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Analysis of the method for ventilation heterogeneity assessment using the Otis model and forced oscillations

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ABSTRACT

Increased heterogeneity of the lung disturbs pulmonary gas exchange. During bronchoconstriction, inflammation of lung parenchyma or acute respiratory distress syndrome, inhomogeneous lung ventilation can become bimodal and increase the risk of ventilator-induced lung injury during mechanical ventilation. A simple index sensitive to ventilation heterogeneity would be very useful in clinical practice. In the case of bimodal ventilation, the index (H) can be defined as the ratio between the longer and shorter time constant characterising regions of contrary mechanical properties. These time constants can be derived from the Otis model fitted to input impedance (Z_{in}) measured using forced oscillations. In this paper we systematically investigated properties of the aforementioned approach. The research included both numerical simulations and real experiments with a dual-lung simulator. Firstly, a computational model mimicking the physical simulator was derived and then used as a forward model to generate synthetic flow and pressure signals. These data were used to calculate the input impedance and then the Otis inverse model was fitted to Z_{in} by means of the Levenberg–Marquardt (LM) algorithm. Finally, the obtained estimates of model parameters were used to compute H. The analysis of the above procedure was performed in the frame of Monte Carlo simulations. For each selected value of H, forward simulations with randomly chosen lung parameters were repeated 1000 times. Resulting signals were superimposed by additive Gaussian noise. The estimated values of H properly indicated the increasing level of simulated inhomogeneity, however with underestimation and variation increasing with H. The main factor responsible for the growing estimation bias was the fixed starting vector required by the LM algorithm. Introduction of a correction formula perfectly reduced this systematic error. The experimental results with the dual-lung simulator confirmed potential of the proposed procedure to properly deduce the lung heterogeneity level. We conclude that the heterogeneity index H can be used to assess bimodal ventilation imbalances in cases when this phenomenon dominates lung properties, however future analyses, including the impact of lung tissue viscoelasticity and distributed airway or tissue inhomogeneity on H estimates, as well as studies in the time domain, are advisable.

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1. Introduction

Distribution of ventilation in respiratory system is not homogeneous. In a physiological lung it can be caused by many reasons like the airway tree asymmetry, gravitational effects or individual differences in regional mechanical properties [1]. Under pathological conditions this heterogeneity drastically intensifies, particularly in asthma [2]. The imbalances in lung ventilation affect gas exchange efficiency [3] and increase the risk of ventilator-induced lung injury during artificial ventilation [4,5]. Additionally, bronchoconstriction may lead to self-organized patterns of patchy ventilation [6] which becomes generally bimodal [7–9].

There are many methods to visualise heterogeneity directly, using different imaging techniques [10–13], and deduced indirectly from multiple-breath nitrogen washout [14,15]. All above procedures are not commonly used in routine diagnostics. In contrast, the forced oscillation technique (FOT) is a non-invasive method. In FOT, multi-sinusoidal flow oscillations are generated at the airway opening, and the relationship between the flow and resulting pressure oscillations reflects respiratory mechanics in the frequency domain. It has been found that low-frequency lung impedance, measured by FOT, is extremely sensitive to inhomogeneous airway constriction [16,17].

One of the primary ways to understand real objects and to infer the intrinsic properties from raw measurements is mathematical modelling and computer simulations [18–20]. Many models of different scale and structure, both in the time and frequency domains, were proposed to describe lung mechanics (e.g. [21–23]) and to capture ventilation heterogeneity, e.g. [4,15–17,24–28]. Among them the Otis model [29] and its modifications has been of particular interest. It assumes a simplified lung structure consisting of two uneven compartments arranged in parallel (sometimes completed by central airway properties), with only a few lumped parameters, being easy for mathematical description in the time and frequency domains and thus for a further use. These properties explain why the Otis model has been extensively explored for the last decades, e.g. [24,30–36]. Simultaneously, some controversies over its plausibility and interpretation have cumulated. The most substantial ones concern: weak stability of parameter estimates [37], unidentifiability (i.e. impossibility of assigning unique values to unknown parameters [38]) of the Laplace representation of the model [39], similar effects of parallel ventilation heterogeneity and viscoelastic properties of lung tissue on lung impedance [33,40], and the equivalence of this model to a one-compartment structure when the time constants characterising the two compartments are equal [29,36].

Being aware of the prior use and above limitations of the Otis model, we have investigated its possible application in the assessment of bimodal ventilation heterogeneity using the forced oscillations. Such a patchy behaviour is characteristic for asthmatic bronchospasm and we hypothesise that the model with two parallel compartments may be sufficient to capture the difference between the well and poorly ventilated regions.

Simple indices, sensitive to pathological changes, are very useful in clinical practice and can allow for the use of the appropriate procedures for medical treatment as ventilatory support [23,41]. The knowledge of bimodality may be particularly helpful when using independent lung ventilation [42]. In the case of the Otis model, an index (H) can be defined as the ratio between the longer and shorter time constant. Early studies yielded surprisingly high values of H [32,35]. Since true mechanics of the complex respiratory system is never exactly known, in this work we systematically validate the method using both computer simulations and a physical dual-lung simulator with adjustable mechanical properties.

Successive sections of this paper present the implementation and validation of a computer model for the lung simulator, selection of the optimal excitation waveform, a method for input impedance calculation and a parameter estimation procedure, Monte Carlo simulations with the forward and inverse models showing main factors influencing the result, and the experimental validation of the method by measurements of H for various configurations of lung simulator mechanics. The achieved results demonstrate the strengths and weaknesses of this approach and motivate one to extend this research by taking into account viscoelastic properties of lung tissue, distributed heterogeneity, and analyses in the time domain.

2. Methods

2.1. Computational model for the dual-lung simulator

Bimodal ventilation of the lung can be easy simulated using the two-compartment mechanical simulator Dual Adult Model 5600i (*Michigan Instruments, Inc., USA*). Gas flows into the simulator through a central airway with replaceable, fixed-orifice flow resistor R_C, branching out into two peripheral airways with their resistors R_1 and R_2. They lead to separate elastomer bellows simulating two lungs with compliances C_1 and C_2. The compliances were independently adjusted using a steel springs, which were stretched during inflation. We were able to use the resistors of nominal values of 5 and 20 $cmH_2O/(L/s)$ and to set compliances in the range between 0.01 and 0.1 L/cmH_2O.

Since the number of mechanical settings is limited, a computational forward model for the lung simulator, enabling a wide variety of ventilation simulations under fully controlled conditions necessary to evaluate the method, has been developed. Taking into account the structure of the simulator, inertia of bellows (L_1 and L_2) and gas leakage from this pneumatic system (represented by leakage resistance R_U), an electric analogue of the simulator is shown in Fig. 1.

The mathematical description of the model in the time domain can be derived in the state space, as follows:

$$\begin{aligned}
\frac{dQ_1}{dt} &= -\frac{R_U+R_C+R_1}{L_1}Q_1 - \frac{R_U+R_C}{L_1}Q_2 - \frac{1}{L_1}P_{C1} + \frac{R_U}{I_1}Q,\\
\frac{dQ_2}{dt} &= -\frac{R_U+R_C}{L_2}Q_1 - \frac{R_U+R_C+R_2}{L_2}Q_2 - \frac{1}{L_2}P_{C2} + \frac{R_U}{L_2}Q,\\
\frac{dP_{C1}}{dt} &= \frac{1}{C_1}Q_1,\\
\frac{dP_{C2}}{dt} &= \frac{1}{C_2}Q_2,
\end{aligned} \tag{1}$$