use of more patient safe gases such as O_2 and low concentration of N_2O (3% mean) (Hahn et al., 1993); (Hahn, 1996). They also extended the simple continuous lung model used by Zwart to more complicated models, including dead space, multiple compartments, and tidal ventilation, which allow estimations of dead space, alveolar volume, blood flow and inhomogeneity simultaneously from the experimental sinewave data (Gavaghan & C. E. W. Hahn 1996; Whiteley et al. 2000).

Preliminary clinical studies with both animals (Williams et al., 1994); (Williams et al., 1996); (Williams et al., 1998) and healthy volunteers (Williams et al., 1997) showed close argeements between the inspired sinewave technique and other techniques including single breath CO_2 for measuring dead space, whole-body plethysmography and multiple N_2 washout for measuring alveolar volume, and thermal dilution for measuring plumonary blood flow. These studies verified the potential benefits of the inspired sinewave technique

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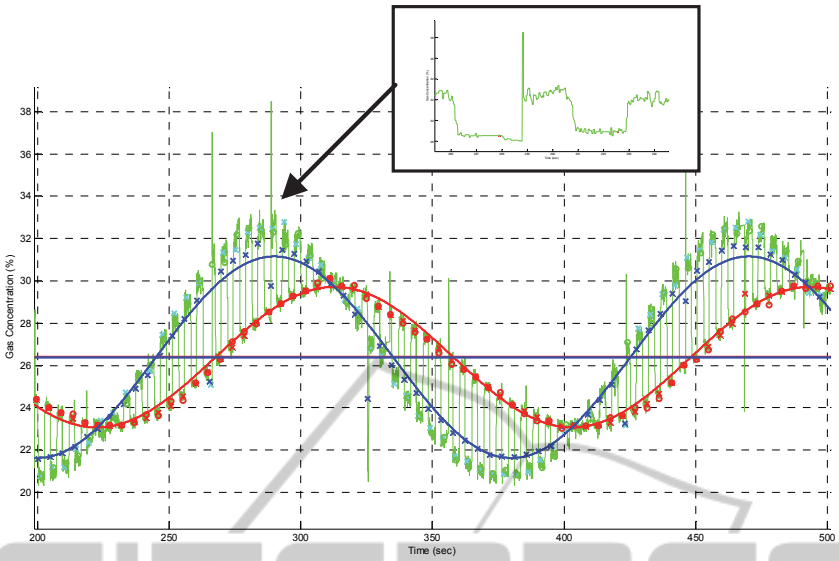

Figure 1: An example of O_2 concentration signal collected in an inspired sinewave lung function test. Green line is the measured O_2 signal. Blue marker and line are the mixed inspired concentration and sinewave. Red marker and line are the end-expired concentration and sinewave. The more attenuated the end-expired concentration, the greater the dead space, lung volume, or pulmonary blood flow.

to noninvasively and simultanesously measure lung function.

The early protype of the device, with which the above studies were carried out, included a pre-mixing gas delivery system and a mass spectrometer for gas analysis. This hardware was cubersome and hindered the progress of making the device a useful clinical tool by the bedside and in the intensive care environment.

A large effort has been made in the past ten years was to find suitable technoligies and designs to miniaturise the hardware components. This was not entirely successful until recently when manufacturers started making mass flow controllers and infrared sensors that were small, accurate, and fast enough for our purpose. These technologies have been adapted into the our later prototype, and futher enhanced from manufacturing settings by our custom software algorithms (Farmery and Hahn, 2000); (Farmery and Hahn, 2001). This is the foundation of our current prototype apparatus, which will be described in the next section.

2 METHOD

2.1 Theory

Fig 1 shows an example of O_2 signal in an inspired sinewave test. The signal jumps from 1 sinewave to another between inspirations and expirations as displayed by the red and green lines. Many lung models can be used to estimate dead space, alveolar volume and pulmonary blood flow from this signal. The simplest one is the continuous lung model, more complicated ones include the tidal one-compartment model and the tidal multiple-compartment model. The more complicated the model, the greater the accuracy and insight can be retrieved. However, the computational complexity also increased. In this introduction paper, we will present the simplest continuous model. Interested readers can refer to (Gavaghan and Hahn, 1996); (Whiteley et al., 2000) for more complicated models.

In the continuous model, the lung is considered similar to the fish gills, in which air flows continuously through a chamber where gases exchange with blood occurs, as shown in Fig 2. The dead space ventilation $\dot{V}_D$ is estimated as:

$$\dot{V}_D = V_D \times rr \tag{1}$$

where rr is the breathing rate per minute, and the dead space V_D is estimated by the Bohr method:

$$V_D = V_T \frac{F_E - F_{\bar{E}}}{F_E - F_{\bar{I}}} \tag{2}$$

where V_T is the tidal volume, $F_{\bar{I}}$ is the mixed inspired concentration, F_E is the end expired

concentration, $F_{\bar{E}}$ is the mixed expired concentration.

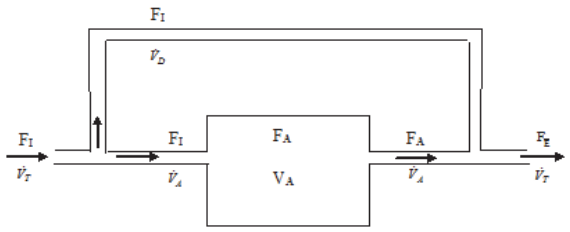

Figure 2: The continuous lung model. The inspired ventilation is branched into two parts: the alveolar ventilation $\dot{V}_A$ which goes through an alveolar chamber, and the dead space ventilation $\dot{V}_D$ which bypass the alveolar chamber.

The alveolar ventilation is estimated as:

$$\dot{V}_A = (V_T - V_D) \times rr \quad (3)$$

The mass balance equation for O_2 is:

$$\dot{V}_A \times F_I(t) - \dot{V}_A \times F_A(t) - \dot{V}_{O_2} = V_A \frac{dF_A(t)}{dt} \quad (4)$$

where V_A : is the alveolar volume,

$F_I(t) = \Delta F_I \sin\left(\frac{2\pi}{T}t\right) + F_{I,0}$: is the inspired sinusoidal concentration, with T the period, $F_{I,0}$ the mean inspired.

$\dot{V}_{O_2}$: the oxygen consumption rate,

$F_A(t)$: the alveolar concentration, $= F_E(t)$ the end expired concentration. At steady state, $F_A(t) = \Delta F_A \sin\left(\frac{2\pi}{T}t + \varphi\right) + F_{A,0}$, with φ the phase difference between the inspired and expired sinewaves, $F_{A,0}$ the mean alveolar

It has been shown from the oxygen-haemoglobin association curve that at high partial pressure of oxygen in the blood pO_2, oxygen saturation sO_2 is approximately unchanged (Williams et al., 1997). The oxygen consumption rate $\dot{V}_{O_2}$ is therefore approximately constant when a sinusoidal inspired

O_2 concentration is applied. The steady-state solution of $F_A(t)$ in (4) is:

$$F_A(t) = \frac{\Delta F_I}{\sqrt{1 + \left(\frac{2\pi}{T}\right)^2 \left(\frac{V_A}{\dot{V}_A}\right)^2}} \sin\left(\frac{2\pi}{T}t + \phi\right) + F_{A,0}$$

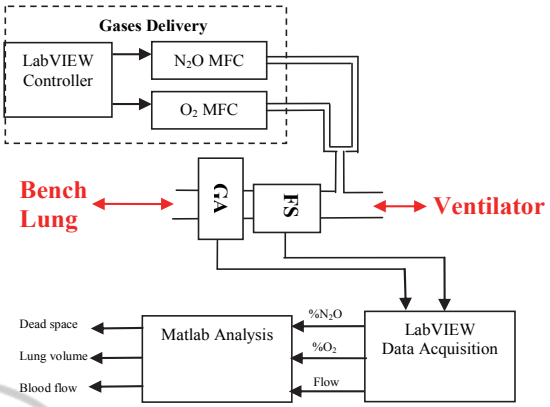

Figure 3: Layout of the Inspired Sinewave Device. The gases delivery system employs mass flow controllers (MFCs) to inject O_2 and N_2O into the breathing circuit. Real-time data is read by the flow sensor (FS) and the mainstream gas analyzer (GA) and fed to LabVIEW and Matlab for estimation of dead space, lung volume and pulmonary blood flow.

Table 1: Experiment 1 – Robustness of dead space estimation.

	Setup 1	Setup 2	Setup 3
Deadspace	108ml	208ml	258ml
Alveolar Volume	2.6L	2.6L	2.6L

(a) Actual bench lung parameters

	Setup 1	Setup 2	Setup 3
Deadspace	110 ± 10ml	206 ± 8ml	260 ± 8ml
Alveolar Volume	2.71 ± 0.14L	2.72 ± 0.14L	2.48 ± 0.16L

(b) Estimations using the proposed method

Estimations of dead spaces and alveolar volumes of 3 different bench lung setups. Values are mean ± 95% confidence.

Therefore,

$$\Delta F_A = \frac{\Delta F_I}{\sqrt{1 + \left(\frac{2\pi}{T}\right)^2 \left(\frac{V_A}{\dot{V}_A}\right)^2}}$$
$$\Leftrightarrow V_A = \frac{T \times \dot{V}_A}{2\pi} \sqrt{\left(\frac{\Delta F_I}{\Delta F_A}\right)^2 - 1} \quad (5)$$

Thus, the alveolar volume can be estimated from the ratio of the magnitudes of the inspired and expired sinewaves.

For N_2O, the formula is slightly more complicated and is given in (Williams et al., 1994). In this case, we have:

$$\frac{\Delta F_E}{\Delta F_I} = \frac{1}{\left[\left(1 + \frac{\lambda \dot{Q}_p}{\dot{V}_A}\right)^2 + \left(\frac{2\pi}{T}\right)^2 \left(\frac{V_A}{\dot{V}_A}\right)^2\right]^{1/2}} \quad (6)$$

where λ is the blood gas solubility of N_2O, $\dot{Q}_p$ is the pulmonary blood flow. Knowing (6) at 2 different periods, we can estimate V_A and $\dot{Q}_p$.

2.2 Hardware

The layout of the device is described in Fig 3. By reading the inspiration flow rate in real time, the software can decide the set-points for the mass flow controllers to inject the desired amount of O2 and N2O. The integrations of concentrations and flow signal give the inspired volume and expired volume of O2 and N2O breath-by-breath. These inspired volumes and end-expired concentration are then fed into a mathematical model of the lung in Matlab to estimate dead space, lung volume, and blood flow.

The gas sensors have accuracy of 2% of reading and step response time of less than 350ms and 5ms time delay. The flow sensor is fast with updating rate of 50Hz and accuracy of 3%.

2.3 Potential Benefits

The 3 main features of IST are as follows.

2.3.1 Measure Simultaneously Dead Space, Alveolar Volume, and Pulmonary Blood Flow

From the theory above, it can be seen that dead space, alveolar volume, and pulmonary blood flow can be estimated simultaneously from eq (2), (5), and (6).

It should be noted that the parameters are estimated independently from O2 and N2O signals (except pulmonary blood flow). The estimations are therefore combined to give better accuracy and robustness.

Table 2: Experiment 2– Robustness of lung volume estimation.

	Setup 4	Setup 5	Setup 6
Deadspace	208ml	208ml	208ml
Alveolar Volume	1.8L	2.2L	2.6L

(a) Actual bench lung parameters

	Setup 4	Setup 5	Setup 6
Deadspace	210 ± 14ml	202 ± 10ml	206 ± 8ml
Alveolar Volume	1.86 ± 0.18L	2.17 ± 0.15L	2.72 ± 0.14L

(b) Estimations using the proposed method

Estimations of dead spaces and alveolar volumes for varying lung volume setups. Values are mean ± 95% confidence.

2.3.2 Does Not Require Patients' Cooperation

The use of mass flow controllers allows any desired inspired O_2 and N_2O concentrations regardless of the inspired flow rate. The estimations can be estimated regardless of any breath length and pattern. This is particularly advantageous with injured or unconscious patients who are impossible to test by spirometry and body plethysmography. Small children and babies are also benefit from this feature.

2.3.3 Indicates Lung Inhomogeneity

It has also been shown that the level of dependency of estimated alveolar volume and pulmonary blood flow on the inspired oscillation periods reflects the inhomogeneities of both ventilation–volume and ventilation–perfusion (Whiteley et al., 2000).

3 RESULTS

With this current prototype, we have started carrying out experiments to verify the device. Initial results include accuracy and repeatability test on a bench lung, and initial human volunteer studies.

3.1 Accuracy and Repeatability

To test the device, we have used a bench lung that can be set at different dead space and alveolar volume configurations. Tables 1 and 2 show results estimated by the device compared to the actual set ups of the bench lung. It has been confirmed that the errors are less than 10% for both dead space and alveolar volume estimations.

3.2 Initial Volunteer Study

We have also started testing the device on human subjects. One study is to estimate functional residual capacity of healthy simultaneously-breathing subjects. Fig 4 demonstrates the results for 7 males and 5 females, showing good agreements with predictions by equations in (Ibañez and Raurich, 1982). Currently, we are carrying out more human studies in the lung function lab at the Churchill hospital – Oxford. These studies include comparisons for FRC between sitting and supine posititions, and between estimations of the device and the body plethysmography. Initial results show good correlations between the estimations by the

device and other methods, verifying the potential of the device to measure lung function parameters noninvasively.

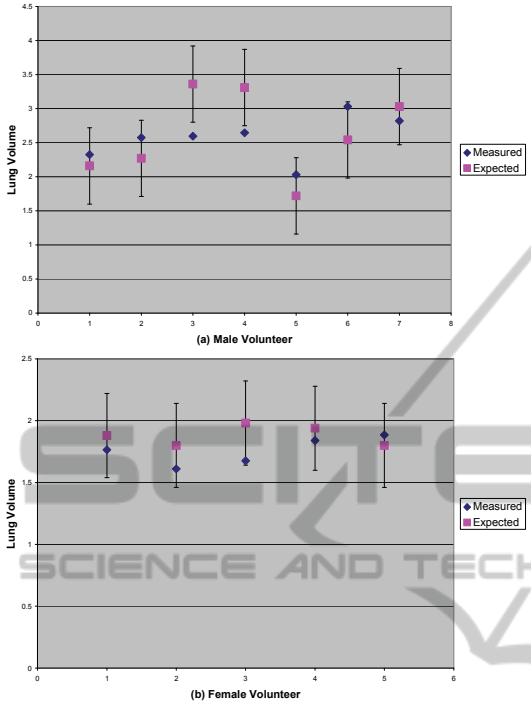

Figure 4: Functional residual capacity estimated by the device for healthy simultaneously-breathing subjects.

4 FUTURE RESEARCH

We will continue to carry more studies of the device in the clinical environment such as besides the bedside and in the intensive care unit. We are currently obtaining ethnic approval to test the device on diseased patients. Patients who come in the lung function for pulmonary test will be asked to volunteer 30 mins to be tested by our device. The test results will then be compared to other tests such as body plethysmography, spirometry, and impulse oscillometry (which are already gathered through the patients' normal test procedure). We hope to gather more evidence of the effectiveness of the device through this study.

We will further refine the design and miniaturize the device, making it more suitable for the clinical environment. In particular, we aim to make the device weighted less than 30kg, mounted on a 40cm x 30 cm x 100cm trolley which can be moved easily around the crowded intensive care environment.

Our goal is to complete an advanced prototype, which is readily marketable to medical device manufacturers by 2014.

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