VALIDATING THE INSPIRED SINEWAVE TECHNIQUE TO MEASURE LUNG HETEROGENEITY COMPARED TO ATELECTASIS & OVER-DISTENDED VOLUME IN COMPUTED TOMOGRAPHY IMAGES

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ABSTRACT

The inspired sinewave technique (IST) is a non-invasive non-ionising method which can measure accurately lung parameters. Six anaesthetised pigs were studied after surfactant depletion by saline-lavage. Paired measurements of lung heterogeneity were taken with the IST and computed tomography (CT). Lung heterogeneity measured by the IST was calculated by the ratio of tracer gas outputs measured at 180s and 60s. In CT images, lungs were manually segmented and divided into different regions according to voxel density. The IST and CT show strong agreement on lung heterogeneity measurements. In the IST ventilation heterogeneity value, the linear correlation in total of six pigs are weaker than individual animal ($R^2=0.33$ vs $R^2=0.67$ on average). The IST perfusion heterogeneity agreements are lower than IST ventilation values due to the IST technical setup. IST has the potential to measure the lung heterogeneity in ARDS animals.

Index Terms— Lung heterogeneity, IST, ARDS, Lung simulation, CT images.

1. INTRODUCTION

The acute respiratory distress syndrome (ARDS) affects 10% of critical care patients and has an associated mortality of 40% [1]. ARDS has a high mortality rate, brings higher hospital costs and survivors have a low health-related quality of life [2]. During the 2019-2020 coronavirus pandemic (COVID-19) [3], [4] a study of 201 COVID-19 patients showed 41.8% of patients developed ARDS and 52.4% died [4]. Having the ability to measure lung heterogeneity at the bedside and provide optimal ventilator setup could help survival in ARDS patients.

Heterogeneity of the lung is the mismatch between ventilation (air coming into the lung), alveolar volume and perfusion (pulmonary blood flow) [5]. Lung heterogeneity has been considered as a critical tool or to support respiratory

diseases classification [6], [7]. Therefore, measuring lung heterogeneity at the bedside could provide the clinician with valuable information with which to optimise the ventilator-settings for patients with lung conditions. Recently, CT imaging has been shown to be able to quantify lung heterogeneity [8], [9]. However, CT puts patients at risk by necessitating transfer to a scanner and exposure to ionising radiation. On the other hand, lung monitoring using the IST has shown potential to capture lung parameters at the bedside [10].

IST has the potential to provide bedside measurement of deadspace volume, effective lung volume (ELV), pulmonary blood flow (Qp) and lung heterogeneity. Measurements of the first three parameters have been validated elsewhere [6], [10]–[12]. IST uses available components commonly used in anaesthetic/intensive care practice and has proven efficacy in spontaneously ventilating healthy volunteers [13]. Lung heterogeneity measured by the IST was first introduced and conceptualised by Tran et al. [14]. To date IST's measurements of lung heterogeneity have not been compared against any established method.

We aimed to compare measurements of lung heterogeneity made by the IST with those made by CT in animals with ARDS. This is the first study to validate IST (a signal processing-based technique in respiratory monitoring) to measure lung heterogeneity.

2. METHOD

2.1. Protocol & animal preparation

Experiments in six anaesthetised pigs were studied at the Hedenstierna Laboratory, Uppsala University, Sweden and approved by the regional animal welfare and ethics committee (Ref: C98/16). The summary of animals' baseline characteristics is shown in TABLE 1. Mechanical ventilation with a Servo-I, Maquet, (Rastatt, Germany) was in volume-

control mode at 20-25 breaths per minute. Tidal volume was 10mL/kg and the inspiration: expiration (I:E) ratio was 1:2.

Fig. 1: Summary of the IST. Panel a is a schematic diagram of the IST lung model. Panel b shows examples of the measured output of IST 180s and 60s period tracer gases. Panel c shows the changes of ELV values measured by the IST when the lung ventilation heterogeneity varies. Similarly, panel d shows the changes of Qp measured by the IST when perfusion heterogeneity changed.

The ARDS model in animals was induced by injuring the lung using Lachmann's method [15]. Mechanical ventilation was disconnected. The installation of 0.9% saline solution (37°C) was transferred to the lung passing through the endotracheal tube. After 30s, we drained the saline out of the lungs and connected the ventilator. This process was repeated until the $\text{PaO}_2:\text{FIO}_2$ ratio (PFR) <300 mmHg (40 kPa) condition was achieved at a PEEP of 5 cmH₂O and FIO_2 of 0.7.

During the experiments, the PEEP level was incrementally changed from 5 through 10, 15 and 20 cmH₂O and decreased back to 15, 10 and 5 cmH₂O. At each PEEP, paired measurements of the lung volume by the IST and CT were performed.

2.2. Inspired Sinewave Test

2.2.1. Device and analysis

The IST applies a forced oscillation of a low dose of N₂O tracer gas with a sinusoidal period which can be determined by the user. A mainstream infrared N₂O and CO₂ sensor and an ultrasonic flowmeter are placed in the breathing circuit between a patient-end heat-moisture exchange filter and the ventilator tubing. At the beginning of each inspiration, a set volume of N₂O is injected into the inspired gas by a mass flow controller. The volume of IST tracer gas is oscillated at periods of 60s and 180s, in Fig. 1.

Input and output of the IST are analysed by the IST analysis (breath-by-breath analysis) to compute the lung parameters [16]. IST analysis is shown in Fig. 2. The IST quantifies the deadspace volume by using modified Bohr method [11] and subsequently the ELV and Qp are calculated according to this one well-mixed lung compartment (Fig. 1a). This simulation of the lung consisted of one deadspace and one alveolar compartment.

However, this simple one compartment might not present fully the heterogeneity of the lung. Therefore, IST requires two different period tracer gas to measure the lung heterogeneity.

TABLE 1

BASELINE CHARACTERISTICS OF N=6 PIGS. MEAN AND STANDARD DEVIATION ARE SHOWN.

Parameter	Mean (SD)
Weight (Kg)	30.3(1.64)
Heart rate (bpm)	99.5(20.5)
Cardiac output (L/min)	3.35(0.38)
Hb (g/L)	88.5(12.0)
FIO_2	0.78(0.02)
SaO ₂ (%)	98.3(0.85)
FIO ₂ : fraction of inspired O ₂ , Hb: haemoglobin, SaO ₂ : oxygen saturation.	

2.2.2. Lung heterogeneity measured by the IST

Theory dictates that in a completely homogeneously ventilated and perfused lung, the values of ELV and Qp recovered from the IST are independent of the tracer gas period used. However, as the degree of heterogeneity increases, the ELV and Qp values (based on the assumption of perfect homogeneity) begin to diverge from true values, and moreover, those values recovered from periods of 60 and 180s also diverge from each other. Consequently, the ratio of these latter values provides an index of the degree of heterogeneity. Example of ELV and Qp changes with simulated lung heterogeneity were presented in Fig. 1c and d.

The IST's ventilatory and perfusion heterogeneity ratios of the lung are given by the following:

$$IST_{Vent-Heterogeneity} = \frac{ELV_{180s}}{ELV_{60s}} \quad (1)$$

$$IST_{Perf-Heterogeneity} = \frac{Qp_{60s}}{Qp_{180s}} \quad (2)$$

where ELV_{180s} and ELV_{60s} the effective lung volume measured by IST 180s and 60s tracer gas periods; and similarly, for pulmonary blood flow (Qp).

2.2. CT image analysis

A Somatom Definition Flash (Siemens, Munich, Germany) was used to acquire images as a series of transverse sections.

with a reconstituted voxel size of 0.5x0.5x5 mm. We conducted a 20s end-expiratory paused without ventilator disconnection to scan the whole-lung volume.

Fig. 2: Signal processing block diagram of the inspired sinewave technique.

The scans were segmented by 3D Slicer (<https://www.slicer.org>). Exclusion of intrapulmonary vessels within regions of increased voxel density was not possible as they were not distinguishable from lung tissue, and these, along with the conducting airways up to the level of the clavicles, were included in the analysis. The Hounsfield unit (HU) boundaries were water with a density of 1 g cm⁻³ (0 HU) and air with a density of 0 g cm⁻³ (-1000 HU) [17]. Lung CT images were divided into three different regions [18] (Fig. 3):

- Atelectasis (including collapse and poor aeration): -500 to +100 HU
- Normally aerated volume: -900 to -501 HU
- Over-distended volume: -1000 to -901 HU

The mass of each lung fraction (e.g. atelectasis) was then calculated using the mean density and volume of each fraction assuming the lung is composed solely of air and water. To quantify the lung heterogeneity using CT images, we assumed that the ratios of atelectasis and over-distended over normally aerated could present the lung heterogeneity.

Statistical analysis was implemented in GraphPad Prism (<https://www.graphpad.com>). IST analysis were performed in Matlab (<https://uk.mathworks.com/>). Linear regression was used to assess the agreement and correlation between two measurement techniques.

3. RESULTS

A total number of 83 measurements of the lung at four different incremental and decremental PEEP levels were analysed. Fig. 4 shows the agreement between IST heterogeneity values and the CT image values in six animals.

In Fig. 4, panels a and b, the overall relationship of the IST ventilation heterogeneity vs CT values were recorded ($R^2=0.33$ in Atelectasis ratio and $R^2=0.18$ in Over-distended ratio). However, there was no linear relationship between CT heterogeneity values and the IST perfusion heterogeneity (panels c and d). Interestingly, the linear relationship in the

individual animal is strong than overall linear relationship. The R^2 values were summarised in TABLE 2. In the comparison of IST ventilation heterogeneity in both CT heterogeneity values, five pigs had strong agreements ($R^2>0.68$) except pig number 4. Similarly, in the comparison of IST perfusion heterogeneity vs CT values, the strongest agreements were observed in pig number 2 and 4.

Fig. 3: Lung heterogeneity measured by the CT images. Panels a and b show the animal lung in PEEP 5 (panel a) and PEEP 20 cmH₂O (panel b). Green: normally aerated mass; yellow: poorly aerated, dark red: atelectasis, red: over-distended.

Additionally, repeated lung heterogeneity measurements using the IST at the same PEEP level during both incremental and decremental changes had variation less than 10%.

4. DISCUSSION

This work fitted into a bigger picture of measuring the lung heterogeneity using a non-invasive technique. The IST has been developed and validated to be used as a clinical tool for lung monitoring at the bedside [6], [19]. In this paper, the IST analysis used a simple one, well-mixed, lung compartment and the heterogeneity of the lung was calculated according to the degree of breakdown of this model. It is a simple technique with no requirement to compute time and power. However, the accuracy of the model might be a concern. In this study, we compared the IST heterogeneity vs values calculated from CT images. Although each technique has its own assumptions and working principles, agreement was observed in individual testing subjects.

We experimented a similar protocol through six animals, but the degree of the damaged lung was different in different pigs. The results were well presented in Fig. 4. In individual animal, CT and IST had a strong correlation.

CT has been used as a standard measurement to quantify the lung and also lung heterogeneity [8], [10]. In this study, we presented a validation of the IST heterogeneity results in CT images. However, CT measured voxel density, so radio dense

material, such as fluid (alveolar flooding) or blood may influence the true atelectasis volume. Manual segmentation also contains limitations.

Fig. 2: Color-coded individual pigs. Comparison of the IST heterogeneity (ventilation and perfusion) vs the heterogeneity indices measured by the CT images (Atelectasis/normally aerated and over-distended/normally aerated ratios) in six animals. Panels a and b show an agreement between the IST ventilation heterogeneity vs CT indices. Besides, panels c and d show the correlation of the IST perfusion heterogeneity. Linear regression analysis was performed.

The mechanical ventilator is a method to save ARDS patients, but it also induces lung injury in case of wrong setup. Therefore, bedside lung monitor could benefit both healthy patients and patients with lung diseases. It also is the final aim of the IST to monitor and suggest the optimal setting for the ventilator.

The IST is suitable for bedside monitoring. IST can measure accurately the effective lung volume and deadspace volume, which are key parameters to personalise mechanical ventilator [20]. The changes in lung volume due to increased PEEP were reported correctly by the IST [10]. Besides, IST shown its advantages to measure accurate value when the patient breathes stably. A sensitivity analysis has pointed out stable breathes and unchanged tidal volume during IST could minimise its technical error [6].

In previous studies, the heterogeneity index measured by the IST has shown its potential to identify COPD patients in comparison with other lung function test [19]. In research, heterogeneity has been used to detect and track patients with

lung conditions [7], [21], [22]. However, there was no standard in measuring lung heterogeneity. For example, the lognormal distribution is used to present the lung heterogeneity with ventilation and perfusion mismatch [7], [21].

TABLE 2
 R^2 VALUES OF THE LINEAR REGRESSION ON INDIVIDUAL ANIMAL

Pig	1	2	3	4	5	6
IST _{Vent} vs A/N	0.75	0.75	0.75	0.25	0.73	0.78
IST _{Vent} vs OE/N	0.68	0.71	0.83	0.38	0.69	0.73
IST _{Perf} vs A/N	0.09	0.43	0.28	0.56	0.26	0.46
IST _{Perf} vs OE/N	0.02	0.68	0.30	0.69	0.39	0.12

IST_{Vent}: IST ventilation heterogeneity ratio, IST_{Perf}: IST perfusion heterogeneity ratio, A/N: Atelectasis/Normal aerated ratio, OE/N: Over-Extended/Normal aerated ratio.

Limitations of this study were mainly using the porcine model to describe ARDS in human. It only can present mild and moderate lung injury [17]. Additionally, there was no comparison with healthy lung. Due to the experimental setup, the animal's lung was damaged before moving into the CT scanner. Furthermore, IST contains its own limitations. IST requires two period-tracer gas tests in series.

Future analysis of the lung heterogeneity can be performed by the IST advance lung simulation. This is an advanced computational technique that uses Bayesian optimisation to match simulated data to measured IST data. Additionally, other research can be carried out in the future based on CT images. Cressoni et al. introduced a filter which can quantify lung inhomogeneity in CT images. This was tested in 148 human data [8]. Additionally, a dynamic single-slice CT scan could provide better images and counter the effect of inspiration-related lung movement [23].

5. CONCLUSION

In this paper, we have validated the use of a non-invasive lung function test (Inspired sinewave technique) to quantify lung heterogeneity in comparison with the CT technique. We demonstrated a potential application for the use of IST as a bedside monitor of lung heterogeneity. Our study warrants further investigation into the use of IST in human clinical medicine.

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