SUMMARY OF THESES

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INTRODUCTION

The lung is a marvelous mechanical ventilation system designed robustly to maintain an appropriate gas exchange in the body, that is to bring oxygen into and eliminate carbon-dioxide from the circulation. In order to achieve this task, the structure of the lung is fairly over-designed. It is composed of an asymmetrically branching network of compliant tubes, the airways, which are imbedded in a nonlinearly viscoelastic tissue matrix, the lung tissues. The surface area available for gas exchange which is packed into the chest cavity is as large as two thirds of a tennis court. Due to this particular design, the lung is capable of maintaining life-sustaining blood gas conditions even in the presence of substantial injury or pathological alterations. However, these alterations in the lung can lead to compromised lung function and discomfort or eventually they can even be life-threatening. Hence, understanding the basic mechanical functioning of the lung under these conditions is essential. Additionally, measurement approaches are needed which are able to provide specific and reliable insight on the mechanical properties and the most important mechanisms that contribute to breathing.

The present thesis summarizes primarily my own and some of my collaborative efforts and contributions to the literature to understand the basic mechanical properties of living tissues, in particular, those of lung tissues, some aspects of signal processing associated with measuring these properties, wave propagation in the airways, certain recent developments in theoretical physics as applied to the airway tree, and some implications of the results to various diseased conditions. The material is divided into three parts according to the main focuses of the publications. Below, I will provide a framework and a brief summary of the results emphasizing their importance and possible applications in biology and medicine, and then provide a more detailed description of the individual studies.

First, I will describe those studies that investigated the basic mechanical properties of the tissues under physiological conditions, that is at low breathing frequencies and large amplitude oscillations (1-8). These studies included measurements and characterization of the nonlinear rheological properties of lung tissues. In particular, I reported the first measurements of lung tissue

properties in man over a frequency range extending far below the normal breathing rates (1). I introduced the first nonlinear viscoelastic models to account for tissue nonlinearity which explained several long standing controversies in the literature (2,3). In another theoretical study, I showed how nonlinearity influences the assessment of apparent transfer and coherence functions measured by pseudorandom input signals and proposed a novel class of pseudo random signals that minimize the bias due to nonlinearity (4). Since their introduction, these input waveforms have been used by several other groups. The most important application of these waveforms was the design of Optimal Ventilator Waveforms introduced by our group (5) which solved the measurement difficulties in obtaining reliable mechanical impedance data in awake humans under physiological breathing conditions. This method has also been adopted by several groups. I applied the above nonlinear models to fit lung tissue data measured in control and following agonist challenge. This analysis lead to an important conclusion about the mechanisms contributing to the mechanics (6). Finally, to account for the particular rheological properties of tissues, I proposed two mechanisms: self-organized criticality within the microstructure of the lung (7), and molecular mechanisms based on reptation theory of branching polymers (8).

The second major area of my studies included experimental and theoretical investigations of wave propagation in structured viscoelastic tubes, such as airways with intermittent soft tissue and cartilage rings (9). These results were then incorporated into models of the airway tree to account for its acoustic characteristics which lead to the development of a general modeling approach that can predict the serial distribution of airway diameters, that is the airway diameters as a function of generation number within the airway tree (10). We then compared these predictions with direct measurements of airway diameters obtained using high resolution computed tomography (11). These efforts may find applications in estimating the locus of the effects of various diseases or drug therapy in a noninvasive manner. In a next study we proposed a new method to measure shear wave propagation in foams which are similar to lung parenchymal tissue (12). Finally, I conducted a study that revealed that the phase velocity of oscillatory waves in the airways is highly dispersive and it is quite different from the constant wave speed derived from flow limitation previously thought to completely describe pressure waves in the airways (13).

The third area of my studies involves the application of some recent concepts in theoretical physics to a particular phenomenon, airway opening. In contrast to previous beliefs that the lung inflates smoothly and continuously, I discovered that from low lung volumes, the inflation of the lung occurs through many discontinuous steps having a wide range of sizes which were called avalanches (14). Since the measured distribution of step sizes was very broad, following a power law, this phenomenon was the first biological example of avalanches that may occur in processes that are in a self organized-critical state which has been proposed as the common underlying mechanism of 1/f-noise and fractals that are so ubiquitous in nature. In a follow-up study, we mapped the airway opening process to percolation problem on a Cayley tree (15) which analysis lead to general conclusions about the origins of power law distributions in tree structures.

The last two studies (14,15) initiated a completely new direction in mechanical ventilation of patients suffering from airway closure or alveolar collapse. It is known that following mechanical ventilation edema can easily develop and airway closure is quite common. A group in Canada reasoned, based on the avalanche behavior of airway openings, that since normally we do not breath at a fixed frequency, a variable breathing rate may help initiate the avalanches in mechanically ventilated patients. They developed a computer-controlled ventilator system which ventilates with a frequency that is chosen randomly from a Gaussian distribution. This type of ventilation provided far better alveolar oxygenation than conventional fixed frequency ventilation and can therefore have a significant impact on ventilation industry.

MECHANICAL PROPERTIES OF SOFT BIOLOGICAL TISSUES

Lung mechanics in humans at very low frequencies (1). The mechanical input impedance of the lung was measured from 0.01 to 0.1 Hz in six healthy subjects by superimposing small-amplitude sinusoidal forced oscillations on spontaneous breathing. Measurements were made with an almost constant volume input (160-180 ml) or an almost constant flow input (20-30 ml/s). No significant difference was found between the two conditions. Lung resistance (R_L) sharply decreased from 0.97 kPa.s/L at 0.01 Hz to 0.27 kPa.s/L at 0.03 Hz and then mildly to 0.23 kPa.s/L at 0.1 Hz. Lung effective compliance (C_L) decreased slightly and regularly from 2.38 L/kPa at 0.01 Hz to 1.93 L/kPa at 0.1 Hz. The data were analyzed using a linear viscoelastic model adapted from Hildebrandt (16) and complemented by a Newtonian resistance (R): $R_L = R + B/9.2f$ and $C = 1/(A + 0.25B + B \log 2\pi f)$, where f is the frequency and B/A is an index of lung tissue viscoelasticity. A good fit was generally obtained with an average difference of 10% between measured and predicted R_L and C_L. R was systematically larger than plethysmographic airway resistance suggesting that lung tissue resistance might also include a Newtonian component. The ratio B/A was not affected by breathing and was 10.6 and 13.6% in the constant volume and constant flow conditions, respectively, which agrees with Hildebrandt's observations in isolated cat lungs (16) as well as in other species (17).

A nonlinear viscoelastic model of tissues (2). There have been a number of attempts recently to use linear models to describe the low-frequency (0-2 Hz) dependence of lung tissue resistance (R_{ti}) and elastance (E_{ti}). Only a few attempts, however, have been made to account for the volume dependence of these quantities, all of which required the tissues to be plastoelastic. In this study we specifically avoid invoking plastoelasticity (16,17) and, for the first time, we develop a nonlinear viscoelastic model based on the Volterra theory of nonlinear functionals, that is also capable of accounting for the nonlinear and frequency-dependent features of lung tissue viscoelasticity. The model parameters were identified by fitting the model to data obtained in our previous study from dogs during sinusoidal oscillations. The model was then used to simulate pressure-flow data by use of various types of ventilator patterns similar to those that have been employed experimentally. R_{ti} and E_{ti} were estimated from the simulated data by use of four different estimation techniques commonly applied in respiratory mechanics studies. We found that the estimated volume dependence of R_{ti} and E_{ti} is

sensitive to both the ventilation pattern and the estimation technique, being in error by as much as 217 and 22%, respectively.

Nonlinear phenomena in tissue mechanics (3). The impact of nonlinearities on the assessment of respiratory tissue mechanics was examined using a block structured model (BSM) featuring both flow ($\dot{V}$) and tidal volume (V_T) nonlinearities. The model consists of an airway compartment (AC) in series with a tissue compartment (TC). The AC is a series connection of a resistance, inertance, and a nonlinear $\dot{V}$-dependent element. The TC is composed of a linear Kelvin body in cascade with a nonlinear polynomial system. Analytic results showed that: 1) the lack of V_T-dependence using sine waves does not mean that the system is linear; 2) the hysteresivity (i.e., the normalized hysteresis area of a cycle) of a wide class of such tissue models is independent of V_T offering a simple microstructural mechanism for the observed coupling between resistance (R) and elastance (E). If those stress bearing elements within the tissue where the dissipation comes from can be characterized as linear, physically realizable systems, then the real and imaginary parts of their impedances can be expressed from each other, i.e. they are interrelated (e.g. through the Hilbert transformation). In addition, if the interactions among these elements are nonlinear, but nondissipative (like those induced by displacement limiters), then, at the overall level, one would find a nonlinear dissipative system with coupled resistance and elastance. Furthermore, R from the step response of the TC was ~30% smaller than from sinusoids. Below 1 Hz, R and E of the BSM showed a negative V_T-dependence. These together resolve the long-standing controversy that the difference between dissipations in the time and frequency domains requires a plastoelastic model (16). Above 1 Hz, R increased with frequency and V_T due to $\dot{V}$-dependence. Analysis of the response of the BSM to composite signals revealed how linear airway resistance can be overestimated due to $\dot{V}$-dependence and tissue properties can be underestimated due to harmonic distortion and cross-talk induced by V_T associated nonlinearities.

Apparent transfer and coherence functions in nonlinear systems (4). There is an increasing need in physiology to estimate nonparametric linear transfer functions from data originating from biological systems which are invariably nonlinear. For pseudo random (PRN) input stimuli, we derived general expressions for the apparent transfer (Z) and coherence (γ^2) functions of nonlinear systems that can

be represented by a Volterra functional series. It is shown that in the case of PRN signals in which the frequency components are integer multiples of other components the estimates of Z are seriously biased due to harmonic distortion and cross-talk among frequency components of the input. When the PRN signal includes components that are not integer multiples of other components harmonic distortion is avoided, but not necessarily cross talk. Here the estimates of Z remain poor without a noticeable influence on γ^2. To avoid the problems associated with harmonic distortions and minimize the influence of cross-talk, a family of pseudo random signals was proposed which are especially suited for the estimation of Z and γ^2 in mechanical measurements of physiological systems at low-frequencies. The components in the signals cannot be reproduced as linear combinations of two or more frequency components of the input. In a second order system this completely eliminates the bias, while in higher order, but not strongly nonlinear systems the interactions among the components are reduced to a level that the response can be considered as if it was measured with independent sine waves of an equivalent amplitude. It was also shown that the values of γ^2 are not appropriate to assess linearity of the system. The theory was supported by simulation results and experimental examples brought from the field of respiratory mechanics by comparing the input impedance of the respiratory system of a dog measured with various PRN signals.

The Optimal Ventilator Waveform (5). In human subjects there exists no practical and reliable technique for measuring frequency dependence of respiratory resistance (Rrs) and elastance (Ers) from 0-2 Hz with physiological tidal volumes. We present a broadband optimal ventilator waveform (OVW). The concept of the OVW is to create a computer driven ventilator waveform containing increased energy at specific frequencies. The frequencies are chosen so that nonlinear harmonic distortion and intermodulation (crosstalk) are minimized according to Suki and Lutchen (4). The phases at each frequency are then optimized so that the resulting flow waveform delivers sufficient volume to maintain gas exchange while minimizing peak-to-peak airway opening pressure. Simulations with a linear, anatomically consistent branching airway model and a nonlinear viscoelastic model showed (a) that Rrs and Ers estimates from 0.1 - 2 Hz using the OVW are far superior to those from a standard step ventilator waveform (SVW) during healthy and obstructed conditions; and (b) that the OVW reduces the influences of harmonic interactions. Using a servo-

controlled oscillator we applied individual sine waves, an OVW containing energy from 0.15625 - 2.4 Hz, and an SVW to healthy humans and one symptomatic asthmatic before and after bronchodilator therapy. The OVW was markedly superior to the SVW and always provided a smooth estimates of Rrs and Ers throughout the frequency range. For the asthmatic subject the advantages of the OVW were dramatic. Prior to bronchodilation the Rrs was highly elevated and the Ers increased markedly with frequency, Post bronchodilator the level of Rrs and the frequency dependence of Ers decreased. The majority of the difference between Ers before and after bronchodilator occurred above 0.6 Hz. While based only on a single asthmatic, these data suggest a dominant influence of airway constriction and lung inhomogeneities during asthmatic bronchoconstriction that is alleviated by bronchodilators. The OVW was able to provide all these features in 20-30 secs of data acquisition time per bronchial state. This is sharp contrast to the 10-20 minutes required for sine wave forcing, and then only out to 0.6 Hz. These results indicate that the OVW approach has high potential for simultaneously probing frequency and amplitude dependence in the mechanical properties of clinical subjects during physiological breathing conditions and perhaps during dynamic bronchoconstriction.

Block-structured modeling of the frequency and amplitude dependence of tissues (6). During lung constriction there is an increase in both the frequency and tidal volume (V_T) dependences of lung tissue resistance (R_{ti}) and elastance (E_{ti}). This suggests that a) significant alterations take place in the mechanisms contributing to both the linear and nonlinear characteristics of lung tissues; and b) the frequency and V_T-dependences of R_{ti} and E_{ti} are coupled. We examined these issues for the case of sine wave and special pseudo random inputs by utilizing the theory of nonlinear block structured systems. Two basic model structures were considered: the Hammerstein and the Wiener structures. The Hammerstein structure is a cascade connection of a nonlinear zero-memory (N) system and a linear dynamic process (L). This structure predicts that frequency and V_T dependences of R_{ti} and E_{ti} are decoupled. The Wiener structure is an inverse cascade of these two blocks (i.e., L-N) in which the frequency and V_T dependences of R_{ti} and E_{ti} are coupled. These two structures were combined with a nonlinear airway compartment and fitted to measured airway opening and alveolar capsule pressure-flow time domain data in dogs before and after histamine induced constriction. The best lung model was a linear airway compartment combined with a Wiener structure consisting of a

constant phase linear tissue impedance in cascade with a polynomial nonlinearity suggesting that frequency and V_T dependences of R_{ti} and E_{ti} are indeed coupled during control and constricted conditions. Moreover, histamine caused much larger changes in the linear tissue parameters than in the nonlinear coefficients. We suggest that the primary cause for the increased V_T dependence during constriction is not a change in the nonlinear mechanisms but rather the inherent nonlinear mechanisms become exacerbated through an increase in the magnitude of the linear tissue impedance. We also note that in a very recent work, Ingenito et al. (18) found severe histopathological alterations (such as basement membrane thickening, increased cellularity and hemorrhage) in lung tissue strips following acute lung injury. Furthermore, they also argued that the observed increase in negative amplitude dependence in the challenged strips is not due to increased interstitial collagen and/or elastin. Since nonlinearity of tissue behavior is invariably associated with the collagen fiber network, the study of Ingenito et al. (18) supports our thesis that the increase in amplitude dependence in the challenged lungs may actually originate from pathologic changes of the more viscoelastic tissue components through a structural relationship with the fiber network of the lung.

Lung tissue viscoelasticity: a mathematical framework and its molecular basis (8). Recent studies have indicated that lung tissue stress relaxation is well represented by a simple empirical equation involving a power law, $t^{-\beta}$ (where t is time) (2). Likewise, tissue impedance is well described via a model having a frequency independent (constant) phase with the impedance proportional to $\omega^{-\alpha}$ (where ω is the angular frequency) (19). These models have been shown to provide superior descriptions over the conventional spring-dashpot systems. In this paper we offer a mathematical framework and explore its mechanistic basis for using the power law relaxation function and the constant phase impedance. We show that replacing the ordinary time derivatives with fractional time derivatives (20) in the constitutive equation of the conventional spring-dashpot systems naturally leads to a power law relaxation function whose Fourier Transform is the constant phase impedance with $\alpha=1-\beta$. We further establish that fractional derivatives have a mechanistic basis with respect to the viscoelasticity of certain polymer systems. This mechanistic basis arises from molecular theories that take into account the complexity and the statistical nature of the system at the molecular level. Moreover, since tissues are composed of long, flexible biopolymers (21), we argue below that

these molecular theories may also apply for soft tissues. In our approach a key parameter is the exponent β which is shown to be directly related to the dynamic processes at the tissue fiber and matrix level. By exploring the statistical properties of various polymer systems we can offer a molecular basis for several salient features of the dynamic passive mechanical properties of soft tissues. We presented several candidate mechanisms involving linear (22) and branching fibers (22,23) moving in various environments which all contribute to the macroscopically observable stress-strain relationship in a similar manner: each microscopic mechanism results in a power law relaxation or constant phase impedance behavior. The proportionality factor in the relaxation function seems to depend on the fiber concentration and meshwork characteristics whereas the exponent is perhaps more specific to the mechanism most contributing to the relaxation. Moreover, there is morphological evidence that in the lung tissue there are many branching fibers with a wide distribution of their width and length (24). Thus, mechanisms such as reptation in highly polydisperse systems (25) or the relaxation of star-shaped fibers (22,23), for example, most probably also exist. This suggest a mechanistic basis for the viscoelasticity of lung tissues as represented by the fractional derivative models.

Tissue rheology and 1/f noise (7). In this study, we measured the stress relaxation induced by strain steps in parenchymal tissue strips. The relaxations followed a power law very closely over 3 decades of time, despite the quasi-static stress-strain behavior of the tissue being highly nonlinear. The corresponding tissue impedance was found to vary inversely with frequency. We note that this is highly reminiscent of a phenomenon known as 1/f noise which has been shown to occur ubiquitously throughout the natural world. It has been postulated that 1/f noise is a reflection of the complexity of the system, something like a central limit theorem for dynamic systems. We therefore developed the hypothesis that the power law relaxation of tissues follows from the fact that the lung tissue itself is composed of innumerable components which interact in an extremely rich and varied manner over many length scales. In particular, consider a model of biological tissue in which energy is dissipated among the component molecules, cells and fibers of the biological tissue in a series of cascades as the yield stresses of the contact points between the components are overcome due to stretching the tissue. Each event can alter the yield stress of the nearby contact points altering the probabilities that the nearby points themselves will yield. A number of contact points can then yield in series which

in turn leads to a cascade of these elementary events. Furthermore, if each event is conditional upon the preceding event, then the probability of the entire cascade occuring is given by the product of the individual probability of events and so should follow a log-normal distribution. Such an interdependence of events leading to a cascade is precisely the type of mechanism that has been proposed to produce self-organized criticality (26). If a mechanism like the self-organized criticality is ultimately responsible for power law relaxation functions in soft tissues, then the presence of strong nonlinearities at the elemental level is also necessary. Indeed, such contact mechanisms have been described for molecule-gel (27) and fiber-fiber (28) interactions both of which in a network can lead to stochastic cascades of events. The physiological implications for lung tissue function are that the tissues do not have resonant frequencies or some kind of a characteristic time constant. Since lung tissues must oscillate during breathing, it would be clearly problematic if it preferred to do so at a particular frequency because the frequency of breathing must vary over a frequency range of nearly two decades, or even more across species and under various conditions of rest and excercise (a mouse breaths at around 5 Hz while a resting human may breath at 0.1 Hz). Furthermore, lung tissue is intimate contact with other soft tissues such as the heart, esophagus, pleural sac, and diaphragm. If each of these tissues had their own different optimal frequencies, then there would clearly be problems of efficient operation of the entire organism, unless these optimal frequencies were carefully matched. Since there are no preferred frequencies, the problem does not arise. Thus, from a functional point of view, time/frequency scale invariance allows the organ to adapt to a wide range of conditions. Such dynamic tolerance is similar to the geometric tolerance exhibited by a fractal airway tree to genetic or environmentally induced errors in its development during growth (29).

Another corollary of the above thesis is that the precise nature of the individual components and their interactions are not so important for producing the rheological behavior of biological tissue. All that matters is that there are lots of them and they interact in a sufficiently rich manner. In other words, the macroscopic behavior is a consequence of the ensemble behavior of the components. This may have implications for the current trend in biology of examining systems at ever increasing levels of magnifications. Although cellular and molecular studies are essential for a complete understanding of an entire organ, they will not lead to an understanding on their own. There are important aspects of an entire organ's behavior or function that arises from the

connectivity of the components that can be understood only by considering the biological organ as an entire system.

WAVE PROPAGATION AND ACOUSTIC PROPERTIES OF THE AIRWAY TREE

Wave propagation in trachea, a structured viscoelastic tube (9). Propagation of waves in the airways are important in flow limitation as well as in oscillation mechanics. In 5 excised calf tracheas, we measured phase propagation velocity (c) and input impedance with open (Z_{op}) or closed end (Z_{cl}) for frequencies (f) between 16 and 1600 Hz at two axial tensions (nonstretched, T_N, and stretched, T_S; $T_S>T_N$). From 16 to 64 Hz, c slightly increased due to the viscoelastic properties of the wall tissues. Between 64 and 200 Hz, c was relatively constant and less than the free-field speed of sound (c_0=340 m/s) with values smaller at T_S (140±39 m/s) than at T_N (172±35 m/s). Above 200 Hz, c exceeded c_0 and displayed two maxima at ~300 and ~700 Hz with values of ~360 and ~550 m/s, respectively. For f>1400 Hz c approached c_0. We provide evidence that the two maxima in c were the result of the structured two-compartmental behavior of the wall tissues; i.e., the separate cartilagineous and soft tissues. A non-rigid tube model with its wall impedance composed of two series resistance, compliance, and inertance pathways in parallel simultaneously fit c, Z_{op} and Z_{cl} well and hence provide a link between these data. We also developed a relationship between volumetric wall parameters and the tracheal geometry. Based on these theoretical results, separate material properties such as viscosity and Young's modulus of both the soft tissue (~1 $cmH_2O.s$ and ~0.26 $x10^4$ cmH_2O, respectively) and the cartilage (~3.7 $cmH_2O.s$ and ~2 $x10^4$ cmH_2O, respectively) were estimated. In all five tracheas c decreased with decreasing frequency below 64 Hz. This is in contrast to previous modeling analysis by Guelke and Bunn (30) who predicted that c was independent of frequency below 100 Hz. However, their model did not account for gas viscosity nor the frequency dependence of tissue properties. Peslin and Fredberg (31) concluded from Guelke and Bunn's model prediction that the low-frequency asymptote of c is the Moens-Korteweg wave speed and directly applicable to wave speed associated flow limitation. This conclusion is based on the assumption that wall compliance determining c is independent of frequency and equal to the static compliance. Up to at least 10 Hz, however, the viscoelastic properties of lung tissues are known to cause the tissue elastance to decrease with decreasing frequency. Thus, in an attempt to characterize the frequency dependent features of c, in two tracheas we also measured the pressure ratio P_i/P_o and Z_{cl} from 8 to 128 Hz with an increased frequency resolution (4 Hz). The wall elastance was

systematically larger than the elastance derived from Z_{cl}. The reason for this is that Z_{cl} includes the influence of the compliance of the gas (C_g) contained in the trachea which is not negligible even at these low frequencies (<16 Hz). The frequency dependent decrease of the elastances above 64 Hz is due to the increasing influence of gas inertance. These results demonstrate that the hysteretic properties of the tracheal wall are similar to those of other tissues (17) and are simultaneously reflected in the wave propagation and input impedance data for frequencies below 64 Hz. Since the wall elastance is frequency dependent it is not obvious how to predict the zero-frequency or static elastance which determines the wave speed during flow limitation. These results nevertheless indicate that measures of c and Z_{op} or Z_{cl} data over the higher frequencies provide separate information about the dynamic mechanical properties of both the soft tissue and cartilage in the airway walls, whereas the lower frequency data are influenced by the average viscoleastic properties of these tissues.

Phase velocity and wave speed (13). To test the hypothesis that pressure waves in the airways propagate at the speed obtained from maximal expiratory flow we compared wave speeds (WS) associated with flow limitation and phase velocities (PV) of oscillatory pressure waves in four excised calf tracheae for transmural pressures (P_{tm}) between 0 and -10 kPa. WS was calculated from static area-P_{tm} curves using the acoustic reflection technique. PV was determined by the forced oscillation method between 16 and 1024 Hz according to the methods introduced in (9) . WS ranged from 80 to 120 m/sec slightly increasing with decreasing P_{tm}. PV was relatively constant between 60 and 160 Hz with values between 170 and 310 m/sec. With decreasing P_{tm}, PV also increased, however, at 100 Hz it was 1.5-2.5 times higher than WS at all P_{tm}. In one additional trachea we measured the low-frequency wave propagation. In order to enhance signal-to-noise ratio we used large amplitude oscillation and special pseudorandom signals developed specifically to avoid nonlinearities (4). We found that PV decreased sharply from ~200 m/sec at 7 Hz to ~130 m/sec at 0.23 Hz approaching WS. We suggest that PV is larger than WS due to the nonlinear viscoelastic nature of the tracheal wall, that is because of the differences in airway wall tissue mechanics during small-amplitude oscillations at high frequencies and large amplitude unidirectional wall motion such as a forced expiration. These results may provide an additional explanation why expiratory flow during rapid breathing or expiratory transients such as coughing can exceed the maximum expiratory

flow-volume envelope.

Serial distribution of airway mechanical properties: effects of histamine (10), and comparison with computed tomography (11). Indirect measures of airway diameter such as respiratory system input impedance (Zin) have been widely used to infer or quantify bronchoconstriction or bronchodilation. One such measure, Zin above 100 Hz has been shown to primarily influenced by airway diameters and airway walls but not by lung and chest wall tissues. We measured Zin from 8 to 2048 Hz in five dogs (anesthetized, tracheotomized, vagotomized and mechanically ventilated) during 80 s of apnea after a bolus of intravenous injection of saline or histamine (5 mg). In the control case, three antiresonances in Zin were found in four dogs, whereas only two in one dog. The magnitude and frequency of these antiresonances were significantly altered after bronchoconstriction. To interpret Zin, we developed a model incorporating detailed airway geometry with asymmetrical branching, and nonrigid airway walls based on our previous wave propagation model of the trachea (9). The model fit both the control and the challenged data reasonably and predicted the serial distribution of bronchoconstriction consistent with known effects of histamine, that is the diameters of the most peripheral airways were reduced far more (~30%) of their control values than tracheal diameters which were not significantly altered (<1%). The model predicted absolute tracheal diameters correlated well with direct measures. Control estimates of soft tissue viscosity (0.163±0.042 kPa.s) and Young's modulus (40.6±12.5 kPa) compared closely with values in the literature. These results indicated that bronchoconstriction induced by histamine results in significant changes in the acoustic features of the airway tree which can be easily and noninvasively measured at the airway opening. Additionally, interpretation of such acoustic features by our anatomically detailed model provides physiological parameters relevant to the serial distribution of airway diameters and airway wall properties.

In order to compare the serial distribution of airway diameters predicted by our modeling approach with direct measures, changes in airway diameters were assessed both using our acoustic method as well as high resolution computed tomography in one isolated dog lung. Using the computed tomography, the observed changes in airway diameters between lung volumes of total lung capacity and functional residual capacity were quantitatively consistent with those predicted

by our model from Zin down to diameters of 2 mm which is the resolution of the computed tomography. We conclude that since our method seems reasonably accurate and relies on measurements that can be made in a fraction of a second and nonivasively, it may prove useful in quantifying and locating bronchoconstriction in diseases such as asthma, cystic fibrosis and bronchitis as well as the bronchodilation resulting from therapeutic modalities used to treat these diseases.

Shear wave propagation speed in gas-liquid foam (12). Foams are concentrated gas-liquid dispersions which can be viewed as elastic solids if the volume fraction of the dispersed phase exceeds 0.74. Elastic waves can be propagated in these foams. Longitudinal waves have been measured, but very little is known about shear wave propagation in foams. We generated pure harmonic shear waves in gas-liquid foams inside a cylindrical container using a straw that was attached to a loudspeaker. The motion of the straw generated radially propagating stress waves in the foam. We measured their phase-frequency relationship which exhibited approximately linear dependence. The shear wave speed was calculated from these relationships using a mathematical model which assumed that the foam was an isotropic, ideally elastic continuum, and the boundary conditions were radially symmetric and axially infinite. The relationship between shear wavespeed and shear modulus was used to estimate the shear modulus of the foam. The overpressure was also measured in the foam and the ratio of the shear modulus and the overpressure was found to be 0.76 which is about two to three times higher than the values reported in the literature for static measurements. We suggested that this discrepancy was due to the dynamic character of shear wave propagation in the foam at the level of air-liquid interface. These results may have implications to shear wave propagation in parenchymal tissues.

AVALANCHES IN AIRWAY OPENINGS

Avalanches and power law behavior in lung inflation (14). Closing and opening phenomena are abundant in physiological tree structures; examples include the respiratory tree (32) or different parts of the circulatory system (33). The significance of closing and opening is, for example, that if airways do not open for a large portion of inspiration then regional hypoventilation and hence impaired gas exchange occurs. Also, vessel closure leads to a cessation of blood flow with impaired blood supply to the periphery. Furthermore, the high value of critical opening pressure may be responsible for myocardial injury associated with ischemic cardiac arrest during open heart surgery. These problems are especially important with advancing age or in pulmonary/circulatory disease. Previous work on closure or opening were invariably limited to studying the determinants of these phenomena in single airways or vessels. In this study, we used an experimental technique (34,35) that is sensitive to very small regional volume changes in the lung. Via novel modeling and statistical analysis of the results, we found that the global behavior of lung inflation may be more sensitive to the interactions among the openings of airways than to the specific mechanisms that govern the openings of individual airways. In particular, the data have conveyed convincing evidence that 1) airway opening is a discontinuous process associated with overcoming a hierarchy of threshold opening pressures; 2) there is a wide range of opening threshold pressures in the lung; 3) airways do not open individually, but in avalanches: opening of one airway may initiate the opening of many others; 4) statistics made on quantities related to lung inflation, such as the airflow resistance of small terminal airway, revealed that the sequence of openings is not a random process: it is governed by power law distributions and possibly by long-range correlations. We interpreted the power law distributions as arising from the avalanches triggered by overcoming the threshold values that are distributed in the tree structure. Thus, these power law distributions govern the recruitment of terminal airspaces in lung inflation. These are novel elements in the respiratory tree, and suggest a new fundamental role for the set of opening threshold pressures in the airways. Furthermore, a power law distribution in a process usually involves time and/or spatial correlations extending over a significant portion of the data, i.e., long-range correlations. Long-range correlations can act as organizing principles in complex nonlinear systems and have been found in several biological phenomena including cardiac beat-to-beat intervals (36,37) or the nucleotide sequences

along DNA chains (38). These concepts are very general and may find a very broad application in biology. Indeed, the avalanche process of airway opening is the first biological process explicitly demonstrating similarity to the self-organized criticality that has been proposed as the common underlying mechanism for 1/f noise and fractals (26). These ideas may also provide substantial new insight into a variety of physiological phenomena encountered in the respiratory and circulatory trees (e.g., pressure-volume curves, phase IV slope, ventilation distribution or blood supply to the periphery).

A statistical mechnical approach to airway opening (15). In this theoretical follow up work of our initial discovery of avalanches in lung inflation (14), we set out to examine the origins of power law distributions in airway opening. We developed a statistical mechanical model of lung inflation to investigate the distribution of volumes opened by the first avalanches. We showed that the dynamics of lung inflation can be mapped to a percolation problem in a tree structure, or Cayley tree, with the inflated lung volume corresponding to a percolation cluster. This exact mapping enabled us to analytically derive the volume distribution of the first avalanches. Two cluster size definitions were examined. In the first definition, the size of a cluster was the number of opened alveoli by the avalanche. The physiological motivation is that gas exchange only takes place in the alveoli which are in communication with the trachea. In the second definition, the size of an avalanche was taken as the number of airways that become connected to the trachea during inflation. The physiological rationale for this is that at low lung volumes there is always some trapped air, that is air that is not in communication with the top of the tree remains trapped behind airways that are closed. Therefore it may not be necessary that an avalanche reach the bottom of the tree for it to connect alveoli with the trachea. The conclusions from this study are very general: 1) the treelike structure of the airways is sufficient to explain the existence of power law distributions; 2) the results provide indirect evidence that the airway reopening threshold pressures in the periphery of the lung are distributed almost uniformly; and 3) higher pressures for at least short periods of inspiration might be necessary to open up larger atelectatic alveolar areas which may find important applications in the design of appropriate waveforms for artificial ventilation of patients who suffer from substantial airway closure and alveolar collapse.

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Publications relevant to the theses:

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