Point:Counterpoint: Lung impedance measurements are not more useful than simpler measurements of lung function in animal models of pulmonary disease

**POINT: LUNG IMPEDANCE MEASUREMENTS ARE MORE USEFUL THAN SIMPLER MEASUREMENTS OF LUNG FUNCTION IN ANIMAL MODELS OF PULMONARY DISEASE**

Research on pulmonary disease relies increasingly on the use of animal models, commensurate with the progression of our ability to manipulate the genome and recreate noxious environmental conditions in the laboratory. Accordingly, any self-respecting biomedical research institution these days will have set up some kind of advanced animal facility. This costs a huge amount of money and involves excruciating politico-regulatory monitoring. How idiotic would it be then to throw away a significant fraction of the biological information embodied in any animal model that is produced from such effort and expense? The very fact that we are debating here the issue of lung impedance versus simpler measures of mechanics shows that some investigators still consider this an open question. I will now end the debate by explaining why impedance contains more physiological information than simpler measures of mechanics, and so by definition must be more useful.

The assessment of lung mechanics is central to the phenotypic characterization of any animal model of pulmonary disease, and many approaches have been developed. Let me first dispatch with the widely used enhanced pause (Penh) by pointing out that it has been completely discredited as a means of measuring lung mechanical function (1, 3, 14). Valid assessment of lung mechanics involves probing the lung with some kind of perturbation and observing the consequences. The level of detail that this reveals about the inner workings of the lung depends very much on the richness of the perturbation. A very simple perturbation, for example, is a single step increase in lung volume. The relative increase in airway opening pressure produced by this perturbation yields a measure of the overall lung stiffness (elastance) and is affected by a variety of pathologies. For example, an increase in elastance can result from fibrosis of the parenchyma (8), closure of airways (24), edematous filling of alveoli (13), hyperinflation (23), or inactivation of pulmonary surfactant by plasma proteins (26). Thus, while measuring elastance may be useful for discerning the presence of pathology, it hardly narrows the field of specific causes.

A perturbation with more diagnostic potential is an oscillating volume change, such as that applied during conventional mechanical ventilation. Some investigators have used the peak to pressure (P), flow (V), and volume (V) signals that vary with time (t; Ref. 5). Nevertheless, two independent parameters can still only provide an extremely limited window into the inner mechanical workings of a system as complicated as the lung. Just how limited is evidenced by the substantial variation of both R and E with the perturbation frequency, f. In normal animals, this f dependence is largely due to the viscoelastic properties of lung tissue (12). In disease, the situation may be complicated by the development of regional heterogeneities in lung mechanical function that further accentuate the f dependence of R and E (18). A comprehensive assessment lung mechanics thus requires that R and E be measured as two independent, yet complimentary, functions of f. Together, they constitute a complex function of frequency known as pulmonary input impedance, Zin. The real part of Zin is called resistance because it equals R in Eq. 1 at any particular value of f. The imaginary part of Zin is known as reactance and is equal to −E/2πf in Eq. 1. Recent work (10, 11, 20) has established that Zin in normal mice is extremely well described up to 20 Hz by the following model, first described for the lung by Hantos et al. (12),

$$Z_{in}(f) = R_N(f) + \frac{G - iH}{(2\pi f)^2}$$  \hspace{1cm} \text{(2)}

where R_N is a Newtonian resistance, G and H characterize the dissipative and elastic properties, respectively, of the lung tissue, and α is determined by G and H. Equation 2 also describes Zin in the mouse even during mild to moderate bronchoconstriction (6, 20, 24) as well as in various other pathological situations (2, 7, 16). Zin in mice can thus be accurately characterized under a wide range of conditions by only three parameters. Its real utility, however, lies in the fact that R_N, G, and H have functionally important physiological interpretations. R_N is essentially equal to airway resistance (Raw; Ref. 22), so a change in R_N can be taken as accurate indication of a global change in airway caliber. Changes in G and H, which together characterize the viscoelastic properties of the tissue in a normal lung (12), can be indicative of two distinct types of mechanical derangement. Derecruitment of a portion of the lung causes G and H to increase in the same proportion (2, 4), while increased regional heterogeneity of mechanical function throughout the lung causes G to increase relatively more than H (4, 17, 21).

By tracking the changes in R_N, G, and H that occur immediately following administration of a methacholine aerosol, we can differentiate between exaggerated smooth muscle shortening versus increased closure of small airways. This has allowed us to infer that acutely allergically inflamed BALB/c mice are hyperresponsive because their airway epithelium is physically thickened and not because of any significant changes in the
contractility of their airway smooth muscle (24). By contrast, when BALB/c mice are treated with an intratracheal instillation of poly-L-lysine they become hyper-responsive because of increased smooth muscle shortening (6). We also invoked changes in $R_N$, $G$, and $H$ to show that administering methacholine as an aerosol induces a significant amount of airway closure (24) that is virtually absent when the methacholine is injected intravenously (15, 25). Equation 2 has also been used to interpret measurements of $Z_{in}$ in other species (10, 12).

So now to address the question of whether impedance really is more useful than simpler measurements of lung function in animal models of pulmonary disease. In view of the foregoing discussion it will be obvious to enlightened readers that the answer is affirmative, but as a service to the recalcitrant skeptic, I will explicitly point out what clinches the case. $Z_{in}$ allows one to discern, with a reasonable degree of confidence, how an experimental intervention differentially affects airway caliber, derecruitment of lung units, and regional heterogeneity of function. This level of inference is not possible with simpler measures of lung function because they simply do not contain the required physiological information. This is not to say, of course, that $Z_{in}$ is the last word in the assessment of lung function. It is actually only the first term in a potentially infinite series of ever more complicated complex functions of frequency that describe the general nonlinear dynamic system (19). Nevertheless, $Z_{in}$ currently represents the state of the art for assessing lung function in animal models of pulmonary disease and constitutes a significant advance beyond the simpler methods that dominated investigations in the old days.

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COUNTERPOINT: LUNG IMPEDANCE MEASUREMENTS ARE NOT MORE USEFUL THAN SIMPLER MEASUREMENTS OF LUNG FUNCTION IN ANIMAL MODELS OF PULMONARY DISEASE

The goal of any pulmonary function test is to provide insight into functional and structural changes that occur with lung disease. In animal models, airway resistance and lung elastance (the mathematical inverse of compliance) have long been the traditional variables for assessing pulmonary function, despite there being a limited understanding of their structural foundations. Between these two, airway resistance is more closely linked to structure, because in an idealized model lung with
Lung elastance is a simple variable to both define and measure. A stiffer lung is one that takes a greater pressure change to reach a given volume change, but very many factors can alter elastance in both normal and pathologic lungs, including lung volume, smooth muscle contraction, surface tension, and the rate at which the measurement is made. Any pathologic changes in lung structure may impact on each of these normal variations. In addition, although most lung researchers intuitively link lung elasticity with the parenchyma beyond the ends of the airways, this is not necessarily the case. It can be reliably shown that if one simply contracts just the cartilaginous conducting airways, there is a substantial and reversible change in lung elastance (14). Thus despite it being far easier to measure than airway resistance, lung elastance is less clearly related to lung structure than airway resistance.

Despite these concerns with resistance and elastance, they provide intuitive insight and have been the gold standard for assessment of pulmonary function in animal models since the 1950s. However, in an effort to deal with observations that these variables were observed to vary with breathing frequency (5, 16, 19), impedance models began to be described over 30 years ago (3). These models were not widely used for many years, partly because the measurements were difficult to obtain and interpret. In the last 15 years, however, it has become increasingly popular to measure respiratory impedance, particularly in animal models. Respiratory impedance is defined simply as the ratio of time-varying pressure and flow and is often displayed in graphs with real and imaginary magnitude and phase components plotted as a function of frequency. Impedance has recently gained further support, since it can now easily be measured in both humans and animals. But just because something is easy to measure does not mean that it is proper or even useful. A similar state of affairs has been highlighted in the past 10 years by the widespread improper use and interpretation in mouse models of the nonsensical index, Penh, whose only redeeming value is that it is easy to measure (1). In fact this ease of measurement of Penh has ensured its continuous use by those either unaware of its problems or who just lack the knowledge, the motivation, or the energy to make an appropriate measurement that more closely reflects airway responsiveness (2, 7, 11, 12, 15, 17). As impedance has now also become simple to measure with computerized ventilators, the question being considered here is, what can respiratory impedance tell us about lung structure and pathology?

To address this question, we will limit discussion to the constant phase model (6). Although there have been many other models of respiratory impedance (8, 10, 13, 18), the constant phase model has rapidly surfaced as something of a gold standard in the literature, particularly since the advent of ventilators with computational software that provide model variables from a brief respiratory pause. The variables in the model are G, η, Rn, H, and inertance, but besides the resistance (Rn) and elastance (derived from H), to my knowledge there has not been any substantive evidence that the other impedance variables, G, η, and inertance, have ever been correlated in animals or humans with any specific lung pathology.

The variable G is commonly interpreted to be a measure of dynamic properties of the parenchyma (although it has units of elastance). Given its nebulous definition, however, investigators are not even consistent with how it is discussed in published papers, being referred to as tissue viscosity, or tissue resistance, or tissue viscosance, or tissue damping, or avoiding any attempt at structural relevance, simply G. Despite this confusion, given the key role of G in the constant phase model, it is quite justifiable to ask whether G is something that changes in asthma or in COPD. Can therapies be designed to correct the defect in G? When stated this way, these questions sound a bit ludicrous, the more so since there has been no theoretical way to link G to any structural defect in the lung and the model itself has not been shown to have any predictive value.

Along these lines, many papers also show the frequency dependence of both real and imaginary parts of the impedance. But what, for example, does the frequency dependence of the imaginary part of the impedance phase angle tell us about lung structure? Yes, there is modeling and speculation about how this frequency-dependent behavior may relate to ventilation heterogeneity (9), but among the many published papers that show pictures of the changes in frequency dependence with interventions, it is never clear what insight such data provide into the structural pathology. Indeed most investigators often just extract the airway resistance from the impedance data and limit their discussion to just that, or perhaps occasionally elastance as well. Lastly, it is worth noting the potential value of what was originally called hysteresivity (4), a variable represented in the constant phase model as η (=G/H). Although η originally had great promise as a variable that could link dissipative and elastic processes within a single stress-bearing element (the structural damping hypothesis), in the almost 20 years since it was first published, it has not lived up to this billing. A quote from that original work is quite prescient, “Whether the structural damping hypothesis will supplant its classic counterpart (i.e., resistance and elastance) will be based, ultimately, on the criteria of simplicity with which each organizes observation, resolves anomalies, and elicits or elucidates notions of underlying mechanism” (4). It seems quite clear that the model has yet to overcome these hurdles.

On the basis of the above considerations, it should be clear that if one wants both to know something about lung structure and to be able to follow structural changes with developing pathology, then measuring impedance offers very little beyond a simple measurement of resistance and elastance. Resistance remains the best of the variables, because there is a direct link with airway size. Elastance relates to how easy it is to inflate the lung, and while the link between structural elements, the interstitial matrix, and the measurement of elastance may not be fully understood, elastance still provides a good conceptual and intuitive characterization of lung pathologic changes. On the other hand, G and η provide neither conceptual nor intuitive insights into such pathologic changes. These considerations clearly put the onus of proof on those who would want to continue to make these measurements and fit them to a theoretical model.

To summarize, lung impedance has been measured for at least 30 years, but unfortunately during that time little functional or pathologic insight has been provided by such measurements. The primary benefit of such work has been to
modelers who use the framework to fit empirical data, but even the best model fits still do not provide new physiological insights. In today’s world, lung impedance is often measured in animal models for no other reason than it can be painlessly measured by commercial ventilators. Until it has been clearly demonstrated what pathologic or mechanistic insights are gleaned from impedance measurements, it seems silly to make these measurements and perhaps even sillier to continue to report them in publications.

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REBUTTAL FROM DR. BATES

Dr. Mitzner and I clearly differ in our opinions about the usefulness of lung impedance (4, 6). However, we do agree on certain key things, such as the lack of utility of Penh, which, as my worthy opponent rightly points out, has seduced many investigators solely on account its ease of use (1). But then he makes the error of suggesting that this unfortunate state of affairs also applies to impedance because equipment is now available to measure it with relative ease (6). While there is no question that a certain amount of confusion currently reigns over the physiological interpretation of lung impedance, this is not a reflection of any fundamental shortcoming in the quantity itself. Rather, the shortcoming resides in the community of scientists who use it. Indeed, Dr. Mitzner says as much, for example, when he accuses investigators of lack of consistency in the use of the constant-phase model parameter G (6). As I stated previously (4), in a homogeneous lung G reflects the dissipative properties of the lung tissues. However, both analytical investigation (2) and simulation studies with anatomically accurate models of the lung (5, 7) have shown that changes in G relative to H (tissue elastance) can be used to infer the development of lung derecruitment versus regional ventilation heterogeneities. These are nontrivial physiological insights that, along with those provided by RN (airway resistance) and H, have been used to advantage in several recent studies (e.g., Refs. 3, 5, 8). Dr. Mitzner also charges that “investigators often just extract airway resistance from the impedance” (6). This is true, but again it simply reflects ignorance, not fundamental futility. If investigators choose to discard some of the information present in an experimental measurement, the fault (if there is any) lies with them. To be fair, lung impedance can only be properly interpreted in physiological terms in the context of a mathematical model of the lung (5, 7). This introduces a level of technical complexity that goes beyond what many biomedical researchers are used to, which probably explains how far we have not come in 30 years (6). The utility of impedance thus comes down to an issue of intellectual accessibility, which is consequently its greatest impediment to widespread acceptance. Nevertheless, I firmly believe that an appreciation of the utility of lung impedance is potentially within the grasp of any trained scientist and well worth the effort.

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**REBUTTAL FROM DR. MITZNER**

It is nice to see that Dr. Bates and I have much in agreement. First, we both agree that it is important to measure resistance, whether it be $R_n$ or $R_{rs}$ at a given frequency. Second, we also agree that airway closure might be very important in lung pathology and that a simple measurement of elastance might easily quantify this. It is clear that if part of the lung is closed off, the lung elastance will increase, and one does not need the constant phase model to tell us that. Third, as I noted already, although the issue of heterogeneity is perhaps the only area where impedance may provide some value, until the assumptions underlying this are better supported by experimental data, the utility of this remains to be seen. And finally, we clearly both agree that those investigators who continue to use Penh as a measure of airway responsiveness are treading a disingenuous and unscientific path.

The difference between us, however, is that we both see a very different utility in extraneous uninterpretable data. My esteemed colleague unfortunately makes an incorrect assumption that more physiological information “by definition” must be more useful. The 20th century literature on pulmonary function testing is replete with physiological data from new and improved measurements, which unfortunately have consistently failed to provide insights into disease pathology. When Dr. Bates states that changes in G have a functionally important physiological interpretation, he of course conveniently fails to tell us what this might be. What is perhaps even more frightening is in Dr. Bates’ conclusion, where he threatens us with measurement of a “potentially infinite series” of additional terms! The situation is not unlike the current ability of researchers to do a gene chip analysis whenever possible. While this might at some point provide useful information, most often it provides lists of hundreds of genes that are up- and downregulated to varying degrees, and even then only those that change by at least 100%. Experimental data without some meaningful link to structure and function provide little insight into what we really want and need to know. We need more investigators to invoke the principle of scientific parsimony, commonly attributed to the 14th century logician, William of Ockham, whose razor is often paraphrased as, “All things being equal, the simplest solution tends to be the best one.” In this case, resistance and elastance currently provide as much (or as little) useful insight as impedance, and the burden of proof is clearly on those who feel the need to increase this complexity.