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MECHANICS OF THE LUNG IN THE 20TH CENTURY

Wayne Mitzner, Ph.D.

The Johns Hopkins Bloomberg School of Public Health, Baltimore MD

Abstract

Major advances in respiratory mechanics occurred primarily in the latter half of the 20th century, and this is when much of our current understanding was secured. The earliest and ancient investigations involving respiratory physiology and mechanics were often done in conjunction with other scientific activities and often lacked the ability to make quantitative measurements. This situation changed rapidly in the 20th century, and this relatively recent history of lung mechanics has been greatly influenced by critical technological advances and applications, which have made quantitative experimental testing of ideas possible. From the spirometer of Hutchinson, to the pneumotachograph of Fleisch, to the measurement of esophageal pressure, to the use of the Wilhelmy balance by Clements, to the unassuming strain gauges for measuring pressure and rapid paper and electronic chart recorders, these enabling devices have generated numerous quantitative experimental studies with greatly increased physiologic understanding and validation of mechanistic theories of lung function in health and disease.

A. Introduction

The history of respiratory mechanics covers an enormous area, and much of the early and ancient history with additional source material is covered elsewhere (180). In this chapter, we will consider more recent aspects of respiratory mechanics as they involve quantitative, physical, and physiological principles and analyses in the study of the lungs. Interest and work associated with respiratory mechanics prior to the 20th century generally arose as part of a broader emphasis either on a clinical disease or general physiological principles. While this emphasis still provides a strong motivation for the more recent studies of respiratory mechanics, in the modern era, the primary objective of many studies is often the mechanical properties themselves. New technical advances, funding from government and private agencies, and a general increase in the numbers of professional scientists, led to a tremendous increase in studies of respiratory mechanics in the latter half of the 20th century. Although there were dozens of important and influential investigators in this period, one individual stands out from this group. That person is Jere Mead (Figure 1), who spent his career at the Harvard School of Public Health writing seminal papers and encouraging and training countless numbers of students, fellows, and faculty. His legacy from this period is long and deep, and although he died in the summer of 2009, his influence will be felt for decades. As a footnote to this legacy, in February of this year (2011), one of Dr. Mead's

fellows, Peter Macklem, suddenly passed away. Dr. Macklem (Figure 2) was an energetic and enthusiastic disciple of Mead, who spent much of his career championing the importance of respiratory mechanics, particularly in human subjects. In fact, Dr. Macklem was one of the reviewers of this article, and the author gratefully acknowledges his critical review and comments. His knowledge of events during most of the years covered by this document led to many corrections and revisions that greatly improved the quality and accuracy of the manuscript.

Lung mechanics can be divided into two parts. Statics includes the forces acting on the lung affecting volumes and elastic behavior. Dynamics considers the forces moving air, together with related topics such as flow patterns and resistance. Recently, and notably in this series in *Comprehensive Physiology*, the term mechanics has been extended to cellular and subcellular phenomena, but this area will not be discussed in this chapter on macroscopic lung mechanics.

Here we will of necessity limit the topics to a few major ones, which have had a great influence on our understanding of lung health and disease. These include the following: lung volumes, lung tissue elasticity, lung surface forces, lung viscous forces, airway resistance, mechanical coupling between the parenchyma and blood vessels and airways, lung impedance, and forced expiration.

A. Static (quasistatic) mechanical properties

1) Elasticity and pressure-volume (PV) curves

In the literature there is no convention on the terminology for the elastic properties of the lung in terms of the time course over which they are measured. Measurements vary over a frequency range over 4 orders of magnitude, from pressure-volume maneuvers as slow as hours (0.01 Hz) to oscillation mechanics at frequencies up to 100 Hz. A number of investigators often refer to measurements made a fixed (arbitrary) time after step changes in volume as static measurements, but in fact with any change in volume, the pressure never completely stabilizes, although the changes become increasingly smaller. Hence, other investigators refer to these very slow changes as quasistatic, and this is the term we will use here. In general, measurements done at a time scale substantially less than a normal respiratory breathing frequency will be considered quasistatic, and those at or above normal breathing frequency will be considered dynamic.

i. Measurement of lung volumes and pressure-volume (PV) curves—Although measurement of a post-mortem pressure-volume curve was done as early as 1852 by Hutchinson (66), lung mechanics was not a major objective. One of the earliest detailed considerations of quasistatic elastic properties of the lung is the now classic study of von Neergaard (122). In this elegant work he designed studies to investigate the importance of surface tension in the air-liquid interface. The importance of surface forces in lung elasticity had already been mentioned by Rohrer (150), but he himself did nothing to investigate this further. That was left for von Neergaard, who did this by comparing expiratory pressure-volume curves of air-filled and liquid-filled lungs, arguing that the only essential difference between the two was the abolishment of the air-liquid surface tension in the liquid-filled

lung. He found that the liquid-filled lung had a greater volume for the same distending pressure than when it was air-filled, and rightly attributed the difference to the reduction of surface tension (Figure 3). A striking feature of these experiments is how he was able to degas the lung with a vacuum so that it could be filled with liquid without air contamination. Despite this novel groundbreaking experimental design, von Neergaard unfortunately did not have the necessary techniques to accurately measure surface tension in lung extracts, and many of his estimates of surface tension in alveoli were much too high. For reasons not entirely clear, this pioneering set of experiments was essentially ignored and soon forgotten, until the discovery of the low alveolar surface tension of alveolar foam 26 years later (133). A captivating discussion of von Neergaard's watershed paper can be found in the recollection by John Clements (22).

There is another interesting anecdote related to the discovery of surfactant. Although Macklin had suggested the existence of surfactant in 1954, even suggesting its origins in what we now refer to as alveolar type II cells (94), this work was not yet widely known. Thus, in the same year, Ted Radford published a clever analysis whereby he was able to estimate the surface area of the alveoli by using histological estimates of alveolar size and estimated surface tension (146). In this analysis, the values he arrived at for surface area were about an order of magnitude lower than the surface area calculated morphometrically. Radford stated that either the alveolar diameters provided by the anatomists were artifactually too low or the estimated surface tension at the alveolar wall was much lower than what was expected based on measurements by von Neergaard and those of blood serum (i.e., on the order of 50 dynes/cm). Radford felt he had to make a decision on where the error arose, and he ended up choosing the wrong answer. He decided that the processing shrinkage and distortion led to gross errors in the estimation of alveolar size by the anatomists. One year later the English physical chemist, Richard Pattle, published his classic paper documenting the fact that extracts of lung tissue had properties that could greatly lower surface tension (133). In this brief *Nature* paper, Pattle states, "Means of keeping the surface tension low must therefore be part of the design of the lung. It is thus evident that the alveoli of the lung are lined with an insoluble protein layer that can abolish the tension of the alveolar surface." This initial discovery of lung surfactant was followed by a number of further studies by Pattle (132, 134) and by Clements and associates (23–25). By isolating lung extracts and then measuring the surface tension with a Wilhelmy balance during surface expansion and compression, Clements was the first to show that surface tension could be reduced to very low values during compression, and that there was considerable hysteresis of the surface tension vs. area graph (23). Radford continued to work on this problem and published curves (shown in Figure 4) from experiments in cat lungs (145), which have been and continue to be widely used in many textbooks to help explain the impact of alveolar surface tension on lung mechanics. This figure shows results from a single lung, which demonstrate the basic concepts. To anyone who has tried to measure such curves with saline and air inflations and deflations in the same lung, these are remarkably clear results. Most commonly there is some tissue hysteresis in the saline curves, and these do not flatten at the same maximal lung volume. Furthermore, most of the hysteresis in this figure in the air filled lung results from the high opening pressures of collapsed airways, and has little to do with the alveolar surface-area hysteresis as measured by Clements.

The role of airway closure in healthy lungs has been debated for some time. Determination of residual volume (RV) in experimental animals is done by making transpulmonary pressure negative, which collapses airways, as confirmed by a flat pressure-volume (PV) slope. In humans, it is also likely that there is airway closure at RV, since the PV hysteresis increases substantially, when done starting from RV. Several experimental studies in humans have provided good evidence of airway closure at volumes below FRC (18, 35). The functional effect of airway closure was also assessed in humans by measuring the “closing volume,” an index initially derived from the tail of a washout of tracer gas (30, 81), and later from the tail of the nitrogen washout curve (29), a procedure first described in 1949 by Ward Fowler (40). This index was used for the early detection of small airways disease (17, 99), since it was assumed that the sudden change in slope represented the start of airway closure. While this would be a very useful index, the measurement never became well established, partly due to the fact that the method requires subject training and partly due to limited sensitivity of the method for diagnostic purposes.

Regarding the potential importance of lung surfactant in the PV hysteresis, the basic understanding after its discovery arose from models of alveoli as tiny bubbles. This oversimplified model clearly ignored the fact that the surface forces are supported by an underlying tissue structure, which has both elasticity and structural integrity (see discussion of interdependence below). This situation was analyzed in the 1980s by Ted Wilson and colleagues, who showed how the surface tension should function within the structure of an alveolar duct and moreover, how surface forces in an air-filled lung would impact on the tissue elasticity (184, 185). Figure 5 shows the model they used to explain how surface forces would act in a lung with flat alveolar walls that meet at sharp angles. While the effect of zero surface recoil across the flat walls is largely offset by the greatly increased surface tension recoil in the corners where walls meet, the high recoil in the corners is sufficient to cause tissue distortion and increased tissue recoil. Although the importance of the tissue structure in promoting intrinsic lung stability was emphasized by several investigators (45, 49), this understanding was at odds with common observations of localized atelectasis in intact lungs. This controversy regarding alveolar stability in a heterogeneous lung wasn't clarified until the work by Stamenovic and Wilson (163) was published in 1992. This paper was elegant in its simplicity, and it clearly defined the conditions where local atelectasis could occur, even in a lung with constant surface tension.

Low surface tension on the alveolar surface is also important in preventing water from flooding the alveoli, but this was not emphasized in the years following its discovery and application in premature lungs. Although the fact that surface tension might limit the expansion of neonatal lungs was already anticipated by von Neergaard (122) and others (182), the potential therapeutic use of exogenous surfactants clinically was not immediately considered. However in 1947, Gruenwald studied neonatal lungs and observed that surface tension is a major factor limiting aeration of newborn lungs (52). He went on to conclude that, “addition of surface active substances to the air or oxygen which is being spontaneously breathed or introduced by a respirator might aid in relieving the initial atelectasis of newborn infants.” But it wasn't until there was a better understanding of the development of the surfactant system, that a practical approach of altering the mechanics involved in lung inflation with exogenous substances was seriously considered (4). This

application of a basic understanding of lung mechanical properties to effective therapeutic treatment represents an enviable model for modern day translational research.

After the recognition that a surface-active material was secreted in the lung, there was an immediate search for just what this material was comprised of. The early educated guesses in the 1950s were that it was a mucopolysaccharide or mucoprotein film (23, 94, 133). However, in the early 1960s the lipoprotein composition of surfactant was clearly demonstrated by several independent investigations (12, 15, 73). In 1964, its dipalmitoyl lecithin composition was confirmed when this compound was shown to exist in lung extracts. The source of this surfactant was first suggested by Macklin as what is now called the alveolar type II cell (94). The structural packaging of surfactant in lamellar bodies was also identified at about the same time. Although lamellar structures in alveolar epithelial cells were already identified in 1954 (86), it was not until 1962 that these structures were proposed as the source of alveolar surfactant (16). These authors also recognized that this surfactant system developed relatively late in gestation, and thus if a premature birth was prior to its development, there would be respiratory distress. This recognition of surfactant maturation in addition to its ability to affect the mechanical stability of lungs represents perhaps the major accomplishment of the lung mechanics field, as it has directly led to a number of efforts that have saved the lives of thousands of premature babies. These efforts initially involved methods to accelerate maturation of the surfactant system with glucocorticoids, and later to the administration of exogenous natural or artificial surfactants.

ii. Analysis of PV curves—Measurement of quasistatic PV curves has been carried out since the initial studies of von Neergaard and Radford by too many investigators to list here. Although these PV curves continue to be used in experimental studies, the analysis of such highly nonlinear curves has never been standardized. In the early usage, the hysteresis area (often normalized to the area of the rectangle which encompasses the loop) was used as an index of the presence of surfactant (7), but this never became very common. The main reasons were that to measure the area, one needed a closed loop (which was not always present), and that even if the area could be measured, its magnitude was highly dependent on the starting and ending pressures (or volumes) as well as the rate of cycling (7). Today, there are few basic researchers who even report the inflation limbs in publications, although in the ARDS (Acute Respiratory Distress Syndrome) clinical literature, the shape of the inflation limb can play a key role in setting the level of PEEP (Positive End Expiratory Pressure) on mechanical ventilators. There have been attempts to standardize quantification of the shape of the deflation limbs, since with the development of the lung and surfactant system, the deflation limb progresses from a nearly linear curve to one showing the characteristic nonlinearity seen in all adult lungs. One simple way to do this was to measure the percent deflation remaining at a given pressure, typically 10 or 15 cmH₂O (called the deflation stability and referred to as the %V10, for example) (37, 71, 90). With maturation of the lung this %V10 was shown to increase, and with a loss of surfactant, it would decrease. Other investigators tried to fit part of both the inflation and deflation curves with a single exponential (153, 157), and such a fit provides a coefficient and a rate constant. Interestingly, Salazar and Knowles favored what they called a variable, designated *h*, which was defined as the pressure at 50% inflation, and this is a shape parameter that is clearly

related to the %V10. There have been other metrics from PV curves fit with more complex curves (118, 124, 130, 173), but since all of these are simply empirical descriptors of the shape of the curve, they provide little insight into the structure or the pathology of the lung. While there is clearly a structural basis for the curve shape, determining the underlying factors has not been done. One recent example from the mouse relates to its double humped inflation limb (162). Such behavior has also been occasionally observed in humans (155), and it would be a significant advance if it were possible to determine the structural basis of this double hump. However, this has not been done here (or elsewhere), and thus at the present time, insights gained from the shape of the PV curve remain limited.

Pressure-volume curves are often used to indicate total lung capacity (TLC), analogous to that in human subjects measured at the end of maximal inspiration. Many investigators measure the flat part of the deflation curve at high pressures, and use this as the index of a maximal lung volume. However, this metric is fraught with several potential problems, the first being that the initial part of the deflation limb of PV curves always appears flat, no matter what maximal inflation pressure is used (82, 162). Reasons for this unusual mechanical behavior have not been adequately explained, but its existence makes the measurement of TLC in animal models entirely dependent on the pressure used at the end of inflation limb. This pressure has varied between 20 and 40 cmH₂O in different investigations in different labs and among different species. Although most inflation limbs tend to flatten at higher pressures, they don't normally become truly flat. The mouse lung is particularly unusual in this regard, since the PV curve often doesn't even show any bending toward the pressure axis until pressure exceeds 30 cmH₂O, and continues to steadily enlarge until it ruptures at pressures above 80 cmH₂O (162). The bat lung shows a very similar phenomenon at least up to 60 cmH₂O (82). Nevertheless, even using inflation to a fixed pressure in an animal model to determine the TLC, still does not make it analogous to TLC in humans, since this latter measurement is entirely effort dependent, and not done to any specific inflation pressure. In fact, pressures at TLC in humans ($\approx$ 25 cmH₂O) (26, 85) are somewhat less than what is commonly used in experimental animals. This suggests that TLC in humans could be increased with respiratory muscle training that would further decrease the pleural pressure. That the lung itself in humans does not reach a limit at TLC (i.e., at such relatively low transpulmonary pressures) is supported by observations that divers using glossopharyngeal insufflation can achieve substantial increases in lung volume (85).

2). Mechanical interdependence

One of the challenging conceptual issues related to lung mechanics that students face is how the physical linkages between different components of the respiratory system interact. In this section we will consider first the mechanical interactions between the lung and chest wall, and then the mechanical interactions between structures within the lung parenchyma.

i. Lung-chest wall interactions—The notion that the lung and chest wall are mechanically linked was first described by Leonardo da Vinci (115, 180). Leonardo posed a number of relevant and prescient questions about how the respiratory muscles might interact with the lung, but he did not do any quantitative analysis (115). This complex interaction between the chest and abdominal cavities was discussed in detail in 1964 by Agostoni and

Mead (3). Rohrer was the first to publish quantitative pressure-volume curves of the human lung in the intact thorax, as well as define the pressures on maximal inspiration and expiration (149). An identical graph was generated by Rahn et al, two decades later (147), where the quantitative details of this interaction were pursued in greater depth. Rahn et al went on to amplify another observation by Rohrer (149) showing how the balance of forces between the lung and relaxed chest wall were interdependent, and how this mechanical balance of forces led to the determination of FRC (functional residual capacity). Figure 6, reproduced from their paper, continues to be used to teach physiology and medical students to this day. It is interesting that, although Rahn et al did acknowledge the earlier analysis and findings by Rohrer, they noted that this work was discovered *after* they had completed their study. However, in each of the three places where they mention Rohrer's earlier work, they emphasize that Rohrer's experimental work was done in only a single subject. The irony of this situation is that Rohrer has a comment in his paper, where he states that the elastic pressure and volume relations of the respiratory organs had “previously been studied by Jaquet (70) and Bernoulli (11), a fact I found out about only after I had developed my experimental method.” There is a lesson in this for students as well as senior faculty, about how easy it is to make great discoveries if one fails to read the literature.

ii. Parenchymal interdependence—When the lung is inflated the pressure in the alveoli must exceed that outside the visceral pleura. However, this pressure difference is applied to all alveoli, even those completely surrounded by other alveoli. Thus the question of what forces exist to inflate internal structures of the lung (including airways and blood vessels) is not intuitively obvious. Rohrer was perhaps the first to address this issue in his considerations of how airway resistance changed with lung volume (148). He states, “... since the expanding force in the lung...expands uniformly spreads uniformly in all directions, the bronchi, being everywhere coalescent with the parenchyma, also undergo a corresponding radial pull, so that if we were dealing with homogeneous elastic pipes, we would see a uniform change in length and diameter.” This issue was addressed again in 1961 by a group led by Sol Permutt, in two papers that were concerned with how the blood vessels would be affected when the lung was inflated (64, 140). With a clever set of experiments to separate large and small vessel distensibility, they arrived at a novel explanation that involved two vascular compartments in the lung ... one compressed (the alveolar compartment) and the other expanded (the extra-alveolar compartment) by lung inflation. The expanded compartment consists of the larger pulmonary arteries and veins that are surrounded by lung parenchyma and subjected to the same forces as parenchyma (i.e., pleural pressure), and the compressed compartment consists of vessels in the alveolar septum and subjected to alveolar pressure. In 1969, an article by Mead et al (104), put this mechanism on a more theoretical foundation. In this paper, it was shown how the effective pressure around regions surrounded by parenchyma related to the pressure outside the visceral pleura, i.e., the pleural pressure. This pressure (later termed P_x) could be less than, equal to, or greater than the pleural pressure, depending on the relative volumes of the region and the “hole” in the parenchyma where that region fits. With several clever simplifying assumptions, they were able to obtain quantitative estimates on how large this P_x might be around bronchi, blood vessels, and regions of parenchyma. This important paper provided a mathematical and intuitive basis for what had been utilized by Rohrer

(149) and implicitly assumed by nearly all investigators interested in lung mechanics. In 1972, Wilson established a more solid theoretical basis for this phenomenon, by putting it in the context of a continuum mechanics analysis (183). It considered the lung as an elastic matrix and used this theoretical approach to provide quantitative estimates of the Young and shear moduli of this elastic continuum. This model was later tested and evaluated in a series of studies by Lai-Fook and associates, who examined the relationship between the parenchyma and the airways and blood vessels embedded within (76, 78, 79). These studies showed that the lung parenchyma was easily distorted, with a parenchymal shear modulus on the order of $\approx 0.7 \times$ transpulmonary pressure (P_{tp}). That this is substantially less than the bulk modulus ($\approx 7 \times P_{tp}$) indicates that it is much easier to distort that lung than it is to inflate it. The quantitative link to transpulmonary pressure was later confirmed by an independent approach (161). The net intuitive result of this concept is that “interdependence” resulting from parenchymal attachments alters forces in the lung that promotes homogeneous inflation. Whenever there are situations that lead to heterogeneities, additional forces develop that tend to promote homogeneity. These homogenizing forces play a role not only on regions of parenchyma, but also on the tubular vessels and airways. Although these structures clearly have elastic moduli different from the lung parenchyma, the design of the normal lung is such that the pressure surrounding the intraparenchymal airways is within 1 cmH₂O of the pleural pressure (78). In other words, although the airways are clearly affected by the state of lung inflation, the tubular holes in the parenchyma are designed in such a way that airway size in a healthy lung would be the same if the parenchyma surrounding them were dissected away. This also suggests that the effect of a deep inspiration on the airways is almost entirely a function of the direct effect of that inflation on the airways themselves and the any change in pleural pressure after the maneuver. In situations where there is airway smooth muscle contraction, that alters the elastic recoil of the parenchyma, the effective pressure surrounding the airways can differ from pleural pressure. In a pathologic situation such as emphysema, the loss of alveolar walls results in a loss of elastic recoil, and this smaller (less negative) pleural pressure leads to a less distended airway at FRC, in addition to it being less affected by lung inflation (117).

3) Mechanical effects of gravity

Gravity has an important effect on lung mechanics. Given that lung tissue has such a low shear modulus, the lung will distort under its own weight. This effect will be trivial in a horizontal mouse lung with a vertical gradient of less than 2 cm, but will be substantial in larger lungs such as in humans. A simple analogy is the toy coil spring (known as Slinky), which when held at the top and bottom, shows over-expansion of the coil spacing at the top and relative compression at the bottom.

The result is that in the upright human lung, the lung is more expanded at the apex (that is, the alveoli are larger) and relatively compressed at the base. The differences of alveolar size have been shown histologically in head-up dogs (48). The regional differences of lung expansion have been studied by measuring the regional distribution of inhaled radioactive xenon for different inspired volumes and different pre-inspiratory volumes (14, 110). Figure

7 summarizes the differences in regional expansion of the lung. The weight of the lung also causes regional differences in intrapleural and esophageal pressure (102, 111).

There has been a good bit of discussion in the literature about the nature of this pleural pressure gradient. One fascinating concept was that there was a difference between the pressure in the pleural liquid and the effective surface pressure that functioned to inflate the lung (2, 3, 119, 139). This conceptual difference was used to explain observations that the measured effective pleural pressure down the lung only increased about 0.2 cmH₂O for each cm descent (75, 110). However, if the pleural liquid forms a continuous column, then this pressure should decrease 1 cmH₂O for each cm of descent. One explanation of this was that there were points of contact between the pleural membranes, and that the fluid column was not continuous over the lung surface, and limited to anfractuositities between points of contact. Details of the mechanics of the pleural space are presented elsewhere, but a clever solution that resolves this apparent difference between pleural liquid and surface pressures was presented by Lai-Fook and colleagues (77). This explanation was based on the fact that pleural liquid is not in hydrostatic equilibrium, and that there was always continuous viscous flow occurring in the pleural space. This flow creates a pressure gradient that gives rise to the vertical gradient in pleural liquid pressure being much less than 1 cmH₂O/cm, and effectively makes the average liquid and surface pressures the same.

Some investigators have argued that the regional differences of lung expansion are caused by the differences of intrapleural pressure, but a more correct interpretation is that they are both the result of gravity-induced distortion of the lung. A finite element analysis of the lung in the chest based on the assumption that there are no residual shear forces at the pleural surface can predict both the differences in regional expansion and differences in intrapleural pressure (181).

As expected, exposing the lung to increased acceleration, for example, on a centrifuge where the acceleration vector goes from head to toe, greatly increases the regional differences of expansion. This has been demonstrated histologically in dogs (47). In humans exposed to 3 G_z, essentially all the inspired gas goes to the upper third of the lung because of airway closure of the remaining lung, and all the blood flow goes to the lower third of the lung. The result is almost no effective gas exchange (46). At the other extreme, the distribution of ventilation can become quite uniform, when the acceleration effects are extrapolated to zero gravity (14).

This extrapolation has been confirmed in the absence of gravity as occurs in space flight (microgravity), which alters the distribution of ventilation in a manner consistent with the abolition of gravity-induced distortion of the lung (54, 144). No direct measurements of lung expansion have yet been possible in microgravity although it is known that in space flight there are changes in the shape of the chest wall (109).

B. Dynamic mechanical properties

1). Dynamic compliance

The dynamic compliance (C_{dyn}) of the lung is conventionally defined as the ratio of the tidal volume to the change in transpulmonary pressure that caused that tidal volume. It is normally made at a resting rate during a tidal breath, although as will be discussed below, there has been considerable interest in the frequency dependence of this variable. As with most other respiratory mechanics variables, the earliest consideration related to what we now call dynamic compliance begins with Rohrer. Although Rohrer did not make any measurements of C_{dyn} , as already noted, he did provide the theoretical framework for later investigations of the dynamics of respiratory forces (150). The actual measurements of dynamic compliance or elasticity were first reported by von Neergaard and Wirz (121). These students of Rohrer made measurements of transpulmonary pressure in human subjects, calculated the modulus of elasticity, and then used the results from only two subjects to conclude that elasticity was decreased (i.e., increased C_{dyn}) in emphysema. A number of other early studies also made measurements of C_{dyn} in human subjects, although the reported values show wide variation (21, 125, 128, 164). This variation resulted from a number of different reasons, but measurement of pleural pressure with a pleural puncture was a primary source, since there were nontrivial issues with leaks, distortion, and limited access in humans.

With the utilization by Mead and Whittenberger (107) of an esophageal balloon, much of the variability associated with pleural punctures was minimized. The first use of esophageal pressure to estimate the dynamic pressures in the pleural space surrounding the lung in humans was in 1878 by Luciani (88), who employed balloon-tip catheters devised by Marey for use in his extensive cardiovascular studies (95). Although a water-filled balloon-tip catheter was first used in 1847 by Ludwig to directly measure pressure in the pleural space (as cited by Wirz (186)), the application of esophageal pressure in lung research was not generally appreciated or routinely used until the 1950s. Part of the reason for this relates to the belief that such a measurement would have a considerable error from the properties of the esophageal tissue. In his classic paper on measurement of pleural pressure dynamics (186), Wirz dismisses such esophageal pressure measurements as previously done by Luciani stating, "since the premises are incorrect, there is no incentive to improve the method or extend the problem." A thorough investigation of such a device, however, was done in 1949 by H. Buytendijk, a PhD candidate in Holland, but as this thesis (19) was neither available nor translated into English until several years later, the method was rediscovered in 1952 (31, 44). Buytendijk's dissertation is still not easily accessible, but his findings were discussed by Fry et al (44). All of these works concluded that an esophageal balloon was a good method to estimate pleural pressure. The use of an air-filled balloon instead of a fluid-filled catheter in the esophagus turned out to be critically important, since it was shown a few years later that there could be serious errors imposed with by the weight of the liquid filling the catheter (139). It is important to emphasize the critically important role of esophageal pressure measurement. Without this reliable estimate of pleural pressure, little progress would have been made in the field of lung mechanics in humans. Even so, the measurement of C_{dyn} by itself did not become widespread until the concept was developed

that the frequency dependence of compliance might possibly be a useful marker for lung disease. This will be discussed below in the context of impedance, which is by definition a metric of frequency dependence.

2) Resistive properties

i. Airway resistance—Of all the measurements of lung mechanics, airway resistance is perhaps the one most easily related to lung structure. If one knows the resistance of a cylindrical tube, the material flowing through it, and the nature of the flow, then one knows the diameter of the tube. Although an airway is not perfectly cylindrical, and the whole tree consists of a complex system of different sized branches with varying flows, there is still the intellectual and intuitive rationale that if the resistance is increased a certain degree, the average degree of airway narrowing can be approximated. Even with these assumptions regarding the resistance in an intact lung, no other common metric of lung mechanical properties comes close to that of airway resistance in its ability to relate structure to function. The problem with resistance, however, is that it is not easy to measure, since in order to measure any resistance one needs to know the pressure at both ends of the tubes. Because direct measurement of alveolar is not possible, there have been a number of methods developed in the past century that have enabled indirect estimates of alveolar pressure, with concomitant measurement of resistance.

The first thorough and detailed investigation of lung and airway resistance was done by Rohrer (148). His interest in this work was to determine the resistance to gas flow in the respiratory tract. To this end, he recognized the importance of the airway tree structure, and developed his own approach to make quantitative measurements of airway diameter and length in each branch generation. With this structural information, he then used Poiseuille's law to calculate the total airway resistance, and these calculated values were then compared to measurements of lung resistance in intact lungs. Remarkably, he experimentally justified his use of Poiseuille's law with experiments with smoke in a long 1 cm diameter glass tube that showed persistence of laminar flow at velocities up to 2 m/s. The method Rohrer used to calculate the alveolar pressure was to subtract the elastic pressure from the transpulmonary pressure, essentially the same approach used 40 years later by Mead and Whittenberger (107). In 1927 von Neergaard and Wirz used creative methods to determine airway resistance in human subjects (120). One important one involved the use of a rapid occlusion on inspiration or expiration. They assumed the rapid equilibration value represented the alveolar pressure during flow, and from a simultaneous tracing of flow from a pneumotach, they could calculate resistance as well as fit the data to the resistance equation presented by Rohrer (148). They did the rapid occlusion manually, and this limited the accuracy of the measurement, although they did suggest using a camera shutter for this purpose if air leaks in such a device could be minimized.

An improved method of measuring alveolar pressure with the interrupter method was presented by Vuilleumier (174) in 1944, and this method was rediscovered a few years later by Otis and Proctor in 1948 (127). Although the interrupter method provides a good estimate of alveolar pressure, and has remained in use to the present day in human studies, especially in children (1, 53, 84), it is still not routinely used. An alternate approach to measure

resistance and alveolar pressure was developed by DuBois in 1956 (32), and has become something of a gold standard for airway resistance measurements in humans. The method uses a body plethysmograph to measure lung volumes, and involves a brief panting maneuver to minimize the effects of heating and humidification in the lungs. In addition to providing a direct measure of airway resistance, it also provides absolute lung volumes. It is worth noting that the DuBois method is the only direct way of measuring resistance of the airways, and it is an approach that cannot be done in animal models. Rather, all measurements of resistance in animal models employ indirect methods to estimate the resistance, and most depend on mathematical or mechanical models of the lung structure.

If one uses a simple model of the lungs, consisting of the dynamic changes in transpulmonary pressure being the sum of elastic and resistive pressures as originally presented by Rohrer (149), then it is possible to assess the resistive fraction by solving two simultaneous equations at different points in the respiratory cycle. This was done graphically by Mead and Whittenberger in 1953 (107), and the method was found useful in many subsequent studies in animal models as well as in humans. The same authors validated the method in a subsequent paper (106) by comparing it to the interrupter technique. They concluded that the interrupter method overestimated airway resistance, and that the magnitude of the error in values of resistance by this method made it a reasonable estimate of airway plus tissue resistance, i.e., lung resistance. The interrupter method continues to be utilized in some commercial ventilators, and has also been applied in most experimental animals, including rats and mice (36, 89, 98, 154, 156, 160).

With these three methods of measuring resistance thus well established in the 1950s, there have been few changes made since then in the techniques used. One novel adaptation of the interrupter method was described by Shaw et al (159). This method involved a partial flow interruption with a resistance of known magnitude. The advantage of this method is that no pressure measurement is required. The measured decrement in flow is dependent simply on the relative magnitudes of the added resistance and the lung resistance. This method, however, cannot be used in ventilated subjects or animal models.

One of the important issues that arises whenever the resistance is measured is how much of the resistance is related to the airways and how much is related to dynamic properties of the lung (or chest wall) tissue. A number of studies over the past 50 years have attempted to quantify the “viscosity” of the tissues, but the nonlinearities associated with the volume and frequency dependence of these properties have given rise to widely varying conclusions. This uncertainty led to a number of models and experimental studies dealing with the respiratory impedance (discussed later), which is defined as the ratio of transpulmonary pressure to flow, but with periodic inputs (e.g., breathing), the variables are complex numbers with a magnitude and phase. Resistance is simply a special case of impedance at zero frequency. We will return to the topic of impedance after first considering issues related to tissue viscosity.

There are a number of structural and physical factors that play major roles in the magnitude of the airway resistance. The nature of the flow is of critical importance, since the equations relating airway diameter to airflow resistance are dependent on the flow pattern. If the flow

is laminar then the resistance is inversely related to the 4th power of the diameter, and driving pressure is linearly related to flow. Rohrer determined, however, that pressure is also related to a constant times the square of flow, a fact that he attributed to the fact that the lung airway tree could not be modeled as a simple cylinder (148). However, he never considered the effect of turbulent flow, since he made an unfortunate arithmetic mistake in his calculation of the Reynolds number, which kept it well below the critical value of ≈ 2000 . In 1965 Green published in a relatively obscure journal a graph of airway resistance vs. generation number, based on the dichotomous branching model of Weibel (178) and assuming laminar flow (50). This result showed for the first time that very little of the airway resistance was in the small airways. However, the assumption of laminar flow in airways is weak, and turbulence will significantly increase the resistance. This effect of turbulence was considered in several papers by Pedley, Schroter and Sudlow in the 1970s, which established a comprehensive understanding of the physical principles governing gas flow and mixing in the conducting airway tree (135, 136, 138). These authors emphasized with harsh words the importance of the structural anatomy on gas flow, stating, "It is neglect of this influence of anatomy that led to the naïve descriptions of bronchial airflow early workers assumed" (137). With their more sophisticated analysis, it was now possible to calculate the distribution of airway resistance along the airway tree based on the morphometric data of Weibel (178) and Horsfield and Cumming (63). Figure 8 shows the determination of the resistance of the airways as a function of airway generation, showing the now generally accepted concept that the small airways of the lung comprise a trivial fraction of the total resistance. Note that the data for the lowest curve identified as Poiseuille Flow is taken directly from the curve published by Green (50). These findings, in addition to earlier functional measurements showing a small peripheral lung resistance in dogs (92), provided theoretical support for the small airways being designated the "quiet zone," (101), referring to the fact that early detection of small airway disease would be difficult, since even moderate increases in small airways resistance would be very difficult to detect. However, it is important to emphasize that these calculations were based on morphologic measurements taken from a lungs fixed near TLC, and the extrapolation to FRC may not necessarily be uniform.

Another key component of airway resistance is the activity of the airway smooth muscle. Normal airways have a moderate degree of tone, and with sufficient stimulation, even large cartilaginous airways can be made to close (13). Whether there is any useful function of airway smooth muscle has been questioned (113), but there is little question of its pathologic behavior in asthma. This fact has led to attempts to physically and permanently disrupt the ability of airways smooth muscle to shorten, a process which is now being evaluated clinically (20). Further discussion of the control and regulation of airways smooth muscle mechanics, however, is beyond the scope of this chapter, and appears elsewhere in this Handbook.

One final comment concerning the measurement of resistance relates to the other key variable in its calculation, the gas flow. In 1925, Fleisch described, constructed, and analyzed a pneumotach that could provide a measurement of gas flow in and out of the lungs (39). Like the measurement of esophageal pressure described above, this was an enabling

invention, without which insight on the dynamical aspects of the lung would not have occurred.

ii. Tissue resistance (viscance)—The dynamic aspects of the lung tissue have been given a number of different names, including, tissue resistance, tissue viscance, or simply tissue viscosity. One of the earliest attempts to emphasize and measure the viscoelastic properties of the lung tissue was by Bayliss and Robertson (10). It had been recognized previously that the viscosity of gas in the airways played an important role in airway resistance, but tissue “viscance,” as they called it, had not received much attention. In this work they used hydrogen gas to partition the lung resistance of cats into the airway and tissue components in phase with flow. They found that at a frequency of 18 breaths per minute, the tissue resistance (viscance) comprised from 60 to 80% of the total dynamic resistance. It is interesting that these authors did not cite the work of Rohrer, Wirz, or von Neergaard.

Measurements were made by McIlroy et al (100) using a more careful method of changing the properties of flow by matching kinematic viscosities of gases with different densities and viscosities. In a limited number of normal human subjects they found the tissue resistance to be 30–40% of the total lung resistance. They criticized the results of Bayliss and Robertson as having not taken into consideration the effect of any intrinsic dynamic pressure-volume hysteresis of the lung surface. This criticism, however, could be applied equally well to many later and even contemporary studies. An elegant study by Marshall and Dubois at about the same time (96) was designed to measure the magnitude of tissue resistance in humans by a direct comparison in each subject of the measurement of lung resistance (107) and airway resistance using the plethysmographic method documented by Dubois et al (32). This work showed that the tissue resistance comprised an average of 18% of the total resistance, and was not increased by histamine challenge (which did increase airway resistance). In 1966, Bachofen measured the tissue resistance during quiet respiration in normal and asthmatic subjects, and reported that it comprised 25% of the total lung resistance in normals, but only 12% in the asthmatics (6). This value on the order of 20% in healthy subjects continues to be accepted, and is still present in modern textbooks (179). However, it is important to note that the measurements made by Marshall and Dubois were done at panting frequencies (≈ 2 Hz), and since it is known that tissue resistance decreases with frequency, it is likely that the tissue resistance fraction at normal breathing frequencies was significantly greater.

Thus, this question of how big is the tissue component of lung resistance still remains a bit unsettled even to this day. In 1967, Macklem and Mead published a study using a novel technique known as the retrograde catheter (92). This involved inserting a catheter with a bell on one end into a peripheral airway until the distal end penetrated parenchyma and exited the visceral pleura, as shown in Figure 9. The bell end was then wedged in a small peripheral bronchus. They used this method to partition the airway resistance into central and peripheral regions, and the peripheral region thus includes both peripheral airway and tissue resistance. They found that the resistance of the lung periphery was so small as to be immeasurable at higher lung volumes, and even at lower lung volumes, the tissues plus peripheral airways comprised less than 10% of the total resistance. This work in dogs

supported the conclusion of Marshall and Dubois (96) that suggested a relatively trivial amount of tissue resistance. It is tempting to explain this low value on the basis of frequency, since, as with the studies of Marshall and Dubois and others (38), Macklem and Mead (92) also made measurements at frequencies much above normal. However, they also found a similar low peripheral resistance with a constant flow method that should reflect values at low frequencies. Thus, it is not easy to reconcile this classic study with more recent measurements showing a relatively high tissue resistance (viscoelasticity) at normal breathing frequencies as discussed below.

This issue was reexamined in the 1980s and 1990s with a technique known as the alveolar capsule (41). This method entails gluing a small capsule on the visceral pleura, puncturing the pleura with a needle, and measuring the pressure at the pleural surface. In a sense, this is an extreme version of the retrograde catheter with the peripheral pressure now being made even deeper in the lung at the pleural surface. As a first approximation, any resistance measured between this pressure and pleural pressure should reflect the viscous resistance of the lung tissue. However, any interpretation of what such a calculated tissue resistance would suggest about the viscous nature of the lung needs to include two important considerations. The first is that, in the calculation, the actual flow going to the region with the capsule is unknown in addition to there being a high likelihood of heterogeneous ventilation (61, 80), so certain assumptions must be made in the calculation. Second is the fact that even though one is measuring a pressure close to the pleural surface, both the stiffness and tissue resistance reflect properties of the entire lung structure including the airways (116). Despite these concerns, experiments with the alveolar capsule provide some of the most direct estimates of tissue resistance. Results using the alveolar capsule method have suggested that the tissue resistance at normal breathing rates in many species comprises the major component of lung resistance, typically 60 – 80% of the total, and this fraction often increases with airway smooth muscle contraction (89, 151, 152, 177). However, some studies using the same alveolar capsule method have indicated that the tissue resistance is only about 15% of the total. Such discrepancies even with the same method in the same species make interpretation of the role of tissue resistance in pathologies somewhat uncertain.

An important component of this uncertainty and variability among species in published work stems from the fact that both airway and tissue resistance are dependent on the frequency of ventilation. An attempt to resolve this situation led to the development and publication in 1992 by Hantos et al (55) of a model known as the constant phase model. This model, based on the concept of hysteresivity and structural damping (42), defined the lung parenchyma with two frequency-independent viscoelastic variables, H and G , with H being related to the pure elastic properties, and G being related to the manifestation of viscous properties. This modeling, however, hasn't resolved the issue of the importance of tissue resistance, since this variable will still vary with frequency. It can be shown that $R_t = G / (2\pi f)^\alpha$, where α is a complex function of G and H . Thus, although the constant phase model provides some basis for the manifestation of R_t , it provides no intuitive insight, other than defining how it diminishes as frequency increases. Relating G or R_t to lung structure or pathologic changes in lung disease has not been done.

iii. Resistance through collateral airways—The term collateral ventilation refers to ventilation of a region of lung through “collateral” airways. There exist three possible pathways for such collateral ventilation – channels of Lambert, alveolar pores, and channels of Martin. In a more detailed review of collateral ventilation, it was argued that the primary channels were the channels of Martin (114). This reasoning was based on a process of elimination. In a normal lung, there is good evidence that the alveolar pores of Kohn are filled with alveolar lining fluid, which prevents gas flow between alveoli (8, 131). And if this is true, then calculations show that it would take several hundred cmH₂O to open a 5 µm pore (87). The channels of Lambert only exist at the level of the smallest air passages, and provide a potential short cut to a local alveolus. However, this anatomy limits them to being able to provide collateral ventilation to adjacent alveoli were obstruction to occur at the terminal bronchiole level, which might be important in certain lung pathologies such as pneumoconiosis (33). However, at the level where collateral ventilation is measured with a wedged catheter or bronchoscope in a segmental airway, the channels of Lambert would not be expected to play any significant role.

The pathways described by Martin are small airways that originate at the level of the respiratory bronchiole, but can connect to alveolar ducts somewhat removed from the ones normally supplied that airway. A typical pathway reconstructed and drawn from the data reported by Martin is illustrated in Figure 10. These pathways can connect regions of parenchyma from adjacent lobules, and are thus very different from the channels described by Lambert that connect terminal airways to other alveoli within a lobule. Calculations based on the size and estimated number of the channels described by Martin indicate a sufficiently low resistance to account quantitatively for the degree of collateral ventilation measured in canine lungs (114). One can therefore conclude that the primary pathways for collateral ventilation are normal airways that connect at the level of the alveolar duct.

Ventilation through these collateral airways in a normal lung is likely very small, since there would be a negligible pressure gradient driving flow. However, if an airway becomes obstructed, then ventilation to the obstructed region can only occur via flow through such collateral airways. The first measurements of collateral ventilation were by Van Allen, et al in 1930 (172). In this initial work, a catheter was wedged in a segmental bronchus, and ventilation in and out of this catheter was measured as the surrounding lung was ventilated. They also showed that a whole atelectatic lobe could be inflated by air infusion through the segmental bronchus. Measurement of collateral ventilation in man was first done in 1948 by Baarsma, et al (5), using a wedged balloon tipped catheter. Several other physiologic studies by Van Allen and associates were carried out in the early 1930's (170, 171), but it wasn't until the late 1960's that physiologic interest was renewed by Macklem and associates (60, 188).

Experimentally, a method of measuring the resistance through collateral pathways was first described in a Ph.D. thesis by Hilpert in 1970 (59). The procedure involves wedging a small double lumen catheter into an intralobar bronchus. A flow of gas is then passed through one lumen and the other lumen is used to measure pressure. At end expiration, the pressure in the trachea is atmospheric, and one can then divide the measured pressure by the known

flow to calculate a resistance. This resistance varies among species, and will be infinitely high in species such as the pig that have tightly lobulated lungs (165).

It is worth noting that to the extent this resistance reflects the dimensions of the most terminal bronchioles, respiratory bronchioles, and alveolar ducts, these airways cannot be assessed by any other pulmonary function tests. Normally, in such small airways the rate of bulk flow is so low that movement of gas molecules by diffusion is faster than the rate at which the gas molecules move by bulk flow (129). Since all conventional measures of airway resistance can only reflect airways where there is a pressure drop resulting from bulk flow, these measurements are completely insensitive to changes in these very peripheral airways. However, when this very peripheral resistance is measured with Hilpert's method, only a relatively few number of these peripheral airways are ventilated. This has the effect of increasing the rate of bulk gas flow much above normal, to the point where it far exceeds the rate of diffusion, and where there is now a measurable pressure drop. It is important to emphasize that these "collateral" airways are not different from normal airways. Without airway obstruction, they are normally ventilated with inspiratory and expiratory flows. Their uniqueness only arises from the fact that they can be supplied by two distinct larger bronchi. When studied with the Hilpert method, the flow may be transiently increased to obtain a resistive pressure drop, but this does not render these airways any less normal. This experimental approach thus provides a unique and probably the only means to assess the dimensional changes of very peripheral airways in vivo.

Hogg et al (60), demonstrated that resistance to collateral flow in excised human emphysematous lungs was greatly decreased, suggesting an important role for collateral flow in lung disease. Terry et al (166) studied emphysema patients in vivo using the wedged bronchoscope technique, and they confirmed that the R_p was lower (although they did not quantify this decrease). A decrease in resistance to collateral flow would be expected in emphysema, since with the destruction of alveolar walls there would not only be a progressive enlargement of the alveolar ducts, but also creation of new pathways through the missing walls. However, despite these reports of decreased R_p with emphysema, little is presently understood about the role that collateral ventilation plays in this pathology. Regarding asthma, Menkes and Traustman (108) speculated that, if collateral ventilation were to be beneficial in this disease, such patients should have a lower resistance. Experimental measurements, however, show just the opposite, as asthmatic subjects have nearly an order of magnitude higher resistance to collateral flow than normals (175). Thus if collateral ventilation plays a role in asthma, it would seem that the lower than normal level might actually contribute to the pathogenesis of the disease.

3) Lung input impedance

The input impedance is defined as a dynamic ratio of transpulmonary pressure to airflow, and is commonly analyzed with sine waves as a function of frequency. Although there are many investigators presently studying or using impedance measurements to phenotype lungs, this application to the airflow into the lung lagged by a decade or two the application to the vascular side, where input impedance of both the pulmonary (190) and systemic circulations (112, 123, 187) was used to understand the mechanical properties. Perhaps the

earliest interest in the frequency dependence of the respiratory system stems from the two-compartment resistance-compliance (RC) model presented by Otis et al (126). This pivotal study presented a model (Figure 11) to explain the heterogeneity of ventilation that could develop at different breathing frequencies. It presented a calculation of lung input impedance, and eventually led to a number of studies in human subjects of the frequency dependence of compliance. In being able to detect lung heterogeneity, this frequency dependence of compliance (and resistance) was thought to be an early marker for lung disease (51, 68, 83, 158, 176, 189). Despite these and several other studies showing the frequency dependence in human subjects with different lung pathologies, the procedure was not widely utilized, in part because the technique was not easy to do for routine screening. Furthermore, despite the elegant concepts and innovative model of Otis et al, reasons why compliance might be frequency dependent in pathologic or even normal lungs go far beyond there being just two RC compartments.

Frequency dependence of lung elasticity was studied on a more basic level in the late 1960s and early 1970s by Hildebrandt (56–58, 62). This experimental work and theoretical analysis in the cat lung examined the viscoelastic properties of the lung tissue and surface, and formed the basis for many later models of lung input impedance. The concept that frequency dependence of the lung might be of some analytical value led directly to a number of studies examining the complex respiratory impedance by several investigators beginning in the 1980s (69, 72, 142, 169). Although such studies employed a more sophisticated mathematical analysis than that used by Otis et al (126), the results obtained were still largely descriptive, since there were no mechanical or even intuitive models that could easily be applied to the data.

However, this situation changed in 1992 when Hantos et al (55) published the constant phase model, which did provide some insight into mechanical variables of the lung as a function of frequency. These variables were independent of frequency, although their functional manifestations (e.g., lung compliance or tissue resistance) were not. Application of this model has become increasingly common in recent years, particularly in mouse models. This popularity might not have occurred were it not for a pressing need for investigators to obtain a way to reproducibly phenotype pulmonary function in mouse lungs. To this end, a commercial ventilator was developed that incorporated software that could analyze the impedance spectrum and provide quantification of the variables of the constant phase model. Although use of this model has become quite widespread, the utility of the model to either predict or provide pathological and structural insight is a matter of some controversy (9). Part of this concern relates to the fact that impedance measurements are not commonly applied in human subjects. Reasons for this are not entirely clear, since measurement of impedance can be done noninvasively with little more than a mouthpiece and a device that can generate the requisite forced oscillations. Were forced oscillation to become more common in humans, then a database could be acquired that would provide links to specific lung pathologies. Such knowledge would have considerable relevance to the work in animal models, since presently there is minimal overlap between the mechanics measurements commonly made in animals and those made in humans (i.e., based on spirometry).

4) Spirometry and forced expiration

In present practice, the mechanical properties of the lung in humans are assessed almost exclusively by spirometry. While it is possible to make measurements of resistance within a body plethysmograph, compliance with an esophageal balloon, or impedance using forced oscillation, these latter measurements are only done in limited research settings. This is thus a curious situation, where the essential assessment of human lung mechanics is with a test that is almost never done in animal models used to study human disease. While forced exhalation can be done in animals connected to a vacuum source, generally the interpretation, assumptions, and utility of such data is very limited at best. In this section we will consider how and why spirometry has become the de facto gold standard for human pulmonary function testing.

The origins of the mechanical aspects of the forced exhalation maneuver derive from observations made in the 1950s by Donald Fry (43) and later by Bob Hyatt (67), where it was observed that expired flow seemed to reach a maximum at some level of effort. Although the fact that the potential for airway closure to limit expiratory flow in asthma was already noted by Einthoven in 1892 (34), his understanding of the mechanics was very limited, and he did not consider the importance of this observation for functional assessment. On the other hand, Fry, et al developed the remarkably innovative concept of measuring isovolume pressure-flow curves, which at first glance seems counterintuitive, since it is not immediately clear how one can measure an expired flow if the lung volume is constant. However, by performing repeated expirations with varying subject effort, it was possible to measure the flows at different selected lung volumes, thereby enabling plots of flow vs. transpulmonary pressure for those lung volumes. Although, the clinical application of forced exhalation maneuvers in diagnosing lung disease was first reported by Tiffeneau and Pinelli (168) in 1947, little understanding of the mechanics underlying such maneuvers was available at that time. In 1951, Dayman published a more mechanistic study in emphysematous subjects, which included measurements which attempted to quantify the nature of the flow limitation observed in expiration and the role of lung elasticity (28). However, it wasn't until the elegant and now classic study reported in 1954 by Fry et al (43), that the whole concept of pressure-flow curves during forced exhalation, with resultant flow limitation was clearly described and analyzed. What their work showed was that with increasing effort at lung volumes smaller than about 75% of vital capacity, a point is reached where additional effort no longer results in any further increases in flow. Figure 12 reproduces a 3 dimensional graph from that paper showing flow limitation as a function of lung volume in emphysema. The authors state that, *“this figure illustrates the defects in the mechanics of ventilation in pulmonary emphysema. The key to the problem lies in the fact that if the retractive force of the lung is exceeded by the pressure drop needed to produce gas flow from the alveolus to the extrathoracic bronchi, a net pressure tending to produce compression of the bronchiole is developed. In emphysema the alteration in the normal retractive force of the lung and the increased resistance to air flow in the bronchiole permits the development of positive intrathoracic pressure during expiration at a relatively low airflow. In order to diminish this increased resistance with emphysema, the lung must be maintained in a state of greater inflation.”* This statement is remarkable, since, except for

the anatomic location of the choke point, it represents an understanding of forced exhalation that has not changed much over the past 55 years.

A few years after this initial paper, Hyatt et al published a further analysis where, for the first time, they made use of the flow-volume curve (67). This early work laid the experimental and analytical foundation for analyzing forced exhalation as a pulmonary function test. Of course, what was not yet understood was how the flow limitation actually occurred. This analysis was first described in the same year in two different ways, by two different research groups (105, 143). Both of these analyses provided intuitive and heuristic arguments. In the work by Mead et al, the concept of the equal pressure point (EPP) was developed. This analysis defined a point in the airway where the lateral pressure in the airway lumen equaled the pleural pressure. During exhalation, all airways downstream to this EPP would be under dynamic compression, and increasing expiratory efforts after maximal flow was reached, served to increase this dynamic compression and thus its resistance to flow. In the other analysis by Pride et al (143), the expiratory flow limitation was modeled using a Starling resistor (141). This was a device used by Ernest Starling to keep a constant afterload in his experiments on cardiac function, consisting of a collapsible tube in a pressurized box (74). Pride et al used this model to define a critical airway transmural pressure (defined as P_{tm}') at which a bronchus would collapse, thereby limiting further increases in flow. Each of these models considers the resistance to flow through the upstream segment, although at any given lung volume the pressure gradient driving this maximal flow in the EPP model is the elastic recoil pressure (P_{el}) at that volume, whereas in the Starling resistor model it is $P_{el} - P_{tm}'$. These conceptual models are thus quite compatible, and they were both useful in supporting Fry's concept that the airways that determined the magnitude of flow during flow limitation were the smaller upstream airways. Fry, et al, however, incorrectly assumed that the actual flow limiting segment was in the small bronchioles, whereas, Mead, et al and Pride et al, correctly considered the smaller airways open and providing the resistance to flow between alveoli and the location of the effective flow limiting segment point. The anatomic location of this segment was shown by Macklem and associates to lie in larger airways (91, 93). This mechanical understanding added important support for the continued use of forced exhalation as a relatively simple noninvasive pulmonary function test. The fact that the lung elastic recoil plays a major role in the magnitude of the forced expiratory flow, however, is often not recognized or ignored.

The theoretical basis for flow limitation in the lung, however, had to wait another 10 years. In 1977, Dawson and Elliot published an analysis that put this phenomenon on firm physical grounds (27). This analysis explained the mechanism limiting forced expiratory flow when local flow velocity in intrathoracic airways reaches the local speed of pressure wave propagation. The point at which this occurs was called the choke point. The wave speed (c) is a function of just the specific compliance of the airway [$(\Delta A/A)/\Delta P$] and the gas density (ρ) and is given as $c = 1/\sqrt{\rho[(\Delta A/A)/\Delta P]}$. To quote the authors, "This theory offers improved intuition to the work on mathematical modeling and an improved precision to the ideas of the intuitive models that have been used to explain the observations." Although this theoretical analysis was a major step forward in our understanding of flow limitation, the practical application of the theory was limited, since it depended on several factors that are

not well known, especially the pressure-area relations as a function of distance along the airway tree. Nevertheless, the use of the wave speed and choke point concepts documented in this paper are now an accepted part of any description of flow limitation in airways during forced expiratory flow.

Concluding Comments

The earliest and ancient investigations involving respiratory physiology and mechanics were often done in conjunction with other scientific activities. While several had substantial impact on our general knowledge, it wasn't until the middle of the 19th century that systematic quantitative studies of the mechanical aspects of respiratory physiology first began. This history of lung mechanics has been greatly influenced by critical technological advances and applications, which have made experimental testing of ideas possible. From the spirometer of Hutchinson (65), to the pneumotachograph of Fleisch (39), to the measurement of esophageal pressure (31, 44), to the use of the Wilhelmy balance by Clements (23), to the unassuming strain gauges for measuring pressure and rapid paper and electronic chart recorders, these enabling devices have generated numerous experimental studies with greatly increased understanding and validation of theories. With regard to lung mechanics, there was a 40-year period from after the 2nd World War to the mid 1980s, when much of our current understanding was secured. As Mead noted in 1996 with regard to forced expiration (103), "...all of these more recent studies are of details. The major work is done." This comment is more generally true in the lung mechanics field, and in the past 15 years, most of the technological advances have been at the cell and molecular level. While the mechanics at these levels is no less important, the technology has not yet had much impact at the macroscopic level. The one exception, however, is the steady progressive advances in imaging technology. For example, much of our understanding of the airway tree structure has been based on a number of morphologic studies that detailed the structural dimensions in just a very few individual lungs at a single fixed pressure (63, 178). Thus, none of the anatomic variability in the tree structure among individuals has been well described, and the impact of this normal variability on lung mechanics, especially expiratory flow, is unknown. However, with modern imaging capabilities that can provide resolutions down to the micron level, this information can now be readily obtained and stored digitally (167). Another challenging frontier in lung mechanics relates to the understanding of the microscopic structural factors that give rise to the macroscopic viscoelastic properties of the lung. With computational capabilities and multiscale modeling, at some point it can be anticipated that new knowledge arising from cell and matrix mechanics can be incorporated into models that will enable prediction of mechanical properties in healthy and diseased lungs.

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Figure 1.
Picture of Jere Mead (c. 1985), who impacted nearly every facet of lung mechanics in the 20th century.

Figure 2.

Picture of Peter Macklem, who trained with Jere Mead, and became a strong advocate of the importance of respiratory mechanics measurements throughout his career. This picture dates from 1988, when Dr. Macklem was honored by his appointment as an Officer of the Order of Canada.

Figure 3.

Deflation pressure-volume curves of a canine left lung. Curve **a** shows an air inflated lung; curve **b** shows a saline filled lung; and curve **c** is difference between the two, i.e., the calculated elastic recoil force due to surface tension alone. The ordinate shows the pressure in cm H₂O and the abscissa shows the volume in mL, which is opposite to the more conventional orientation (e.g., see Figure 4). From Von Neergaard (122).

Figure 4.

Experimental air and saline pressure-volume loops from a single cat lung. With air inflation from residual volume, the airways did not begin to open until pressure exceeded 10 cmH₂O. Data from Radford (145).

Figure 5.

This figure demonstrates the model by Wilson and Bachofen, which illustrates how surface tension operates in the lung parenchyma consisting of flat alveolar septal walls. The surface forces are large at the corners where the septal walls meet (upper drawing, curvature R) and at the edge of the openings of the alveolar mouths (lower drawing, curves arrowhead lines). The forces at this latter site are large and serve to compress the walls, leading to folding in the corners, as seen in the upper drawing. Figure adapted from Wilson and Bachofen, 1982 (185).

Figure 6.

The relaxation pressure curve (solid) and its two fractions, that due to the elasticity of the lungs and that due to the chest, diaphragm, etc. (Figure 5, from Rahn et al, (147).

Figure 7.

Regional differences of lung expansion caused by gravity. The vertical axis shows regional lung volume (V_r), expressed as percent of TLC. The horizontal axis shows overall lung volume (V), expressed as percent of TLC below and as percent of VC above. The line of identity indicates the percentile degree of expansion of the regions equal to that of the entire lung. Vertical distance (D) from the top of the lung (in cm) is indicated on each curve. From Milic-Emili et al, 1966 (110).

Figure 8.

Predicted airway resistance as a function of airway generation at 3 different flows and with pure Poiseuille flow (from reference (138), 1970, Elsevier, used with permission). This shows that most of the resistance is in the larger conducting airways. The model was based on the symmetric Weibel branching pattern (178), but a similar conclusion was also found with the asymmetric model of Horsfield and Cumming (63).

Figure 9.

Schematic showing a retrograde catheter wedged in a peripheral bronchus, exiting through the bronchial wall, parenchyma and visceral pleura. This approach enabled partitioning of the central and peripheral lung resistance. From Macklem and Mead (92).

Figure 10.

Schematic reconstruction of the bronchial pathway described by Martin ((97)). The letter designations refer to those in the serial sections shown by Martin. A and B are terminal bronchioles; a₁ and b₁ are first-order respiratory bronchioles; a₂ and b₂ are second-order respiratory bronchioles; a₃ and b₃ are alveolar ducts. The numbers associated with each airway are approximate diameters in mm, estimated from the histological sections.

Figure 11.
Two compartment model of the lung parenchyma presented by Otis et al (126).

Figure 12.

3D graph showing pressure-flow curves as a function of lung volume in an emphysematous subject, from Fry et al (43). Ordinate shows expiratory (positive) and inspiratory (negative) flows, abscissa shows pleural pressure, and lung volume is shown on the plane projecting toward the reader.