

Review

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Measuring the lung function in the mouse: the challenge of size

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Abstract

Measurement of the effects of drugs, mediators and infectious agents on various models of lung disease, as well as assessment of lung function in the intact mouse has the potential for significantly advancing our knowledge of lung disease. However, the small size of the mouse presents significant challenges for the assessment of lung function. Because of compromises made between precision and noninvasiveness, data obtained may have an uncertain bearing on the mechanical response of the lung. Nevertheless, considerable recent progress has been made in developing valid and useful measures of mouse lung function. These advances, resulting in our current ability to measure sophisticated indices of lung function in laboratory animals, are likely to lead to important insights into the mechanisms of lung disease.

Introduction

Much of our current understanding of the normal functioning of the lung and mechanisms of lung disease comes from studies utilizing animals. As one clear example, animal systems of a wide variety of species, including humans, provided the essential mechanistic proof of a link between inflammation and airways hyperresponsiveness that set the stage for current anti-inflammatory therapy [1]. Mice are now widely employed in lung research because of certain advantages this species is thought to provide [2]. Advantages of using mice include a well-understood immunologic system, the vast array of available reagents, a short reproductive cycle, a well-characterized genome, the advent of transgenic technology, and economic factors [2-4]. Using mice as models of human disease, in particular asthma, has certain shortcomings [2,5] only some of which will be covered in this review. For any animal system to yield useful and valid insights into disease it must exhibit an appropriate phenotype. It has be-

come apparent that the valid assessment of lung function in an animal as small as the mouse requires that a number of technical challenges be overcome.

The paucity of information on the measurement of lung function in the mouse has largely reflected the difficulty of measuring the necessary respiratory signals of flow, volume and transpulmonary pressure. This applies particularly to the small gas flows involved [6,7]. However, the work of Martin *et al* in 1988 demonstrated that measurements of pulmonary resistance and compliance could be made in this small species [8]. At about the same time, Levitt and Mitzner clearly illustrated the utility of using mice to explore the genetics of hyperresponsiveness [9,10]. Since these studies, the use of mice to study lung disease has increased dramatically and a number of approaches have been developed in the ensuing years for measuring lung function in mice *in vivo*. In this review we examine these various methods and discuss their

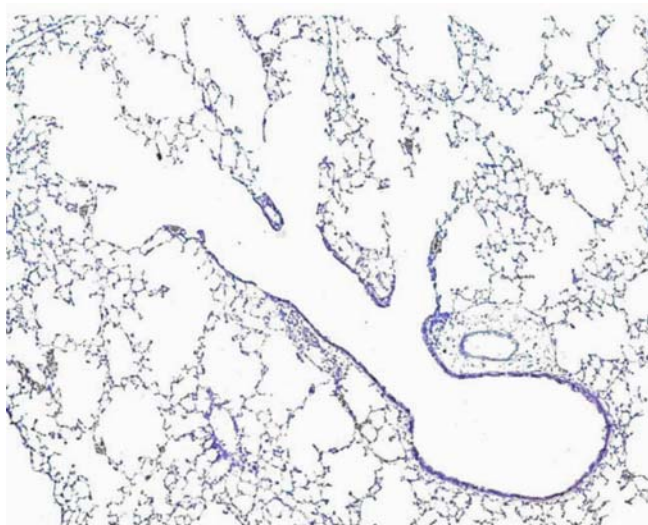


Figure 1
Photomicrograph of the parenchyma and respiratory bronchioles of a mouse (20 gram female BALB/c) lung. Note the rapid branching from a conducting airway into alveolar ducts and the relatively large airways. Stain is H & E with 5 × magnification.

respective attributes. Each approach represents a compromise between accuracy, non-invasiveness, and convenience [11].

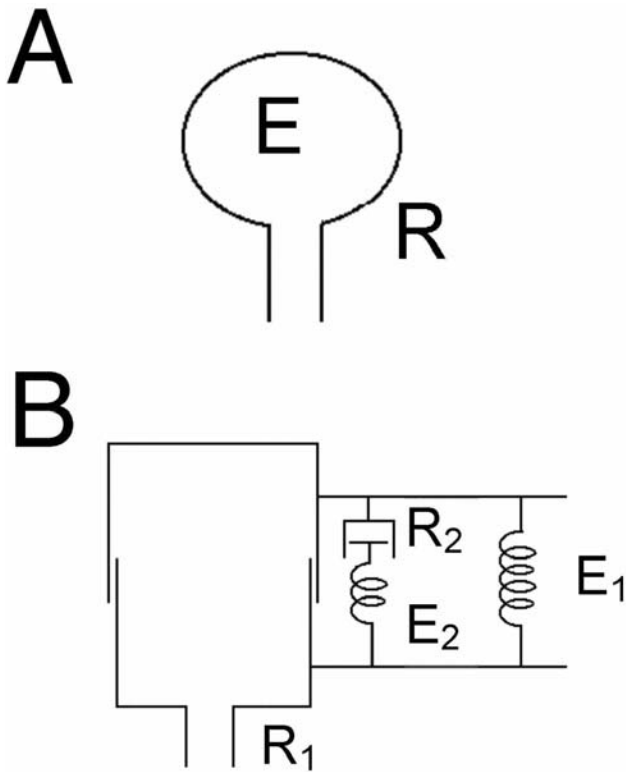
Lung anatomy

One look through the microscope at a section of mouse lung (Figure 1) demonstrates that the mouse lung is considerably different in structure from the human lung, although relatively little has been published about the architecture of the mouse lung compared to other species. What is known about the structure of the mouse lung probably has important bearing on its function [12–14]. The total lung capacity (TLC) of the mouse is about 1 ml compared to 10 ml of the rat and 6,000 ml of a human. Like the human, there are 5 lobes in the right mouse lung, but unlike the human the mouse has only a single left lung. Also unlike the human lung, but similar to the rat, the mouse pleura is thin, yet it is strong enough to be inflated to considerably higher pressures than the 30 cm H₂O normally associated with TLC (W Mitzner, personnel communications). The parenchyma of the mouse lung occupies a smaller fraction of the total lung than that of the rat but more than that of the human (mouse: 18%, rat: 24%, human: 12% lung volume). The alveoli of the mouse lung are smaller (80 μm mean linear intercept (MLI)) than those of the rat (MLI 100 μm) or human (MLI 210 μm). The blood-gas barrier thickness in the mouse (0.32 μm) is similar to that of the rat (0.38 μm) but some-

what smaller than that of the human (0.62 μm), which might have important implications for both gas exchange and parenchymal lung mechanics. The airways constitute a large percentage of the lung in mice (11%) compared to rats (5.7%). Cartilage is present in the mouse trachea but is less well organized than in other species; only the upper part of the trachea has the complete rings seen in other mammals and these rapidly change to plates as one proceeds distally. Mouse lungs have fewer respiratory bronchioles and airway generations (13–17 generations) than do human lungs (17–21 generations) with the airways of the mouse lung exhibiting a monopodial as opposed to dichotomous branching pattern. Two other significant features of the mouse lung are the thinness of the respiratory epithelium and the relatively large airway lumen [12,14]. This large airway caliber is speculated to reduce the flow-resistive load that would otherwise result from the rapid respiratory rate (250–350 bpm) required by the mouse to maintain body temperature [15]. An important functional difference between mice and rats compared to humans is the paucity, or even complete absence, of submucosal glands and the presence of high numbers of Clara cells [12]. Exactly what significance all these anatomical features of the mouse lung have for lung function is speculative, but it has been our experience that the baseline airway resistance of mice that have been sensitized and challenged with antigen differs imperceptibly from that of control animals [16,17]. This suggests that inflammatory processes that could compromise lung function in larger animals (e.g. humans) might have little effect in mice because of their relatively large airway size and/or lack of mucous glands.

Basic mechanical models of the lung

Measurement of the function of the lung, especially assessment of lung mechanics, is typically done in the context of a model of the lung [18–20]. The simplest model is a tube connected to a bellows (Figure 2A). This model works well for a single breathing frequency, but has major limitations when the changes in lung mechanics that occur with alterations in breathing frequency are considered. This is because the resistive and elastic properties of the lung are substantially dependent on breathing frequency. For example, the resistance of the lung falls as frequency increases over the range associated with normal breathing [21]. To model this type of mechanical behavior, spring-and-dashpot assemblies capable of simulating viscoelastic behavior need to be included in the model (Figure 2B). These basic models allow us to develop mathematical expressions, which can be used to quantitatively assess lung mechanics. The parameters of the models, that is, the resistive and elastic values of their individual components, constitute the endpoints we use to assess lung function experimentally.

**Figure 2**

Two common and basic mechanical models of the lung. A: A homogeneously ventilated model consisting of a single elastic balloon (elastance E) served by a single flow-resistive pipe (resistance R). B: A homogeneous model again with a single airway (resistance R_1), but with a Kelvin body consisting of two springs (E_1 and E_2) and a dashpot (resistance R_2) to account for the viscoelastic behavior of the lung tissue.

The viscoelastic model in Fig. 2B does a substantially better job of describing frequency-dependent nature lung mechanics than the model in Fig. 2A. Nevertheless, the simple model in Fig. 2A still serves as the conceptual platform for most studies of lung mechanics and bronchial responsiveness. The mechanical behavior of this model is described by its equation of motion. This equation is based on simple physics and states that the force (pressure) applied to the model is equal and opposite to the opposing force (pressure) the model generates. The applied pressure, P , is that supplied either by the respiratory muscles or a mechanical ventilator. The opposing pressure is made up, in general, of three components: a resistive pressure (P_{res}), an elastic pressure (P_{el}), and an inertive pressure (P_{in}).

Thus,

$$P = P_{res} + P_{el} + P_{in} \quad (\text{Equation 1})$$

P_{res} is described by Ohm's law:

$$P_{res} = R\dot{V} \quad (\text{Equation 2})$$

where R is the resistance of the lung and \dot{V} is flow of gas. P_{el} is described by Hooke's law:

$$P_{el} = EV = \frac{1}{C}V \quad (\text{Equation 3})$$

where E is lung elastance (equal to the inverse of compliance, C) and V is lung volume relative to functional residual capacity. P_{in} comes into play only at frequencies well above those of normal breathing, while both P_{res} and P_{in} become negligible when frequency is extremely low. Thus, the equation of motion relevant to normal breathing is

$$P = R\dot{V} + \frac{1}{C}V \quad (\text{Equation 4})$$

The parameters R and E are both profoundly dependent on breathing frequency and lung volume.

Lung volume

The volume of the lungs has an important influence on its pressure-flow relationships. For example, an increase in lung volume stretches the airways open and so causes airway resistance to fall (tethering). This also makes it more difficult for the airways to narrow when the airway smooth muscle contracts, and represents an important mechanism by which the challenged lung can defend airway caliber [18,22]. Unlike larger laboratory animals, the measurement of lung volume in the mouse is particularly problematic due to its small size. For example, when thoracic gas volume is measured using the conventional Boyle's Law technique, the volumes of air in the transducers used to measure plethysmographic and airway-opening pressures must be small relative to the lung volume, or significant measurement errors will occur. It has only recently been reported that measurement of functional residual capacity (FRC) by this approach is at all feasible [23]. The measurement of FRC with gas dilution is equally difficult, again due to the small size of the mouse lung, and there are only a few reports in the literature on the use of this technique [24]. Other studies of mouse lung volume have used a buoyancy approach [25], a degassing approach [26,27], and even a CT scanner method has been reported [28]. None of these, however, is particularly practical for most study designs. Better techniques for measuring lung volumes in mice are certainly needed, so this will be a fruitful area for future research.

Lung elastance (compliance)

The component of the transpulmonary pressure loss that is out of phase with flow and in phase with volume, as well as the recoil pressure exerted by the lung under static conditions, are caused by the elastic forces within the lung. The loss of elastic recoil within the lung defines emphysema while an increase defines restrictive processes [18,25]. The chest walls and other thoracic structures in mice are extremely compliant, so most elastic recoil measured in an intact animal can be attributed specifically to the lung. Moreover, the elastic recoil of the lung shows considerable genetic variability that needs to be taken into account in study designs [26]. The elastic recoil of the lung is conveniently assessed in terms of the quasi-static pressure-volume (*PV*) curve measured by inflating and deflating the lung in a step-wise fashion. The inspiratory limb of the curve traverses a path through values of *P* that are higher than those of the expiratory limb, the difference between the two limbs being termed hysteresis. Changes in the inspiratory limb of the *PV* curve that cause an increase in hysteresis are taken to indicate enhanced airway closure, such as that observed in humans after dry cold gas inhalation [29] and recapitulated in mice with allergic inflammation [30]. These changes in *PV* characteristics can be sensitive indicators of lung dysfunction and contribute to the genesis of hyperresponsiveness. The shape of the pressure volume relationship is one manifestation of the nonlinear characteristics of lung mechanics in the normal, unperturbed lung. Airflow resistance also exhibits a linear behavior as the airflow reaches high rates of flow as sudden changes in luminal dimensions occur (e.g. vocal chords). The mouse lung exhibits a linear elastic (compliance) behavior that increases following antigen challenge, a change that is most consistent with reopening airways that were closed [29,30]. Airflow is not a linear (i.e. laminar flow regimes) in either condition as it is highly unlikely turbulent flow occurs in mouse lungs due to the small airway diameters, unlike humans where turbulent flow is a common occurrence [30], pointing to a clear limitation of this species in exploring complex airflow conditions.

Phenotyping uncertainty principle

Accurate and valid measurement of lung mechanics in laboratory animals is a balancing act between measurement precision and maintenance of "natural" conditions. This situation is similar to the Heidelberg uncertainty principle of quantum mechanics which states that the measurement of a particle's position interferes with the measurement of its movement, and *vice versa* [31]. In a similar fashion, as we make more precise measurements of lung function in an animal, we are forced to constrain the animal's behavior in a way that departs from the maintenance of natural conditions [11]. At the extreme ends of this continuum are the measurements derived from the free roaming animal in a closed chamber, known

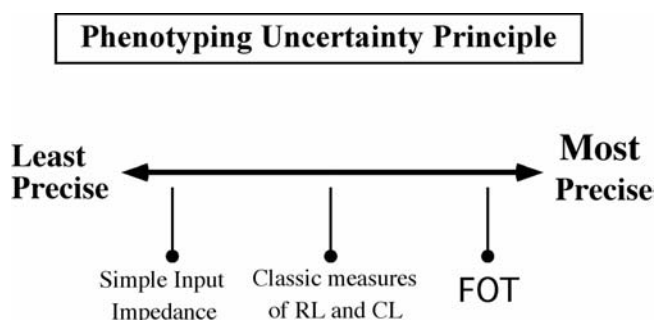


Figure 3

The non-invasiveness-precision continuum of the phenotyping uncertainty principle – see text for discussion.

as unrestrained plethysmography (UP), and the measurement of input impedance using forced oscillations performed in an anesthetized, tracheostomized animal (Figure 3).

Unrestrained plethysmography

This approach to assess lung function involves placing the subject into a small closed box and measuring the pressure changes within the box that occur as the animal breathes [7,11,32]. The animal is conscious and unrestrained. This technique currently enjoys wide popularity (for example see [33]) because 1) it is simple and 2) the mouse remains unharmed after the experiment. The endpoint is the heuristic variable known as Penh, which stands for 'enhanced pause'. It is important to note that there is no linkage between Penh and other variables that are derived from mechanical principles – Penh is merely an empirical derivative of the respiratory variations in box pressure [11]. While an earlier publication demonstrated reasonable correlations between Penh and invasive measures of lung mechanics [32], recent publications draw into serious question the validity of using Penh to measure lung function [7,11,34].

The pressure changes occurring within the box as the mouse breathes are derived first from gas compression and decompression within the thorax – an event linked to the state of lung mechanics – and second from humidification and warming of inspired gas – an event unrelated to lung mechanics. During bronchoconstriction, both components increase [7], but much of this increase is likely due to the increased stimulation to breathe that would arise from chemoreceptor receptors in the lung. Hence box pressure changes should be influenced by chemoreceptor sensitivity and genetics that control responses to chemo- or irritant- receptor stimulation and integration [11,35]. Recent studies show that

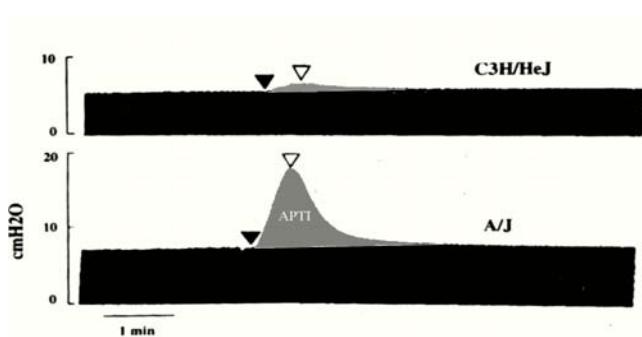


Figure 4

Pulmonary impedance measurements in anesthetized mice. The diagram shows airway opening pressure plotted against time. Volume and flow excursions for each breath are maintained constant by use of a volume-cycled ventilator. Increases in the magnitude of lung impedance following acetylcholine injection are assessed as the increase in pressure above baseline. Note the increased responsiveness in the A/J compared the C3He/J strain of mouse. APTI: Airway pressure time index. Used with permission [38].

changes in $Penh$ depart from mechanical changes during a state of increased box temperature [7,34] in an exactly opposite way during exposure to hyperoxic conditions [34,35] and temporarily [36]. These findings show that $Penh$ is not a valid measurement of the lung function of the mouse except as a measure of patterns of respiration, and it has been known for a long time that patterns of respiration usually have little bearing on lung mechanics. Finally, a response in $Penh$ may also be due to changes in nasal cavity resistance, as the upper airways are very significant contributors (50%) to total lung resistance and their contribution is likely to change depending on the experimental situation [32].

Lung impedance magnitude

The next step on the phenotyping uncertainty continuum (Figure 3) is the measurement of the magnitude of respiratory system or lung impedance. Lung impedance is a complex quantity having both real and imaginary parts (see section 'Forced oscillations and the constant phase model'), and its calculation requires rather sophisticated methods. The magnitude of impedance ($|Z_{rs}|$), however, is easily determined simply as the ratio of the absolute value of the swing in pressure (ΔP) to the absolute value of the swing in flow ($\Delta \dot{V}$) occurring over a breath, thus

$$|Z_{rs}| = \frac{|\Delta P|}{|\Delta \dot{V}|} \quad (\text{Equation 5})$$

As seen in the example in Figure 4, pressure is obtained by placing a pressure transducer at the airway opening, while flow is assumed to be constant as the animal is mechanically ventilated with a volume-cycled ventilator [9,10,37,38]. When a bronchoactive agent is introduced, the peak pressure with each breath goes up, so $|Z_{rs}|$ increases commensurately. Hence, by merely measuring airway-opening pressure, a useful index of lung function is derived. This technique has been used because it is simple and gives a direct assessment of lung mechanics [9,10,37,38].

The major disadvantage of this technique is that even though a direct measure of lung function is made, no insight is obtained as to where in the lung an abnormality might be located. This is a significant limitation if one wishes to explore the mechanisms of bronchoconstriction and whether it reflects, for example, central versus peripheral airways dysfunction. Nevertheless, this simple approach has produced significant advances in our understanding of the genetics of hyperresponsiveness [3,9,10].

Measurement of dynamic resistance (R_L) and compliance (C_L)

A classic approach to assessment of lung mechanics in animals is the measurement of dynamic lung resistance (R_L) and compliance (C_{dyn} or C_L) [3,8,20,38–40]. In the past, this approach was often used to assess central versus peripheral alterations in lung mechanics – a topic of considerable current interest. The calculation of R_L and C_{dyn} requires the measurement of intrathoracic pressure that, in larger animals, is obtained with an esophageal balloon or pleural catheter, but in a mouse is obtained either by opening the chest or by making the reasonable assumption that the chest wall presents little mechanical load compared to that of the lung [26,41,42]. Flow is usually obtained with a pressure transducer but this approach is problematic when miniaturized to the mouse [7,43]. Accordingly, flow is commonly derived from the differentiation of a volume signal, usually obtained from a body plethysmograph [8,40]. The values of R_L and C_L are then derived by fitting the equation of motion (Equation 4) to measurements of pressure, flow and volume.

The measurement of R_L and C_L , while technically challenging, does yield additional insight into the mechanisms of bronchoconstriction over that provided by $|Z_{rs}|$. Generally speaking, an increase in R_L reflects both narrowing of the conducting airways and alterations in the lung periphery (heterogeneous narrowing or closure of distal airways together with changes in the intrinsic mechanical properties of the parenchyma). Decreases in C_L , on the other hand, reflect only events in the lung periphery, particularly airway closure leading to lung unit derecruitment [44]. If the response to an intervention is limited largely

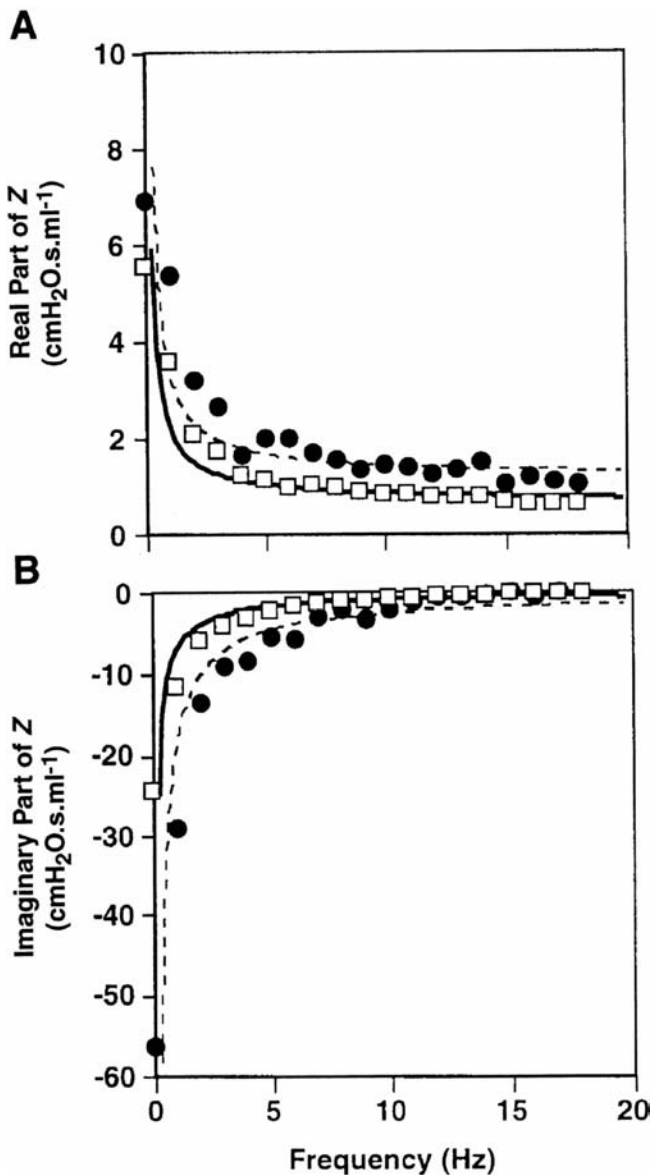


Figure 5
The respiratory input impedance of the mouse. Open squares represent baseline conditions while closed circles show the result of administering an aerosol of methacholine. The solid and dashed lines are the fit provided by the constant-phase model (Eq. 6). Used with permission [17].

to R_L , then a relatively proximal location is implicated for the effect. By contrast, a selective change in C_L is indicative of a more distal site of action [3,8,45]. As an example of this approach, R_L and C_L were clearly shown to be independent variables in mice treated with an antibody agonist for VLA-4, an adhesion protein of the eosinophil [45]. Furthermore, the genetic dependence of these variables

suggests that the factors that control central airway function (reflected in R_L) are different from those that control peripheral airway function (reflected in C_L) [46].

Forced oscillations and the constant phase model

At the far end of the phenotyping uncertainty principle lies the forced oscillation technique (FOT) applied in anesthetized, paralyzed, tracheostomized animals to measure the complex input impedance (Z_{rs}) of the lungs [21]. We have already covered the concept that the magnitude of Z_{rs} ($|Z_{rs}|$) is a generalization of the changes of resistance and compliance, and that Z_{rs} consists of two parts that are both functions of frequency. The real part of Z_{rs} is directly related to the resistance and provides essentially the resistance of the respiratory system at the frequency in question. The imaginary part of Z_{rs} is called the reactance and reflects respiratory compliance at frequencies below 20 Hz in the mouse. Thus, the FOT essentially provides R_L and C_L at each frequency contained in the flow signal applied to the lungs. This requires that the animal be oscillated with a complex flow wave produced by either a loudspeaker [34,47,48] or a computer-controlled piston [6,7,17]. The data of pressure and either flow or volume are converted into the frequency domain by the Fast Fourier transform, and their ratios calculated to yield the real and imaginary parts of Z_{rs} (Figure 5).

The key advantage of this approach, as compared to the determination of R_L and C_L or $|Z_{rs}|$, is that Z_{rs} can be fitted to a more complex model of the lung known as the constant-phase model [49] which makes a clearer distinction between central and peripheral events in the lung. The equation of motion of the constant-phase model is

$$Z_{in}(f) = R_{aw} + i2\pi f I_{aw} + \frac{G_{ti} - iH_{ti}}{(2\pi f)^\alpha} \quad (6)$$

where R_{aw} is the resistance of the airways that are attached to the constant phase element, I_{aw} is the inertance of the gas in the airways (which has negligible effect in the mouse below 20 Hz and can be ignored [17]), G_{ti} is tissue resistance or damping, H_{ti} is tissue elasticity, and i is $\sqrt{-1}$. As R_{aw} is a measure of central airways resistance, it would be expected to change if the airways are significantly narrowed. By contrast, G_{ti} reflects either changes in tissue physical properties or regional airways heterogeneity. If changes in R_{aw} are small, then any changes in G_{ti} most likely represent changes in the parenchyma or very small airways. Acute changes in H_{ti} are likely to reflect lung derecruitment (airway closure) [44], whereas chronic changes in H_{ti} would be expected to reflect changes in the intrinsic mechanical properties of the parenchyma. This technique

is now being successfully and extensively used to assess lung mechanics of the mouse [17,33,50].

Tomioka et al [17] showed that Z_{rs} can be used to track changes obtained with an even more invasive technique [51,52] – the alveolar capsule – where resistance is partitioned into a central airway and a parenchymal tissue resistance component through the direct measurement of alveolar pressure (Figure 6). In this study, the disparate behaviours of R_{aw} , G_{ti} and H_{ti} clearly show that these three quantities are independent parameters that access different aspects of lung function. For example, antigen exposure followed by methacholine challenge caused an enhancement of both G_{ti} and H_{ti} – measures of peripheral lung function – however, changes in R_{aw} , reflecting central airways, were not significantly altered. The enhanced changes in G or H in this acute state may reflect three different mechanisms: derecruitment of lung units as airways close, temporal shifts of tissue movement, and inhomogeneities of airflow distribution. Moreover these data point away from significant alterations in airway smooth muscle function and more towards enhanced or altered secretions that cause dysfunction in small airways. Interestingly, antigen challenge in either sensitized or unimmunized mice caused no significant changes in any of the parameters at baseline before methacholine challenge, likely due to the unique architecture of the mouse lung (see above).

We believe that the well-founded theoretical basis of the FOT, and its rigorous application in mice, will lead to considerable insight into the functioning of mouse models of lung disease.

Conclusion

Measurement of lung function in a creature as small as the mouse presents considerable technical challenges. However, with the exception of the measurement of absolute lung volume and the analysis of blood gases, we have now conquered the challenge of miniaturizing the instrumentation necessary for mouse lung function assessment. Application of advanced techniques such as the FOT coupled with constant-phase model analysis hold particular promise for improved characterization of lung responses to intervention and pathology. With these approaches, we can now unravel the mechanisms of airways dysfunction, the influence of genetics and the immunological factors that define the physiome of the mouse.

Abbreviations

bpm breaths per minute

C_{dyn} dynamic compliance

C_L lung compliance

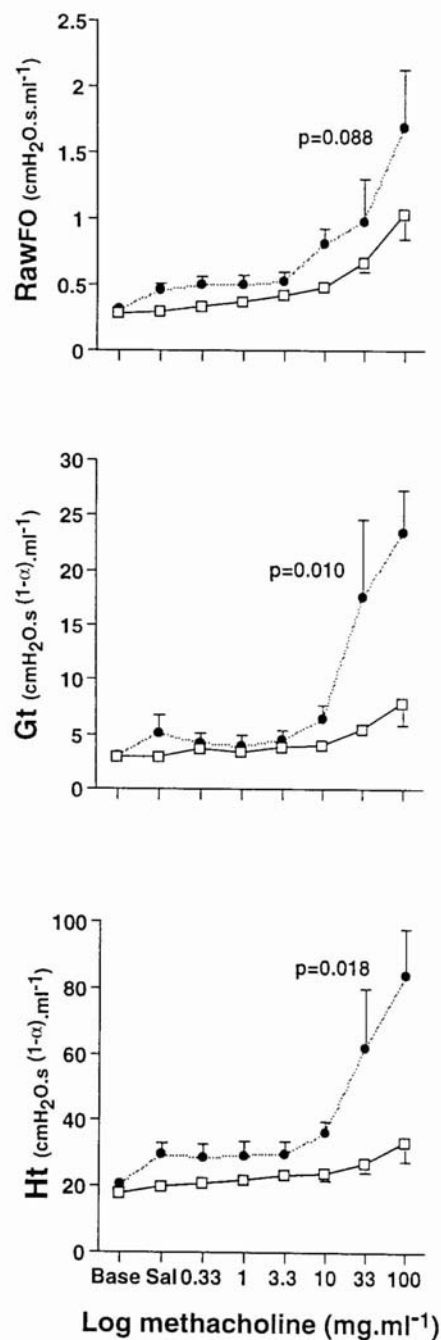


Figure 6

The mechanical response of the mouse lung to methacholine in terms of the parameters of the constant-phase model (see Eq. 6 in text). The open squares correspond to control BALB/c mice, while the closed circles represent mice sensitized to and challenged with ovalbumin. Taken from [17] with permission.

E elastance

FOT forced oscillation technique

FRC functional residual capacity

G tissue damping or tissue resistance

H elasticity

MLI mean linear intercept

P pressure

P_{res} resistive pressure

P_{el} elastic pressure

P_{in} inertial pressure

Penh enhanced pause

R_L resistance

TLC total lung capacity

UP unrestrained plethysmography

\dot{V} Flow

Z_{RS} or Z impedance of the respiratory system

$|Z_{rs}|$ Magnitude of impedance

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