Physiological Measurement

Lung heterogeneity and deadspace volume in acute respiratory distress syndrome animals using the inspired sinewave test

To cite this article before publication: Minh Cong Tran *et al* 2020 *Physiol. Meas.* in press https://doi.org/10.1088/1361-6579/abc0b5

Lung Heterogeneity and Deadspace Volume in Acute Respiratory Distress Syndrome animals using the Inspired Sinewave Test

Minh C. Tran[1,2], Douglas C. Crockett[1], Federico Formenti[3], Phi A. Phan[1], Göran Hedenstierna[4], Anders Larsson[4], Stephen J. Payne[2] and Andrew D. Farmery[1].

[1]Nuffield Division of Anaesthetics, University of Oxford, Oxford. UK.
[2]The Institute of Biomedical Engineering, University of Oxford, Oxford. UK.
[3]Centre for Human and Applied Physiological Sciences, King's College London, London, UK.
[4]Hedenstierna Laboratory, Department of Medical Sciences, Uppsala University, Uppsala. Sweden.

Abstract. The acute respiratory distress syndrome is associated with a high rate of morbidity and mortality, as patients undergoing mechanical ventilation are at risk of ventilator-induced lung injuries. *Objective:* To measure the lung heterogeneity and deadspace volume to find safer ventilator strategies. Then, the ventilator settings could offer homogeneous ventilation and theoretically equalise and reduce tidal strain/stress in the lung parenchyma. *Approach:* The Inspired Sinewave Test (IST) is a non-invasive lung measurement tool, which does not require patients' cooperation. The IST can measure the effective lung volume, pulmonary blood flow and deadspace volume. We developed a computational simulation of the cardiopulmonary system to allow lung heterogeneity to be quantified using data solely derived from the IST. Then, the method to quantify lung heterogeneity using two IST tracer gas frequencies ($180s$ and $60s$) was introduced and experimented in the simulation lungs and in animal models. Thirteen anaesthetised pigs were studied with the IST, both before and after experimental lung injury (saline-lavage ARDS model). The deadspace volume is compared between IST and the SF_6 Washout method. *Results:* The IST could measure the lung heterogeneity using two frequencies tracer gases. Furthermore, the value of IST ventilation heterogeneity in ARDS lungs were higher than in control lungs at PEEP $10cmH_2O$ ($AuC = 0.85$, $p < 0.001$). Deadspace volume values measured by the IST has a strong relationship with the measured values of the SF_6 ($9mL$ bias and limits of agreement from $-79mL$ to $57mL$ in control animals). *Significance:* the potential impact of the IST technique in the identification of ventilation and perfusion heterogeneity during ventilator support.

Keywords: acute respiratory distress syndrome, ARDS, IST, Lung Simulation, Lung heterogeneity.

Abbreviations

ARDS	Acute respiratory distress syndrome
ELV	Effective lung volume measured by the IST (L)
$f_{p,i}$	Perfusion fraction to the lung compartment i
$f_{v,i}$	Ventilation fraction to the lung compartment i
Qp	Blood flow measured by the IST (L/min)
VT	Tidal volume (mL)
V_A	Alveolar lung volume (L)
VD_{IST}	Deadspace volume measured by the IST (mL)
VD_{SF_6}	Deadspace volume measured by the SF_6 (mL)
PEEP	positive end-expiratory pressure
$\dot{V}$	Ventilation (L/min)
$\dot{Q}$	Perfusion (L/min)

1. Introduction

The acute respiratory distress syndrome (ARDS) is characterised by pulmonary inflammation, with significant morbidity and mortality [1]. The prognosis of ARDS has improved within the past decades, with in-hospital mortality rates decreasing from 90% in the nineteen-seventies to approximately 30% in a recent study [2]. Guidelines for mechanical ventilation have probably contributed to this result by reducing ventilator lung induced injury. Thus, the mainstay of ventilator treatment is a reduction in tidal volume (VT), inspiratory and driving pressures, thereby reducing the stress and strain applied to the lungs. But, there is currently no conclusive way of determining optimal ventilation for an individual patient at the bedside.

In ARDS the lung is mechanically very heterogeneous, causing heterogeneous and harmful ventilation. However, the lung mechanics could be homogenised (such as PEEP titration and lung recruitment), resulting in a more homogeneous and thus, less harmful, lung ventilation. Lung heterogeneity is the unequal distribution of the airflow (ventilation) relative to the size of the lung regions to which it is distributed or to the gas-exchange to the bloodstream (perfusion) [3]. There are no easy methods that could be used at the bedside to evaluate lung heterogeneity or to quantify the effect of different manoeuvres and ventilator settings on lung homogeneity [4, 5]. The measurement of the lung homogeneity could potentially benefit ventilated patients.

The Inspired sinewave test (IST) was introduced as a non-invasive test which requires no cooperation from the patients being tested and does not involve ionising radiation. The IST applies a forced oscillation of a low dose of N_2O tracer gas with a sinusoidal period which can be determined by the user. IST result provides lung function parameters, including deadspace volume (VD), effective lung volume (ELV) and pulmonary blood flow (Qp) [6, 7, 8, 9, 10]. The IST results, including deadspace volume and effective lung volume provide suggestions to optimise the ventilator setting. Furthermore, it is proposed that by using two tracer gas frequencies, IST can quantify the ventilatory heterogeneity of the lung. In the previous study, the IST, used in combination with data from another lung function test (plethysmography), can detect changes in ventilatory heterogeneity which occur normally with age in healthy participants [8]. In another research in simulated patients, IST showed a potential to

identify simulated patients had emphysema (ventilation heterogeneity) and pulmonary embolism (perfusion heterogeneity) [11]. There is thus potential to develop the IST such that lung heterogeneity could be determined solely from the IST data, and without recourse to other techniques.

We have, therefore, developed a model to quantify the degree of the lung heterogeneity using the IST. Then, we experimented the IST heterogeneity results in anaesthetised piglets using only IST data. The experiments included measurements before and after the lung was damaged by following the saline lavage protocol (ARDS model). We also compared the absolute deadspace volume measured by the IST to that obtained from SF_6 washout.

2. Materials and methods

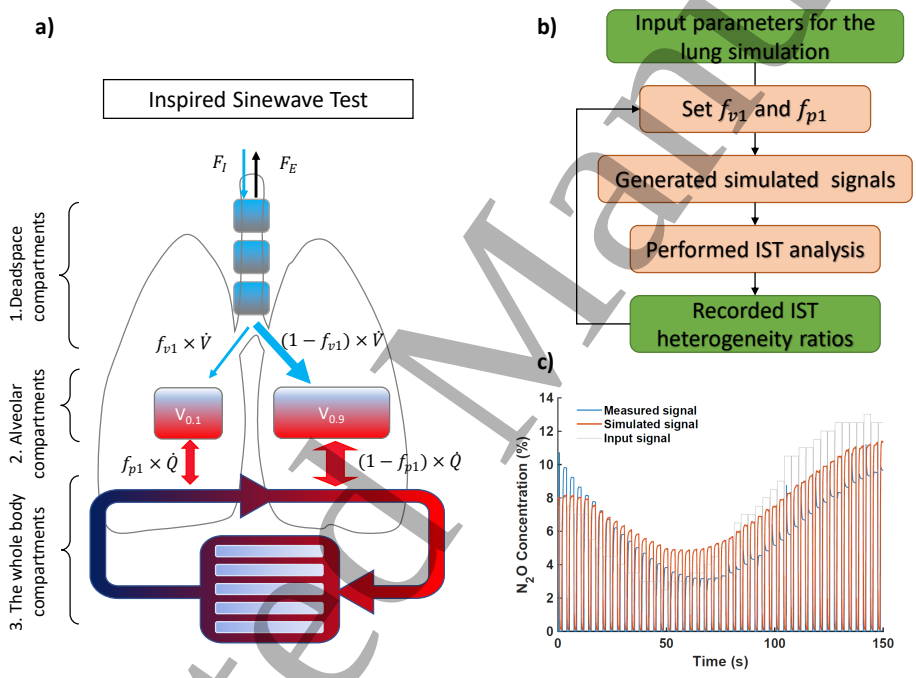

Figure 1. Panel a shows a schematic diagram of the two-compartments tidal lung simulation. The fraction of lung volume is set at 0.1 and 0.9. The ventilation heterogeneity is controlled by parameter f_{v1} and the perfusion heterogeneity is f_{p1}. Panel b shows a flow diagram to experiment the IST heterogeneity ratios using the lung simulation. Panel c shows the example of the IST measured and simulated exhaled (F_E) signals in responding to the 180s period input tracer gas (F_I) at PEEP $10cmH_2O$.

2.1. Measurement protocol

We developed a two-compartment lung simulation to provide a theoretical framework to understand the ventilation and perfusion heterogeneity values measured by the IST.

Then, the IST was performed in animal models before (control) and after lung injury (ARDS). After that, these IST heterogeneity indices are calculated and compared with the $PaO2 : FiO2$ ratio (a clinical indicator shows hypoxaemia). Additionally, deadspace volume measured by the IST were compared with the values measured by the SF_6washout.

Animals were anaesthetised and instrumented; Table 1 summarises baseline data. Thirteen pigs were mechanically ventilated (volume-control ventilation) at $20 - 25$ breaths per minute, with a VT of $10mL/Kg$ and an inspiratory/expiratory ratio of $1 : 2$ (Servo-I, Maquet, Rastatt, Germany). The right internal jugular vein was cannulated and a pulmonary artery catheter was inserted using pressure monitoring and used to measure pulmonary artery pressure continuously and cardiac output via thermodilution intermittently.

During the IST, N_2O tracer gas, added to the inspired air, was oscillated with periods of $60s$ and $180s$. PEEP levels were incrementally changed from 5 through 10, 15 and 20 cmH_2O. $PaO2 : FiO2$ ratio and paired measurements of deadspace volume by the IST and SF_6washout test (VD_{IST} and VD_{SF6}) were recorded at each PEEP level. SF_6 washout test is the lung measurement technique to measure the lung volume and deadspace volume using SF_6 tracer gas [12]. After the measurements in the control group, lung injury was induced as described below, and the same measurements were repeated in the injured state.

2.2. Inspired Sinewave Test heterogeneity indices

Table 1. Animal baseline characteristics for $n = 13$ animals.

Parameters	**Control**	**Injured**	**p**
Weight (Kg)	29(2)	-	-
HR (bpm)	86(12)	85(11)	0.42
CO (L/min)	3.4(0.8)	3.2(0.4)	0.26
pH	7.38(0.07)	7.25(0.08)	0.0004
PaO_2 ($mmHg$)	$144(119 - 161)$	$96(85 - 195)$	0.39
FIO_2	$0.4(0.3 - 0.4)$	$0.8(0.7 - 0.9)$	0.0002
PFR	$377(304 - 513)$	$128(101 - 248)$	0.0002

Mean (SD) or median (95% confidence interval) for non-parametric data are shown. CO: cardiac output calculated by thermodilution, PaO_2: arterial O_2 partial pressure, FIO_2: fraction of inspired O_2, PFR : $PaO2 : FIO2$ ratio.

In the IST analysis, the deadspace volume inside the lung, VD_{IST}, was firstly measured using the modified Bohr method [13]. Secondly, ELV and Q_p were calculated from a model assuming one well-mixed lung compartment [8].

Theory dictates that in the completely homogeneously ventilated and perfused lung, the values of ELV and Qp recovered from the IST are independent of the tracer gas period used. The IST accuracies of ELV and Qp values are published elsewhere

[14, 15]. 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. The IST ventilatory and perfusion heterogeneity ratio 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}/ELV_{60s} is the effective lung volume measured by IST 180s or 60s tracer gas periods; and similarly for Qp (pulmonary blood flow).

2.3. Lung heterogeneity simulation model

A heterogeneous lung was simulated by compartments, including 3 serial deadspace compartments [16], 2 alveolar compartments (tidal compartments) [9, 17, 18] and 5 compartments to present the whole body (lung, viscera fast, viscera liver, lean and fat) [19]. All compartments were linked together by conservation of mass equations. The significance of this simulation was a suitable testing for the IST and it also had clear settings in two tidal lung compartments to quantify the lung heterogeneity. Simulated patient is $70Kg$, $2.5L$ of lung volume and $5.0L/min$ pulmonary blood flow.

The volume fraction of the two tidal lung compartments were fixed at 0.1 and 0.9. Ventilation and perfusion fractions to the first lung compartment (0.1 fraction of volume) were changed to f_v and f_p. The ventilation and perfusion fractions to the second compartment (0.9 fraction of volume) were calculated by $1 - f_v$ and $1 - f_p$.

Due to the model setting, the lung was homogeneous when $fv_1 = 0.1$ and $fp_1 = 0.1$. An increase in value of fv_1 caused the mismatch of the ventilation and higher lung ventilation heterogeneity. Similarly, when fp_1 increased, the lung perfusion heterogeneity also raised. A schematic diagram of the lung simulation is presented in Figure 1. The full model development and modelling parameters are described in the appendix A.

2.4. Ethical approval

This study adhered to the *in vivo* Experiments (ARRIVE) guidelines [20]. In the Hedenstierna Laboratory, Uppsala University, Sweden, thirteen pigs were studied under the auspices of the regional animal welfare and ethics committee (Ref: C98/16).

2.5. Lung injury

Lung injury replicated the ARDS conditions in the animal model. Lachmann's method was applied to induce lung injury [21]. The ventilator was disconnected and 0.9% saline solution (37^oC) was instilled into the lungs via the endotracheal tube. The saline was drained out of the lungs after 30s. The protocol was repeated until $PaO2 : FIO2$ was less than $300mmHg$.

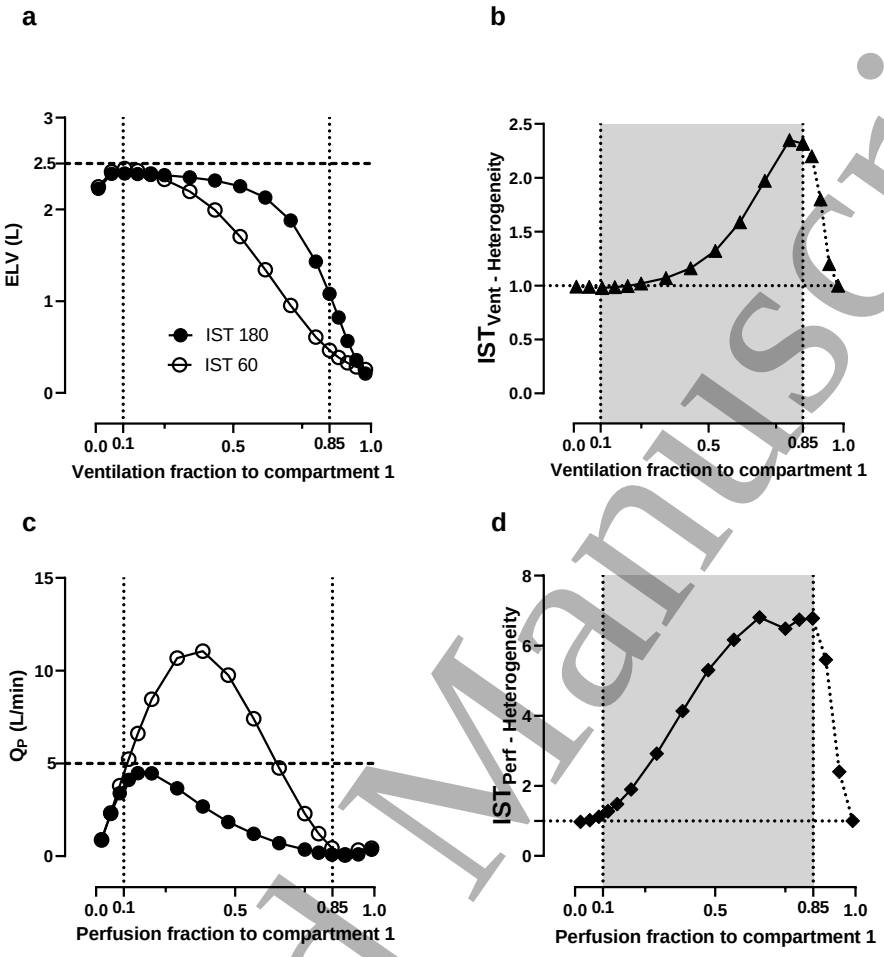

Figure 2. The divergences of the IST recovered values and IST heterogeneity indices in simulated heterogeneous lungs. Panels a and b show the IST values in different variations in ventilation heterogeneity and panels c and d show the changes in perfusion heterogeneity. The lung is assumed to be homogeneous when the "ventilation fraction to compartment 1" (x-axis) is 0.1 ($fv_1 = 0.1$, the first vertical dash lines). Each point in the x-axis presents one lung condition with the heterogeneous increased from 0 to 1. In panels b and d, the simulation would breakdown beyond the grey regions.

2.6. Statistical analysis

We used the Student's t-test to compare two parametric data groups and Wilcoxon signed-rank test for non-parametric data. We then analysed the Area Under The Curve (AuC) of the Receiver Operating Characteristics (ROC) curve to show the degree or measure of separability between control and injured [22]. The linear regression and Bland-Altman plots were used to analyse the relationship between paired measurements from the IST vs the SF_6 [23]. Lung simulations were developed and validated in Matlab (MathWorks, USA, www.mathworks.com). Statistical tests were

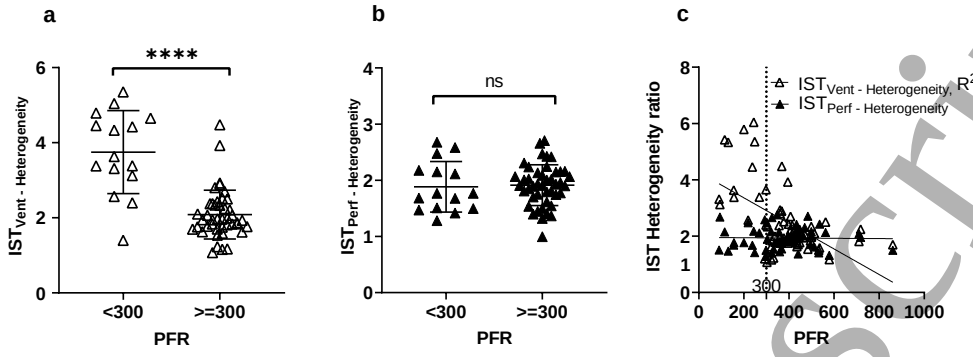

Figure 3. Validation results of the IST heterogeneity ratios. Panels a and b show the comparisons of IST heterogeneity indices to the $PaO2 : FiO2$ ratio (PFR). The Student's t-test comparison of the IST heterogeneity indices between two groups: $PFR < 300mmHg$ and $PFR > 300mmHg$ are performed. Panel c shows the linear relationship between IST heterogeneity indices and PFR. **** $= p < 0.0001$, ns = non-significant.

performed in Graphpad Prism $v8.1.2$ (GraphPad Software, USA, www.graphpad.com).

3. Results

The ability to measure the lung heterogeneity in the IST were assessed by the simulated heterogeneous lungs, in Figure 2. The difference between control and ARDS lungs in the IST ventilation and perfusion heterogeneity ratios were analysed by statistical tests in Figure 4. 6 animals in the total of 13 had the measurements at PEEP 15 and $20cmH_2O$. Additionally, a total of $n = 72$ paired VD measurements in 13 pigs at four different PEEP levels were analysed. Statistical analyses revealed that VD_{IST} and VD_{SF6} was not different in both control and ARDS lungs.

3.1. IST Lung heterogeneity values in simulated data

Figure 2 shows the IST results in the simulated heterogeneous lungs. Theoretically, in a homogeneous lung or a healthy lung, the IST results do not depend on any sinewave period. As the heterogeneity value increases, the ELV and Qp values of the 60 and $180s$ sinewave periods start diverging, Figure 2 a. Tracking the degree of divergence could provide the index of lung heterogeneity in panel b.

When the ventilatory fraction assigned to compartment 1 (which comprises 10% of the lung volume) is 0.1 ($fv_1 = 0.1$), the lung is assumed to be entirely homogeneous. Thus, ELV values at both $60s$ and $180s$ were recorded at approximately $2.46L$ (98% similar to the set value of $2.5L$) in Figure 2 a. When the fv_1 increased from 0.1 to 0.9, the heterogeneity of the lung was progressively increased. As a result, ELV values declined in both frequencies (panel a) and, moreover, the decrease in ELV at 60s was greater than in ELV at $180s$. This divergence, represented as a ratio of $IST_{Vent-Heterogeneity}$, is shown in panel b.

Values outside of the grey region (0.1 to 0.85) introduce more complexity to the model, so were not included. When ventilation heterogeneity increases to such a level

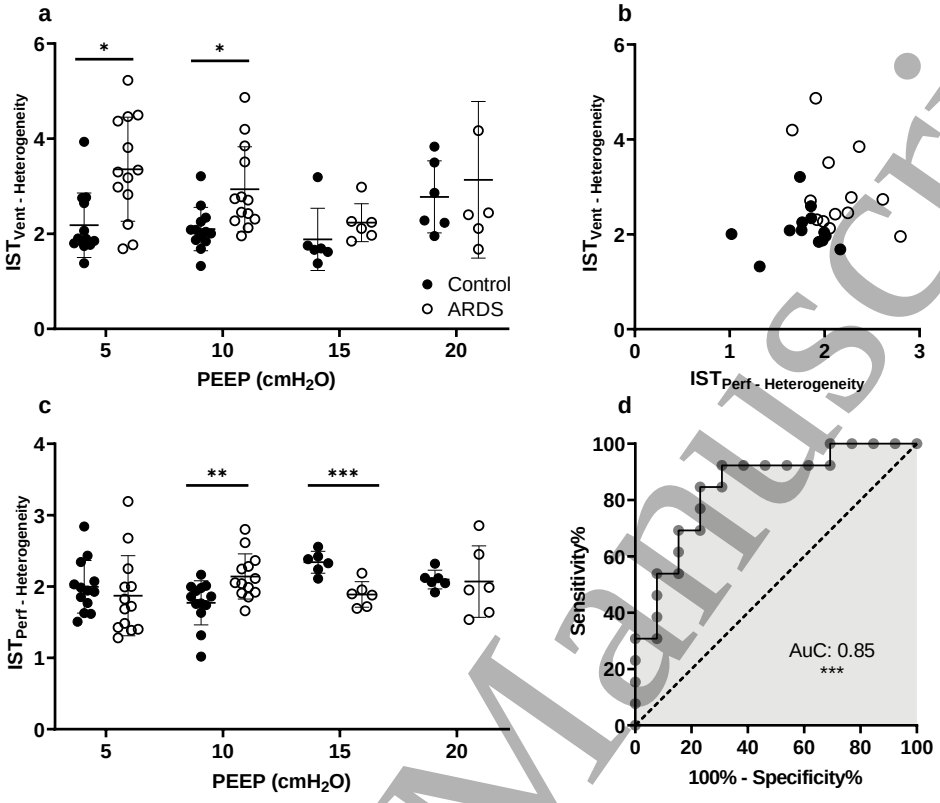

Figure 4. IST heterogeneity ratios in control and ARDS animals at different PEEP levels. Panel a shows IST ventilatory heterogeneity and panel c shows perfusion heterogeneity. A scatter plot in panel b shows the IST ventilation against perfusion heterogeneity indices at PEEP $10cmH_2O$. Panel d is the receiver operating characteristic curve between ARDS and control at the PEEP level of $10cmH_2O$. Student's t-tests were performed. *** $= p < 0.001$, ** $= p < 0.01$ and * $= p < 0.05$.

that 100% of ventilation is delivered to compartment 1, then ventilation would by definition return to being fully homogeneous, albeit very maldistributed (the lung just becomes a single, small compartment). Similar to the ventilation, when the perfusion fraction to compartment 1 is 0.1 ($fp_1 = 0.1$, perfect perfusion homogeneity), the ratio of these values predicts the degree of perfusion heterogeneity ($IST_{Perf-Heterogeneity}$ in panel d). A healthy lung should have the heterogeneity ratios about 1. The homogeneity of the lung will get worst when the ratios are further away from 1.

3.2. IST heterogeneity indices, a comparison between control and injured animals

Figure 3 shows the relationship of the IST heterogeneity indices vs the $PaO2 : FiO2$ ratio. The ratio of arterial $PaO2$ and inspired oxygen fraction ($PaO2 : FiO2$ or PFR) is used clinically as a broad indicator of gas exchange dysfunction [24, 25]. $PaO2 : FiO2 < 300mmHg$ indicates significant gas exchange impairment [24]. Figure 3a and b compare the IST heterogeneity values in between animals had the

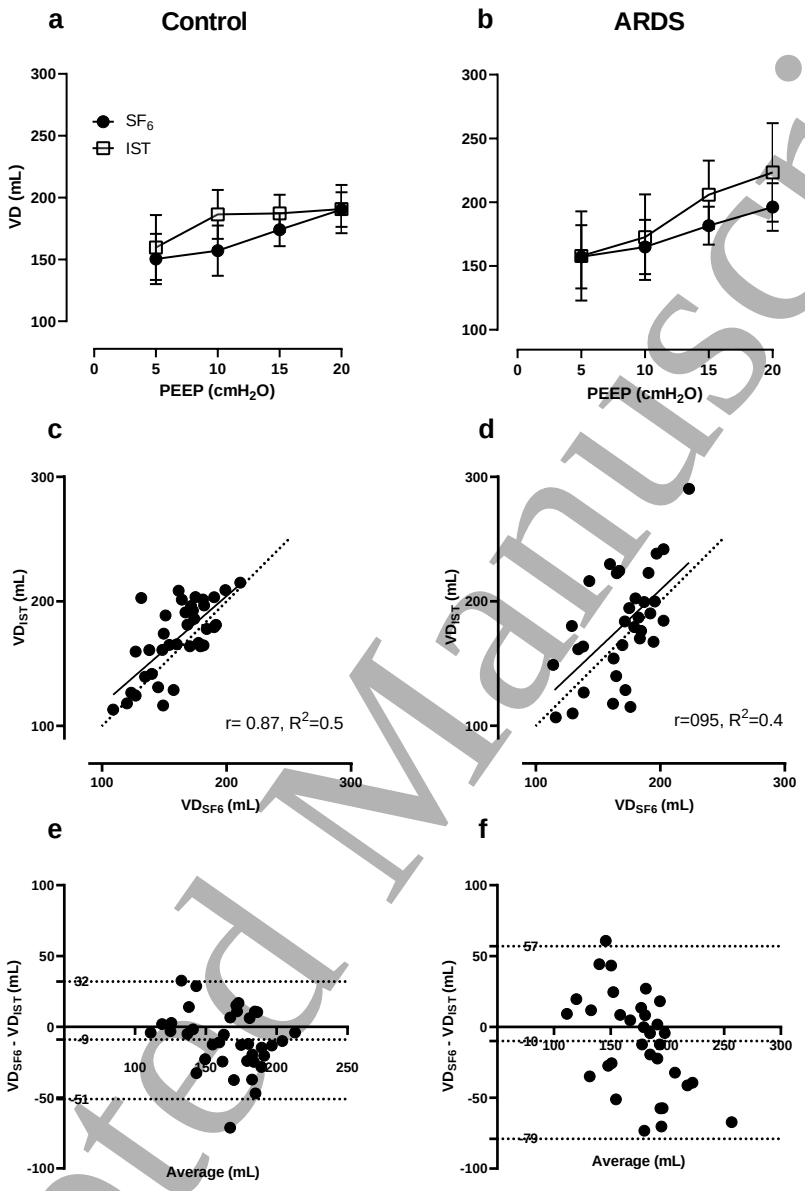

Figure 5. The deadspace volume comparison between the IST and SF_6 washout test. Panels a and b show paired VD_{IST} and VD_{SF6} measurements in control (pre-injured) and ARDS lungs (post-injured). Panels c and d show linear regressions of absolute deadspace volume measured by the IST and SF_6. The continuous lines are regression lines and dashed lines are the reference lines. In panels e and f show Bland-Altman plots, the bias lines are centre horizontal dash lines; and the top and bottom dash lines are the limits of agreement.

$PaO2 : FiO2$ smaller $300mmHg$ and greater than $300mmHg$. As for the PEEP values used, they are not specifically controlled in this comparison. In panel a,

there was a significant difference in IST ventilatory heterogeneity value in between $PFR < 300mmHg$ and $PRF >= 300mmHg$ (mean values of 3.9 vs 2.1, $p < 0.0001$), in panel a. Panel c shows linear regression analysis of the IST heterogeneity ratios vs the PFR. There was a linear relationship of the PFR with the IST ventilation heterogeneity ratio ($R^2 = 0.31, p < 0.05$), but not with the IST perfusion ratio.

The IST heterogeneity indices in control and injured groups at different levels of applied PEEP are shown in Figure 4a and c. At low PEEP levels (5 and $10cmH_2O$) the mean heterogeneity indices in the injured lungs were higher than in control (3.4 vs 2.2 at the PEEP of 5, and 2.9 vs 2.1 at PEEP $10cmH_2O$, $p < 0.05$ for both) in Figure 4a and 4c. The injured group at low PEEP also shows a greater scatter of the IST heterogeneity values. The application of PEEP from 5 through $15cmH_2O$ reduced mean heterogeneity within the injured group and also reduced data scatter, indicating a stabilising effect of PEEP, In Figure 4c, the IST perfusion heterogeneity ratio shows significant differences at PEEP 10 ($p < 0.05$) and 15 cmH_2O ($p < 0.001$). In panel b, a clear scatter plot shows the significant difference between control and injured animals at PEEP $10cmH_2O$. Control animals have the IST heterogeneity values about less than 2.1 and the values of the injured animals are higher.

Additionally, the ROC curve was applied to classify control vs ARDS at the PEEP $10cmH_2O$. The area under the curve was 0.85 ($p < 0.001$) with 95% confident interval was form 0.69 to 0.99.

3.3. Deadspace volume, a comparison of IST to SF_6

Figure 5 shows the relationship and correlation between deadspace volume measured by the IST and the SF_6. In general, deadspace volume increased when the PEEP was raised, and the ARDS group had larger deadspace volumes than control, panel a and b. SF_6 measurements had smaller variations compared to the IST. There was a robust relationship between VD_{IST} and VD_{SF6}: the linear regression slope was 0.87 with a $R^2 = 0.5$, in the control group, panel c. The volume bias was $9mL$ (limits of agreement $-79mL$ to $57mL$) in control and similarly, $10mL$ (limits of agreement $-51mL$ to $32mL$) in ARDS lungs (Figure 5, panels e and f).

4. Discussion

This research shows the ability of IST to measure lung heterogeneity and absolute deadspace volume, in uninjured lungs and ARDS model of lung injury compared with the 'gold standard' SF6 washout technique. The IST heterogeneity indices have the potential to identify ARDS vs control subjects with reasonable diagnostic accuracy; the area under the ROC curve = $0.85 (p < 0.001)$ at a PEEP of $10cmH_2O$. Additionally, deadspace volume measured by the IST had a small bias ($10mL$) compared with measured values of the SF_6.

A previous study of lung heterogeneity in human patients measured by the IST did not achieve any significant outcome because of the wide variability in the severity of conditions in the study population. Our research in animals, in which we were able to standardise and control the degree of lung injury more reliably, proved more insightful. Bruce et al. showed that ventilation heterogeneity could be determined by using the IST values in combination with the plethysmography results [8]. However, in this study, for the first time, we used only the IST results to measure the heterogeneity of the lung without the need for plethysmography. We

have implemented the simulation model and have used it to understand the IST heterogeneity indices and their boundaries. Healthy simulated lung should have the IST heterogeneity ratios of 1, although healthy human subject would not quite achieve this.

The IST has shown potential strengths including working as a bedside monitor and a diagnostic tool. Firstly, it can be used with spontaneously ventilating subjects. In this research, mechanically ventilated animals were investigated. Further study in ventilated patients could improve IST development. The IST also can measure the size of the 'baby lung' (equivalent to a small well-ventilated compartment) and results compare well to the SF_6 and CT scan data in ventilated animals [15]. We show that the heterogeneity of the lung changes with applied PEEP, a potential interest to the bedside clinician seeking to optimise ventilator settings. Secondly, at the appropriate ventilator setting, significant differences between control and ARDS conditions were distinguishable ($AUC = 0.85$). The results of this study could pave the way for study of disease classification using lung heterogeneity at the bedside. Patients could benefit as a result of better-informed ventilation setting, and the reduction of the ventilator induced lung injury [26, 27].

In addition, this study reveals the ability of the IST to measure the absolute deadspace volume which compares well to the SF_6 wash in-washout method. The correlation between the two methods had a slope of 0.87, $R^2 = 0.5$ and the limits of agreements were from $-51mL$ to $32mL$ in control lungs. Clinically, deadspace volume has a strong association with mortality risk in those patients with ARDS, wherein the risk of death increased by 22% for every 0.05 increase in the VD:VT [28].

We implemented a lung simulation to show how lung heterogeneity can be captured by the IST. However, the simulation and our work contain limitations. The lung simulation with two alveolar compartments may not be enough to represent the complexity of real-life lung heterogeneity. In Figure 2, the heterogeneity index is only valid between certain limits of ventilatory misdistribution (within the grey zone) Outside this region, the simulations break down as described above (in result section). Of note, whereas in the simulation, perfect homogeneity gives a heterogeneity index of 1, healthy subjects do not achieve this value (it being closer to 2). This is not surprising given that even in healthy ventilation is not perfectly uniformly distributed. A better simulation, including the effects of hypoxic pulmonary vasoconstriction could be developed in future [17, 29]. Furthermore, only six animals were studied at PEEP 15 and $20cmH_2O$ because in two cases, the pigs were too unstable to tolerate such high levels of PEEP; and these experiments were undertaken in parallel with data collection for other studies. Further research could extend the relevance between the IST heterogeneity indices and higher PEEP levels.

The inspired sinewave test is a potentially translatable research tool. This research examined the utility of the IST in measuring lung heterogeneity and deadspace volume in ventilated lungs at the bedside. Accurate deadspace volume measurement could help in the prognostication of acute lung injury/ARDS. Furthermore, measurement of the heterogeneity of the lung might be used to quantify the extent of lung injury and inform ventilatory therapy. Our results support further development of these IST heterogeneity indices and its translation to classify lung diseases.

5. Conclusion

The quantitative method of the lung heterogeneity was introduced and experimented by the IST in animal models. The IST ventilation and perfusion heterogeneity ratios have the potential to inform and optimise mechanical ventilation strategy at the bedside in real-time. This work provides a fundamental foundation for the study of lung heterogeneity in clinical trials. The IST also can measure deadspace volume with small bias compared to the measured values by the SF_6. Further research is required to determine how IST could be used to inform mechanical ventilation.

Acknowledgments

The authors are grateful for the important work from veterinary anaesthetists Christian Dancker and William McFadzean, and for the technical assistance from Hanne McPeak and Kristina Britchford.

Funding

This project was funded by the National Institute for Health Research. Grant Number: II-LA-0214-20005.

References

[1] Charlotte Summers, Nanak R. Singh, Linda Worpole, Rosalind Simmonds, Judith Babar, Alison M. Condliffe, Kevin E. Gunning, Andrew J. Johnston, and Edwin R. Chilvers. Incidence and recognition of acute respiratory distress syndrome in a UK intensive care unit. *Thorax*, 71(11):1050–1051, 2016.

[2] Nicolas de Prost, Jean-Damien Ricard, Georges Saumon, and Didier Dreyfuss. Ventilator-induced lung injury: historical perspectives and clinical implications. *Annals of Intensive Care*, 1(1):28, 2011.

[3] John B. West. *Respiratory Physiology-The Essentials*, volume Ninth Edit. 2012.

[4] Charlene S. Stahr, Chaminda R. Samarage, Martin Donnelley, Nigel Farrow, Kaye S. Morgan, Graeme Zosky, Richard C. Boucher, Karen K.W. Siu, Marcus A. Mall, David W. Parsons, Stephen Dubsky, and Andreas Fouras. Quantification of heterogeneity in lung disease with image-based pulmonary function testing. *Scientific Reports*, 6(July):1–10, 2016.

[5] James E. Mountain, Peter Santer, David Patrick O'Neill, Nicholas M. J. Smith, Luca Ciaffoni, John H. Couper, Grant A.D. Ritchie, Gus Hancock, Jonathan P. Whiteley, and Peter A. Robbins. Potential for non-invasive assessment of lung inhomogeneity using highly precise, highly time-resolved, measurements of gas exchange. *Journal of Applied Physiology*, page jap.00745.2017, 2017.

[6] Phi Anh Phan, Cathy Zhang, Daniel Geer, Federico Formenti, Clive Hahn, and Andrew Farmery. The Inspired Sinewave Technique: A Comparison Study With Body Plethysmography In Healthy Volunteers. *IEEE Journal of Translational Engineering in Health and Medicine*, 5(April), 2017.

[7] D. C. Crockett, J. N. Cronin, N. Bommakanti, R. Chen, C. E.W. Hahn, G. Hedenstierna, A. Larsson, A. D. Farmery, and F. Formenti. Tidal changes in PaO 2 and their relationship to cyclical lung recruitment/derecruitment in a porcine lung injury model. *British Journal of Anaesthesia*, 122(2):277–285, 2019.

[8] Richard M. Bruce, Phi Anh Phan, Edmund Pacpaco, Najib M. Rahman, and Andrew D. Farmery. The inspired sine-wave technique: A novel method to measure lung volume and ventilatory heterogeneity. *Experimental Physiology*, 103(5):738–747, 2018.

[9] Clive E.W. Hahn and A. D. Farmery. Gas exchange modelling: No more gills, please. *British Journal of Anaesthesia*, 91(1):2–15, 2003.

[10] Lei Clifton, David A. Clifton, Clive E W Hahn, and Andrew D. Farmery. Assessment of lung function using a non-invasive oscillating gas-forcing technique. *Respiratory Physiology and Neurobiology*, 189(1):174–182, 2013.

[11] Minh C Tran, Douglas C Crockett, Phi A Phan, Stephen J Payne, and Andrew D Farmery. A tidal lung simulation to quantify lung heterogeneity with the Inspired Sinewave Test. In *42nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC 2020)*, pages 13–16, 2020.

[12] A. Larsson, D. Linnarsson, C. Jonmarker, B. Jonson, H. Larsson, and O. Werner. Measurement of lung volume by sulfur hexafluoride washout during spontaneous and controlled ventilation: Further development of a method. *Anesthesiology*, 67(4):543–550, 1987.

[13] Phi Anh Phan, C. E.W. Hahn, and A. D. Farmery. A modification of the Bohr method to determine airways deadspace for non-uniform inspired gas tensions. *Physiological Measurement*, 38(7):107–117, 2017.

[14] Richard M. Bruce, Douglas C. Crockett, Anna Morgan, Minh Cong Tran, Federico Formenti, Phi Anh Phan, and Andrew D. Farmery. Noninvasive cardiac output monitoring in a porcine model using the inspired sinewave technique: a proof-of-concept study. *British Journal of Anaesthesia*, 123(2):126–134, 2019.

[15] Douglas C. Crockett, Minh C. Tran, Federico Formenti, John N. Cronin, Göran Hedenstierna, Anders Larsson, Phi A. Phan, and Andrew D. Farmery. Validating the inspired sinewave technique to measure the volume of the 'baby lung' in a porcine lung-injury model. *British Journal of Anaesthesia*, (September):0–30, 2020.

[16] Chris D Harrison, Phi Anh Phan, Cathy Zhang, Daniel Geer, Andrew D Farmery, and Stephen J Payne. Modelling mixing within the dead space of the lung improves predictions of functional residual capacity. *Respiratory Physiology & Neurobiology*, 242:12–18, 2017.

[17] J. P. Whiteley, A. D. Farmery, D. J. Gavaghan, and C. E.W. Hahn. A tidal ventilation model for oxygenation in respiratory failure. *Respiratory Physiology and Neurobiology*, 136(1):77–88, 2003.

[18] J. P. Whiteley, D. J. Gavaghan, and C. E.W. Hahn. Modelling inert gas exchange in tissue and mixed-venous blood return to the lungs. *Journal of Theoretical Biology*, 209(4):431–443, 2001.

[19] A. Barry Baker and Andrew D. Farmery. Inert gas transport in blood and tissues. *Comprehensive Physiology*, 1(2):569–592, 2011.

[20] Carol Kilkenny, William J. Browne, Innes C. Cuthill, Michael Emerson, and Douglas G. Altman. Improving bioscience research reporting: The arrive guidelines for reporting animal research. *Animals*, 4(1):35–44, 2013.

[21] B. Lachmann, B. Robertson, and J. Vogel. In Vivo Lung Lavage as an Experimental Model of the Respiratory Distress Syndrome. *Acta Anaesthesiologica Scandinavica*, 24(3):231–236, 1980.

[22] Tom Fawcett. An introduction to ROC analysis. *Pattern Recognition Letters*, 27(8):861–874, 2006.

[23] J. Martin Bland and Douglas G. Altman. Agreement between methods of measurement with multiple observations per individual. *Journal of Biopharmaceutical Statistics*, 17(4):571–582, 2007.

[24] Todd W. Rice, Arthur P. Wheeler, Gordon R. Bernard, Douglas L. Hayden, David A. Schoenfeld, and Lorraine B. Ware. Comparison of the SpO2/FIO2 ratio and the PaO 2/FIO2 ratio in patients with acute lung injury or ARDS. *Chest*, 132(2):410–417, 2007.

[25] Niall D. Ferguson, Eddy Fan, Luigi Camporota, Massimo Antonelli, Antonio Anzueto, Richard Beale, Laurent Brochard, Roy Brower, Andrés Esteban, Luciano Gattinoni, Andrew Rhodes, Arthur S. Slutsky, Jean Louis Vincent, Gordon D. Rubenfeld, B. Taylor Thompson, and V. Marco Ranieri. The Berlin definition of ARDS: An expanded rationale, justification, and supplementary material. *Intensive Care Medicine*, 38(10):1573–1582, 2012.

[26] Gary F. Nieman, Joshua Satalin, Penny Andrews, Hani Aiash, Nader M. Habashi, and Louis A. Gatto. Personalizing mechanical ventilation according to physiologic parameters to stabilize alveoli and minimize ventilator induced lung injury (VILI). *Intensive Care Medicine Experimental*, 5(1):1–21, 2017.

[27] Laurent Brochard, Arthur Slutsky, and Antonio Pesenti. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *American Journal of Respiratory and Critical Care Medicine*, 195(4):438–442, 2017.

[28] Richard H. Kallet, Hanjing Zhuo, Kelly Ho, Michael S. Lipnick, Antonio Gomez, and Michael A. Matthay. Lung injury etiology and other factors influencing the relationship between dead-space fraction and mortality in ARDS. *Respiratory Care*, 62(10):1241–1248, 2017.

[29] Sara K. Alford, Edwin J.R. Van Beek, Geoffrey McLennan, and Eric A. Hoffman. Heterogeneity of pulmonary perfusion as a mechanistic image-based phenotype in emphysema susceptible smokers. *Proceedings of the National Academy of Sciences of the United States of America*,

107(16):7485–7490, 2010.

[30] C E Hahn, a M Black, S a Barton, and I Scott. Gas exchange in a three-compartment lung model analyzed by forcing sinusoids of N2O. *Journal of applied physiology (Bethesda, Md. : 1985)*, 75(4):1863–1876, 1993.

[31] A D Farmery, King's King's College London. Guy's, and St. Thomas's School of Medicine. *Interrogation of the Cardiopulmonary System with Inspired Gas Tension Sinusoids*. PhD thesis, 2008.

Appendix A. Appendix

The lung simulation consisted of 3 pace compartments, 2 tidal lung compartments and 5 body compartments with a shunt block. In the 2 tidal lung compartments, the fraction of lung volume was fixed at 0.1 and 0.9. Parameters for the lung simulation are summarised in Table A1. This lung simulation has been described and validated elsewhere [11].

Table A1. Simulation parameters for the tidal lung simulation. Where fv is the ventilation fraction to the first lung compartment and fq is the perfusion fraction to the first compartment.

Parameter	**Value**
Deadspace volume (mL)	150
Alveolar volume (L)	2.5
Pulmonary blood flow (L/min)	5
Shunt (L/min)	0
Tidal volume (L)	0.5
Ventilation fraction	$[fv, 1-fv]$
Alveolar volume fraction	[0.1, 0.9]
Perfusion fraction	$[fq, 1-fq]$
IST forced time period (s)	$180s$ and $60s$
Respiration Rate ($Breaths/min$)	12
Inspiration time (s)	1.5

The *ode*45 solver and Simulink-Matlab were chosen for simulation. Ten mixing compartments of deadspace are included in this model. The equation of each deadspace compartment during inspiration:

$$V_{M,i}\frac{dF_{M,i}}{dt} = \dot{V}_A(t)(F_{M,i-1}(t) - F_{M,i}(t)) \tag{A.1}$$

where i is the number of deadspace compartments (from 1 to 10); and $F_{(M,1)}(t) = F_I(t)$ and $F_{M,10}(t) = F_{IA}(t)$. $V_{M,i}$ is the deadspace volume of the compartment i and $\dot{V}_A(t)$ is the ventilation at time t. The equivalent equation during expiration is:

$$V_{M,i}\frac{dF_{M,i}}{dt} = \dot{V}_A(t)(F_{M,i}(t) - F_{M,i+1}(t)) \tag{A.2}$$

where i is from 1 to 10 and $F_{M,1}(t) = F_E(t)$ and $F_{M,10}(t) = F_A(t)$. F_I, F_{IA} and F_E are the fractional concentrations of the tracer gas coming into the deadspace

compartment, coming out from the deadspace compartment to the lung compartment and exhaling from the deadspace to the environment, respectively.

The deadspace compartments are serially connected with 2 parallel lung blocks. These lung blocks are generated from physiological equations of the tidal lung [9]. Inspiration:

$$V_A(t) = f_{Volume} \times \bar{V}_A + \frac{V_T \times t}{t_i} \tag{A.3}$$

Expiration:

$$V_A(t) = f_{Volume} \times \bar{V}_A + V_T \times exp(-\gamma(t - t_i)) \tag{A.4}$$

where γ is the rate-constant of expiratory flow, $V_A(t)$ is the alveolar volume, V_T is the tidal volume and t_i is the inspiration starting time. $\bar{V}_A$ is end-expired alveolar volume. In the first compartment, $f_{Volume} = 0.1$ and the second compartment $= 0.9$.

The whole compartments are linked together by governing equations which represent the equilibrium of the mass concentration of the tracer gas. $C_{\bar{v}}$ and C_a are the mixed venous and pulmonary end-capillary gas concentrations, respectively. In the first lung compartment. Inspiration:

$$\frac{d}{dt}(V_A(t).F_A(t)) = f_v.\dot{V}_{A,i}(t).F_{IA}(t) + f_p.\dot{Q}_{p,i}(C_{\bar{v}} - C_a) \tag{A.5}$$

Expiration:

$$\frac{d}{dt}(V_A(t).F_A(t)) = f_v.\dot{V}_{A,i}(t).F_A(t) + f_p.\dot{Q}_{p,i}(C_{\bar{v}} - C_a) \tag{A.6}$$

each compartment has their own fraction of ventilation f_v and fraction of perfusion f_p, in Table A1. The body compartments of a standard human consist of five different tissues inside the human body with different tissue-gas coefficient [30, 19].

$$V_i^* \frac{dC_i(t)}{dt} = \dot{Q}_i(C_{\bar{a}}(t) - C_i(t)) \tag{A.7}$$

where V_i^*, C_i and $\dot{Q}_i$ are the equivalent blood volume, concentration of the tracer gas and blood flow rate of i compartment. V_i is given by the following equation where $V_{(b,i)}$ and $V_{(t,i)}$ are the blood and tissue volumes of each body compartments and $\lambda_{(t,i)}$ is the Ostwald tissue-gas coefficient of each compartment. These values are given in [31].

$$V_i^* = V_{b,i} + \frac{\lambda_{t,i}}{\lambda} V_{t,i} \tag{A.8}$$

The Ostwald coefficient is a relation between the concentrations of the tracer gas in the blood to the fractional concentration in the lung. λ is the blood-gas partition coefficient. The body temperature is assumed to be constant (37^oC), so the Ostwald coefficient is stable.

$$C_a = \lambda \times F_A \tag{A.9}$$

Since, $\dot{Q}_T = \dot{Q}_S + \dot{Q}_P$. The mixed-arterial concentration $C_{\bar{a}}$ is given below with $\dot{Q}_S$being the shunt flow rate, $\dot{Q}_P$ pulmonary blood flow rate and $\dot{Q}_T$ total blood flow:

$$C_{\bar{a}}(t) = \frac{\dot{Q}_S}{\dot{Q}_T} C_{\bar{v}}(t) + \frac{\dot{Q}_p}{\dot{Q}_T} C_a(t) \tag{A.10}$$