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Pulmonary Mechanics: A System Identification Perspective

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Abstract—**The mechanical properties of the lungs are important determinants of its ability to function properly, and may become severely compromised in disease. Being able to assess lung mechanical function is thus crucial to the diagnosis of many lung diseases and for following the progress of therapy. Assessing lung mechanical function is essentially an exercise in system identification, whereby measurements of pressures and flows made at certain sites are linked in terms of mathematical models. Most often, the lung is assumed to function as a linear dynamic system, allowing determination of its input impedance over a range of frequencies. In mice, for example, impedance is frequently determined between 1 and 20 Hz. The interpretation of impedance in physiological terms is central to its utility as a diagnostic tool, and is best done with reference to a suitable mathematical model. Currently, the most widely used model for animal studies of lung disease consists of a single flow-resistive airway serving a uniformly ventilated alveolar region surrounded by tissue having a constant-phase impedance. This model has also been employed in human studies, and allows the mechanical properties of the lungs to be subdivided into those reflecting the conducting airway tree and those due to the behavior of the lung periphery. The parameters of this model have been shown in animals to change characteristically following interventions that mimic human pathologies such as asthma and acute lung injury. Furthermore, these changing parameter values can be linked to specific physical processes occurring within the lungs.**

I. Introduction

THE lung is a system of conduits and elastic units that must undergo cyclic stretching and compression throughout life. Consequently, the mechanical properties of the lung are critically important to its ability to function properly. These properties may become severely deranged in a number of common lung diseases that include asthma, emphysema, and pulmonary fibrosis. Understanding the pathological derangements in these diseases rests in large part on being able to link changes in the mechanical function of the lungs to abnormalities in the organ's internal structure. Being able to infer structure from function is both a key goal of medical diagnosis and the central aim of system identification. Accordingly, the engineering methodologies of system identification are naturally suited for application to the study of lung physiology.

The mechanical properties of the lung can be encapsulated in terms of its input impedance, under the assumption that it behaves like a linear dynamic system. Input impedance is interpreted in physiological terms using an appropriate mathematical model of the lung. There are a number of such models that have been employed, depending on the experimental conditions and the frequency range over which impedance is measured. The way that the parameters of a model change with an intervention, or in the presence of pathology, allows for the possibility of diagnosing lung disease and of understanding some of the mechanisms underlying them. In this review, we describe some of the principal ways in which models of lung impedance have advanced our understanding of the link between structure and function in the lung. Understanding this link is a vital step in gaining an understanding of the abnormalities associated with disease.

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II. Input Impedance of the Lung

A. The Forced Oscillation Technique

There are a variety of different signals pertaining to lung mechanical function that can be measured at various sites around the body, but the most commonly used are the pressure and flow of air at the entrance to the airways of the lungs (this is typically at the entrance to the mouth in a human subject, and is frequently at the proximal end of the trachea in experimental animals). Conventionally, flow ($\dot{V}$) is considered the system input, while pressure (P) is the output. System identification applied to the lungs then begins with the application of a controlled $\dot{V}$ signal to the lungs while the resulting P signal is measured. The experimental methods used to implement system identification in the lungs constitute what has come to be termed the *forced oscillation technique*.

The forced oscillation technique has been applied in both human subjects and a wide variety of animal models of lung disease. In terms of the latter, the main species currently under investigation is the mouse. Measuring lung mechanics in the mouse is technically challenging because of its small size, but recently a computer-controlled mechanical ventilator known as the *flexiVent* (Scireq, Montreal, Quebec) has become widely used for this purpose. The *flexiVent* is able not only to maintain life support for anesthetized, tracheostomized animals, it can also act as a general system identification platform by allowing arbitrary volume perturbations to be applied to the lungs via the tracheal opening with a bandwidth to 20 Hz or more [1].

B. Measuring Impedance in Mice

If $V(t)$ is a broad-band volume perturbation applied to the tracheal opening, and $P(t)$ is the pressure measured at the same site, then the input impedance, $Z(\omega)$, is given by the ratio

$$Z(\omega) = \frac{P(\omega)}{i\omega V(\omega)} \quad (1)$$

where ω is angular frequency and $P(\omega)$ and $V(\omega)$ are the Fourier transforms of $P(t)$ and $V(t)$, respectively. In practice, $V(t)$ typically consists of a sum of discrete sinusoidal components spanning the frequency range of interest, and the ratio in Eq. 1 is calculated between average cross-power and auto-power spectral densities determined by dividing the volume and flow data sets into a set of overlapping windows. Choosing the frequencies of the input sinusoids to have frequencies that are mutually prime reduces the harmonic distortion in Z that can arise as a result of system nonlinearities [2].

C. Models of Lung Impedance

The simplest physiologically reasonable model of the lung consists of an elastic unit, representing the lung tissue, connected to the end of a flow-resistive conduit, representing the airways. The differential equation of motion of this model is

$$P(t) = R\frac{dV(t)}{dt} + EV(t) \quad (2)$$

where the parameters R and E represent lung *resistance* and *elastance*, respectively. The impedance of this model is

$$Z(\omega) = R - \frac{iE}{\omega}. \quad (3)$$

A real lung is obviously vastly more complicated that this simple formula would suggest, and indeed more complicated impedance formula have been shown to provide better descriptions of measurements of input impedance [3, 4]. However, very accurate fits to measured impedance spectra below 20 Hz in a variety of species, including the mouse, have been achieved with the so-called constant-phase model of impedance [5] given by

$$Z(\omega) = R_N + iI_{aw} + \frac{G - iH}{\omega^{\alpha}} \quad (4)$$

where

$$\alpha = \frac{2}{\pi}\tan^{-1}\frac{H}{G}. \quad (5)$$

R_N is a Newtonian resistance that has been shown to closely approximate that of the airway tree [6]. I_{aw} is an inertance due to the mass of the gas in the central airways, and plays a negligible role in Z for mice below 20 Hz [7]. G and H are parameters that characterize, respectively, the elastic and dissipative properties of the lung tissue. The ratio of the real to the imaginary parts of the tissue component of Z (i.e. G/H) is independent of frequency, so tissue impedance has constant phase.

III. Impedance and Airways Responsiveness

Obstructive lung diseases such as asthma frequently involve bronchospasm, where the smooth muscle surrounding the airways contracts at inappropriate times and to an abnormal degree. Even a normal level of bronchospasm causes an increase in the magnitudes of both the real and imaginary parts of impedance; the part increases because the airways narrow and thus increase their resistance to air flow, and the parenchymal tissues of the lung become distorted which increases their elastic stiffness. The propensity for bronchospasm can be assessed by determining the responsiveness of lung impedance to challenge by smooth muscle agonists. Airways hyperresponsiveness is marked by an excessive increase in lung impedance following challenge with a standard dose of agonist.

Figure 1 shows an example of Z measured in a mouse together with the fits provided by Eq. 4. The data shown were collected in our laboratory under a protocol approved by the Animal Care and Use Committee of the University of

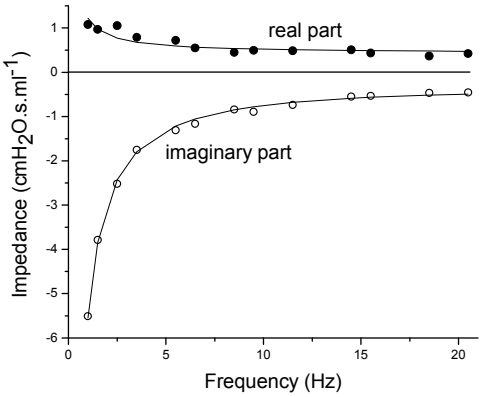

Fig. 1. Example of input impedance measured in a mouse (symbols) and the fit to it provided by Eq. 4.

Vermont. The parameters of the constant-phase model (Eq. 4) are : R_N = 0.42, G = 4.2, and H = 29.5 (all parameters in units of $cmH_2O.s.ml^{-1}$). These parameter values are normal for a typical mouse, but all of them may become significantly altered in disease or following interventions such as challenge with a smooth muscle agonist. This model has also been widely applied in larger animals [5], yielding parameters values that scale appropriately with the inverse of lung size.

Airway narrowing causes an increase in airway resistance (R_N), as expected [6]. However, severe bronchoconstriction also frequently leads to closure of a significant number of small airways [8, 9], which reduces the volume of lung tissue available to receive the imposed perturbations in $V(t)$. This increases the values of G and H in proportion to the lost volume. Additionally, bronchoconstriction is invariably

a heterogeneous process, occurring to varying degrees throughout the lung. The resulting heterogeneities in mechanical function cause G to increase more than H [10-12], so an increase in the ratio G/H serves as a useful indicator of the development of regional heterogeneities throughout the lung.

Analysis of the dynamic changes in Z during the onset of bronchoconstriction can also lead to important physiological insights into the processes taking place inside the lungs. For example, the rate of increase in R_N during the first few seconds following a bolus injection of methacholine reflects the rate at which the airway smooth muscle is able to shorten against any opposing mechanical loads [13]. Computational modeling of an elastic airway embedded in lung parenchyma shows that the rate of increase in RN is affected by both airway wall and parenchymal stiffnesses, allowing both to be estimated [14].

IV. Changes in Impedance in Acute Lung Injury

The measurement of input impedance in mice has been used extensively to elucidate the mechanical derangements occurring in a variety of other lung pathologies. An example is acute lung injury, a condition in which sudden massive pulmonary edema threatens to cause a patient to effectively drown in their own fluids. The acute lung injury resulting from aspiration of vomit can be modeled in mice by tracheal instillation of hydrochloric acid of the appropriate pH. This causes large regions of the lungs to collapse (derecruit) during subsequent mechanical ventilation.

Collapsed lung regions can be recruited by applying a deep inflation, but measurements of impedance during subsequent mechanical ventilation show that derecruitment reoccurs with a time-scale and a magnitude that reflects the severity of the lung injury [15]. These data can be fit by a computational model that accounts for the dynamics of airway closure and re-opening [16], the results of which suggest that impairment of surfactant function is the principle biophysical derangement behind the increased propensity for lung units to derecruit following acid injury [17].

V. Conclusions

System identification techniques applied to lung mechanics have allowed us to probe the inner workings of the lung and their derangements in various pathologies. In particular, measurements of lung input impedance using the forced oscillation technique permits the flow-resistance of the conducting airway tree to be discerned independently of the rheological properties of the lung tissues. This has allowed the consequences of airway narrowing to be distinguished from the effects of complete airspace closure, leading to an increased understanding of the mechanisms responsible for airways hyperresponsiveness and derecruitment.

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