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Lung simulation to support non-invasive pulmonary blood flow measurement in Acute Respiratory Distress Syndrome in animals*

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***Abstract*— Patients undergoing mechanical lung ventilation are at risk of lung injury. A noninvasive bedside lung monitor may benefit these patients. The Inspired Sinewave Test (IST) can measure cardio-pulmonary parameters noninvasively. We propose a lung simulation to improve the measurement of pulmonary blood flow using IST. The new method was applied to 12 pigs' data before lung injury (control) and after lung injury (ARDS model). Results using the lung simulation shown improvements in correlation in both simulated data (R^2 increased from 0.98 to 1) and pigs' data (R^2 increased from <0.001 to 0.26). Paired blood flow measurements were performed by both the IST (noninvasive) and thermodilution (invasive). In the control group, the bias of the two methods was negligible (0.02L/min), and the limit of agreement was from -1.20 to 1.18 L/min. The bias was -0.68 L/min in the ARDS group and with a broader limit of agreement (-2.49 to 1.13 L/min).**

***Clinical Relevance*— the inspired sinewave test can be used to measure cardiac output noninvasively in mechanically ventilated subjects with and without acute respiratory distress syndrome.**

I. Introduction

Acute respiratory distress syndrome (ARDS) and acute lung injury are forms of respiratory failure caused by widespread rapid inflammation in the lungs. ARDS is usually treated with mechanical ventilation in Intensive Care Units (ICU). In 2019, a global pandemic occurred with the spread of the Coronavirus (COVID-19), related closely to the ARDS [1]–[3]. Although ARDS necessitates mechanical ventilation, the latter can itself worsen the underlying lung injury. Therefore optimal ventilator setting and continuous bedside lung monitoring can benefit patients with ARDS.

Several bedside lung monitoring methods have been developed and validated [4], [5]. According to measured lung parameters at the bedside, clinicians can reduce harm to patients by providing optimal ventilator settings. The inspired sinewave test (IST) is a non-invasive method to quantify lung function, including lung heterogeneity, effective lung volume and pulmonary blood flow [6]–[8]. The IST does not use ionising radiation and does not require patient effort.

The monitoring of the pulmonary blood flow or cardiac output (CO) can guide the management of surgical patients at high risk of haemorrhage

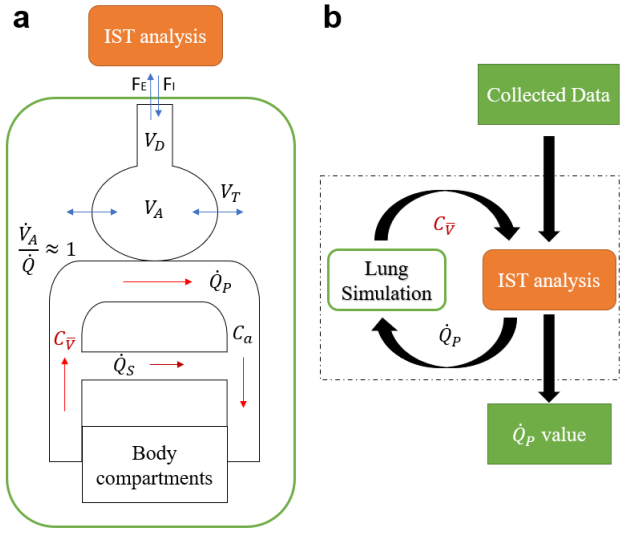

Fig. 1. Schematic diagram of the lung simulation (panel a) and the model analysis program using the lung simulation (panel b).

or haemodynamic dysfunction [9]. The current gold standard for measuring CO is thermodilution [10]. Because the thermodilution procedure requires an invasive procedure, the use of this technique has been declining in favour of less invasive methods. The IST can non-invasively measure CO via a respiratory gas exchange technique.

One advantage of measuring CO with IST is that theoretically, CO can be recovered without measuring the mixed venous concentration of tracer gas, thus allowing measurement to be completely non-invasive. Early studies, however, have shown that recovery of CO was imprecise at higher values.

We hypothesised that we could achieve more accurate pulmonary blood flow results by including a simulation of the mixed venous signal in our analysis. We tested this hypothesis in simulated experimental (porcine) datasets. The relationship

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between pulmonary blood flow and PEEP level was assessed in both control and injured lungs (or ARDS animal model).

II. Material and Method

A. Experimental protocol

Twelve anaesthetised pigs with 29 kg (SD 2) were studied by the IST both before lung injury (control) and after lung injury (ARDS). Lachmann's method was applied to induce lung injury to simulate the ARDS in an animal model. The experiments were performed in the Uppsala University Hospital. Animal preparations have been detailed elsewhere [5]. Reporting of the experiments adheres to the Reporting of *in vivo* experiments (ARRIVE) guidelines. Characteristics of animals are included in Table 1.

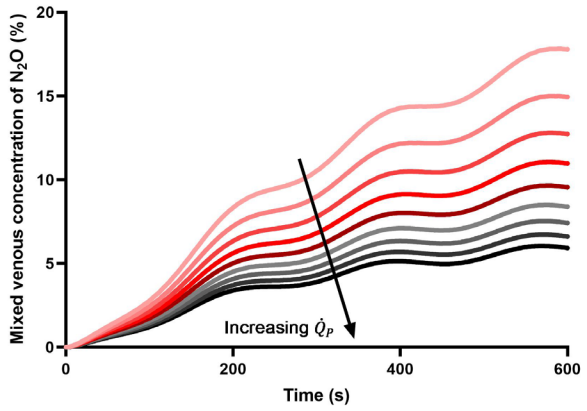

Fig. 2. Simulation of the mixed venous concentration of the N_2O with increased pulmonary blood flow ($\dot{Q}_P$)

During preparation, the ventilator was set to deliver 20-25 breaths/min in volume-controlled ventilation mode with a tidal volume of 10 ml/kg. For each animal, measurements were repeated twice by the IST and thermodilution at each different positive end-expiratory pressure (PEEP) level. While other parameters of the ventilator setting were kept unchanged, the PEEP levels were incrementally increased from 0 to 5, 10, 15 and 20 cmH_2O. Changes in PEEP level typically produce changes in resting lung volume and a reduction in pulmonary blood flow. After measurements in the healthy animals, lung injury was induced, and measurements of CO using IST and thermodilution were repeated. For injured lungs, the PEEP level of 0 cmH_2O was not studied.

B. Inspired Sinewave Test

IST is a simple and noninvasive method to measure cardiopulmonary indices. [11], [12]. By using oscillating tracer gas, the dead space volume (VD), effective lung volume (ELV) and blood flow rate ($\dot{Q}_P$) can be calculated. IST applies a forced oscillation of a low dose N_2O tracer gas with a sinusoidal period which can be determined by the user.

The IST analysis program takes the input (concentration of N_2O in both inhaled - F_I and exhaled breaths - F_E) and produces the outputs (VD, ELV and $\dot{Q}_P$). A one-compartment lung was assumed to represent the whole lung in the breath-by-breath analysis. The mass balance equation of the tracer gas of two consecutive breath ($n-1$ and n) is:

$$F_{E,n-1}V_A + F_{I,n}(V_{T,n} - V_D) + F_{E,n-1}V_D - \lambda \times \dot{Q}_P \times (F_{E,n} - C_{\bar{v}})\,\Delta t_n = V_A F_{E,n} + V_{T,n} F_{E,n} \quad (1)$$

where:
$F_{I,n}$: the inspired concentration of breath nth.
$F_{E,n}$: the end expired concentrations of breath n.
λ: the solubility of N_2O in blood, $\lambda = 0.47$.
$C_{\bar{v}}$: the mixed venous concentration,
Δt_n: the duration of breath nth.
$V_{T,n}$: the tidal volume of breath nth.

In previous studies, the unknown mixed venous concentration ($C_{\bar{v}}$) was assumed to equal to the mean of the inspired sinewave concentration at a steady-state F_I^0. This assumption was based on the notion that the mean mixed venous, inspired and end-tidal concentrations would all be equal a equilibrium. It was also assumed that the oscillation would be fully damped in the mixed-venous signal. However, due to increased $\dot{Q}_P$ errors at high flows, we suspected that this assumption might not be valid. We, therefore, propose a method to simulate the mixed venous concentration from a developed lung simulation to support the calculation of the absolute $\dot{Q}_P$ value.

TABLE I. Characteristics of the animals (N=12) [mean (SD)]. P-values show results of either paired Student's t-test (parametric data). CO = cardiac output calculated by thermodilution, PaO_2 = arterial O_2 partial pressure, FIO_2= fraction of inspired O_2, PFR= PaO_2/FIO_2 ratio.

Parameter	Control	ARDS	p
Weight (Kg)	29(2)	-	-
HR (bpm)	86(12)	85(11)	0.42
CO (L/min)	3.2(0.4)	3.5(0.8)	0.26
pH	7.38(0.07)	7.25(0.08)	0.0004
FIO_2 (%)	0.4(0.1)	0.8(0.1)	0.0002
PaO_2(mmHg)	144(30)	96(28)	0.39

C. Lung simulation to support IST analysis

A tidal lung simulation was developed to support the IST analysis program. A schematic of the model is shown in Fig.1, panel a. In this model, the lung is assumed to be homogeneous and represented by one compartment. This lung simulation has been introduced and validated elsewhere [6], [13].

In this work, the lung simulation above was used to generate the mixed-venous concentration of N_2O ($C_{\bar{V}}$) for the IST analysis. However, the mixed-venous concentration was influenced by the pulmonary blood flow $\dot{Q}_P$. Fig. 2 shows mixed-venous N_2O concentration vs blood flow changes while performing the IST in simulated data. Therefore, a simple optimisation was integrated into the algorithm to suggest the $C_{\bar{V}}$ values before calculating the $\dot{Q}_P$. A diagram of this method was shown in Fig.1 panel b.

Parameters for the lung simulation were taken from the literature [14]. These data represented a healthy lung with

different pulmonary blood flow values, ranging from 2 L/min to 7 L/min. The lung model simulated a 70 Kg man with 2.5 L of alveolar volume and 150 mL of deadspace volume. The lung was assumed to be homogeneous. The computational model was developed in Matlab-Simulink (www.mathworks.com) with the *ode45* solver. Sensitivity analysis for the model and the model verification are presented elsewhere [6], [13], [15].

D. Statistical analysis

The relationship between paired measurements of CO made with thermodilution and the IST was analysed using linear regression and Bland-Altman analysis [16].

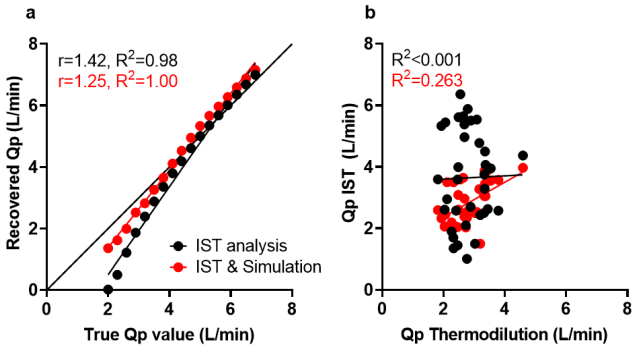

Fig. 3. Comparison of pulmonary blood flow measurement by the conventional IST analysis vs IST analysis using lung simulation. Panel a shows the comparison in simulated data with 20% tidal volume noise. Panel b shows the comparison of both methods (paired IST and thermodilution) in control pigs.

III. RESULTS

A total of 130 paired measurements in twelve animals at different PEEP levels were recorded. The values of repeated measurements of the pulmonary blood flow were averaged due to the negligible variations (5% in thermodilution and 10% in IST).

Fig. 3 shows the improvement in agreement in paired measurements when using the new method (IST & Simulation) compared to conventional IST analysis in simulated data (panel a). The R^2 is increased, and the slope approximates to 1. Furthermore, the new method also corrects the underestimation of results at low $\dot{Q}_P$ (less than 3L/min). In panel b, the $\dot{Q}_P$ measured by the IST analysis with lung simulation (red points and line) show an improved correlation with the value measured by the thermodilution in healthy pigs (R^2 =0.263).

Fig. 4 shows the comparison of paired measurements of absolute $\dot{Q}_P$ measured by IST with simulation support vs thermodilution in 12 pigs. Generally, the correlation between IST and thermodillution was more robust in the control group than in the ARDS group. Average $\dot{Q}_P$ measured by thermodilution was 2.8 (±0.6) L/min in control and 3.0 (±0.6) L/min in ARDS. $Average\ Q_P$ measured by IST was 2.9 (±0.6) L/min in control and 3.7 (±1.2) L/min. As PEEP was increased, $\dot{Q}_P$ decreased by 0.9 L/min overall. Furthermore, at the PEEP 5 and 10 cmH_2O in the ARDS group, IST overestimated the blood flow compared to thermodilution by 30%.

In the control group, the standard deviation at each PEEP level was smaller than the same results in the ARDS group. In Fig. 4, panel c, Bland-Altman analysis of paired measurements in the control group shows the mean bias was 0.02L/min, and the limits of agreement range from -1.2 to 1.18L/min. In Fig. 4, panel d, Bland-Altman analysis of paired measurements in the ARDS group shows more bias than in the control group (-0.68L/min). Fig.4 panel d shows the bias in the ARDS group is proportional to the magnitude of $\dot{Q}_P$.

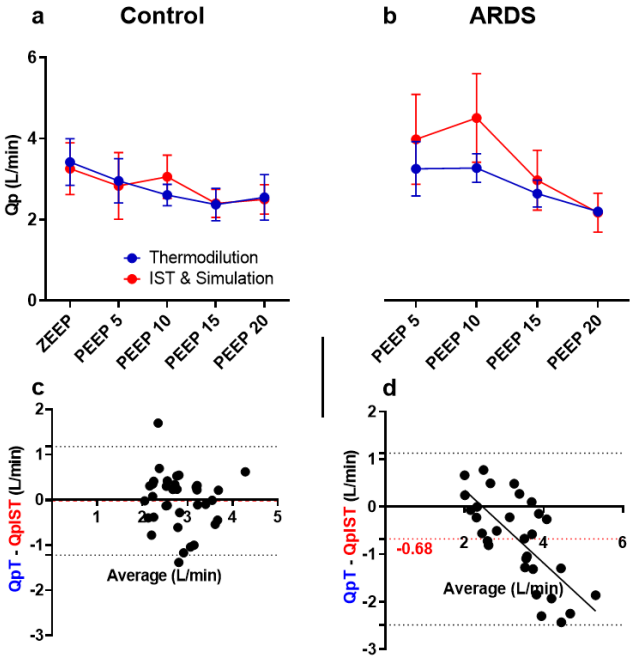

Fig. 4. Comparison of pulmonary blood flow measured by the thermodilution and IST in both control and ARDS lungs. Panels a and b show the effect of PEEP levels on pulmonary blood flow. Mean and standard deviation are shown. Panels c and d show Bland-Altman anlaysis of the comparison between paired measurements of $\dot{Q}_P$ made with IST and thermodilution. Red dash lines are the mean bias, and black dash lines are the limit of agreement.

IV. DISCUSSION

Our results show that in both uninjured lungs and injured lungs (ARDS model), IST can measure pulmonary blood flow accurately in mechanically ventilated pigs. This study applied a new lung simulation to improve measurement of $\dot{Q}_P$ by the IST to overcome a previous limitation. These results improve the impact of the IST at bedside lung monitoring, which can be used to suggest the optimal mechanical ventilation setting.

Thermodilution is considered the gold standard method to monitor cardiac output. However, it is not used widely as it is highly invasive and is complicated to set up [17]. Clinicians prefer noninvasive and less skill demanding methods such as a Doppler ultrasound for pulmonary blood flow measurement. Respiratory measurements like the IST can potentially help with idealised and objective pulmonary blood flow monitoring. The Bland-Altman analysis of absolute values showed a good agreement in between IST and thermodilution

(0.02 L/min in control and -0.68 L/min in ARDS models). The Bland-Altman plot of the control group illustrated a normal distribution, while in the ARDS group, the error increased with the absolute value. This suggests the possibility to develop a statistical method to improve IST's measurement of $\dot{Q}_P$ in the ARDS lung.

The IST has been shown to be a suitable bedside lung monitor. It offers several strengths, including accurate measurement of pulmonary parameters, commercial availability and ease of use at the bedside [5], [6], [13]. In addition, as IST does not rely on a fixed inspiratory flow, it can be used in spontaneously ventilating patients.

Both thermodilution and the IST captured the decline of $\dot{Q}_P$ as PEEP level increased. According to Fig. 4 a and b, when the PEEP levels increased, the CO slightly declined in both control and ARDS groups. PEEP optimisation might reduce the development of lung induced injury and ARDS [18], but there is a trade-off with reducing CO. Further research should be carried on to understand the relationship between measured IST parameters and optimal settings for mechanical ventilation.

This work contains several limitations. It was not possible to analyse the ability of IST to track trends in CO. This was because CO was not artificially altered, except for the changes caused by PEEP. The current study uses a pig model which does not translate directly to humans, and the use of saline-lavage does not entirely comprise all the features of ARDS lungs.

Another proof-of-concept study concluded that IST and thermodilution have good agreement in capturing the trend of CO as it was increased/decreased [7]. Our study fits into the gap of comparing the absolute values of CO. However, there is still room for developing the $\dot{Q}_P$measurement by the IST in the future. Future development of IST should include assessing its use in mechanically ventilated human patients. A pilot study has been established to test this in the John Radcliffe Hospital, Oxford, UK.

V. Conclusion

A mathematical simulation was introduced to boost the performance of the non-invasive beside lung monitor test (IST). We show that the IST is a suitable test for mechanically ventilated animals. Furthermore, the IST can accurately measure $\dot{Q}_P$ with smaller bias than thermodilution in healthy and ARDS model lungs. The results of this work support further development of the IST and its translation to human medicine.

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