1 Introduction

1.1 The importance of lung mechanics

Being able to breathe without any apparent difficulty is something that healthy people take for granted, and most of us generally go about our daily lives without giving it a second thought. But breathing is not always easy. A number of common lung diseases can make breathing difficult and uncomfortable. Sometimes these diseases can even make it impossible to breathe at all without the assistance of a machine or another person, a condition known as *respiratory failure*. There are a variety of factors that can lead to respiratory insufficiency or failure, but among the most important are those that involve a compromise in the mechanical properties of the lungs.

Breathing is essentially a mechanical process in which the muscles of the thorax and abdomen, working together under the control of the brain, produce the pressures required to expand the lung so that air is sucked into it from the environment. These pressures must be sufficient to overcome the tendencies of the lung and chest wall tissues to recoil, much like blowing up a balloon. Pressure is also required to drive air along the pulmonary airways, a system of branching conduits that begins at the mouth and ends deep in the lungs at the point where air and blood are close enough to exchange oxygen and carbon dioxide. The mechanical properties of the lungs thus determine how muscular pressures, airway flows, and lung volumes are related. The field of lung mechanics is concerned with the study of these properties.

The mechanical properties of the lung have an important bearing on how we experience our daily lives because they determine, for example, how much effort is needed to take in a breath and how comfortable it feels to breathe. When breathing becomes uncomfortable, usually perceived as a sense of breathlessness known as *dyspnea*, our brains are telling us that we are expending too much effort to do what is normally effortless. In other words, we are sensing that there is something wrong with the mechanical properties of our lungs. This sensation can be reproduced by trying to breathe through a narrow drinking straw which presents a large resistance to air flow. A somewhat similar sensation may be experienced by someone suffering an attack of asthma, when the pulmonary airways constrict and so partially obstruct the flow of air into and out of the lungs. Taking a breath may also not be so easy when the lungs become encased in thick scar tissue, as occurs in a disease known as *pulmonary fibrosis*, somewhat like trying to breathe while wearing a tightly laced corset. But if pathologic abnormalities in lung mechanics are sensible to us as individuals, then they are also measurable using laboratory equipment. Indeed,

physicians regularly assess mechanical abnormalities in the lung in order to diagnose disease. Assessing lung mechanical function is also vital to areas of basic science such as pulmonary pharmacology and immunology.

A great deal is known about lung mechanical function, thanks to the ongoing efforts of a large community of scientists dating back over 100 years. In its formative stages, beginning in the late 1800s and continuing throughout much of the twentieth century, the science of lung mechanics was largely the domain of the physiologist and physician. Over the past several decades, however, the field has progressed to become highly quantitative thanks to the availability of electronic sensors and digital computers. These devices have allowed investigators to acquire extremely accurate experimental data related to lung function. Accurate data are always very interesting to scientists armed with sophisticated methods of data analysis, so the field of lung mechanics has recently been attracting the attention of biomedical engineers, physicists, and mathematicians in increasing numbers. Indeed, we are now at the point where mathematics and computer models play indispensable roles in encapsulating our understanding of lung mechanics.

The field of lung mechanics thus represents a confluence of the biological and physical sciences, and as such requires a multidisciplinary approach in which questions of physiologic function are addressed in terms of underlying physics. The language of physics is mathematics, and its goal is to capture the workings of the world in terms of (ideally, relatively simple) equations that have broad predictive power. Accordingly, the approach taken herein is to systematically develop the equations (mathematical models) that describe lung mechanical function.

1.2 Anatomy and physiology

The physiological aspects of the lung can be rather naturally grouped into a number of almost distinct sub-topics: *gas exchange*, *neural control*, *mechanics*, and *non-respiratory functions* related mostly to defense. Indeed, advanced treatises on the lung invariably partition the subject along these lines, and even the corresponding communities of scientists currently pushing forward the frontiers of knowledge in these various areas remain largely distinct. We are not going to cross these boundaries to any significant degree here, being almost exclusively concerned with lung mechanical function. Nevertheless, it must be remembered that all aspects of pulmonary physiology are vital to the lung's ability to function normally within a human or animal, and to sustain life.

1.2.1 Gas exchange

Living animal cells require a continual supply of oxygen and nutrients, while continually releasing carbon dioxide and other waste products. Single-cell animals can achieve this through direct diffusive exchange with the environment. In larger animals, the increased volume-to-surface area ratios make it impossible for the necessary flux of gases between cells and the environment to be achieved by *passive diffusion* across the body surface. To deal with this problem, nature has evolved the *cardio-pulmonary system*, an intermediary

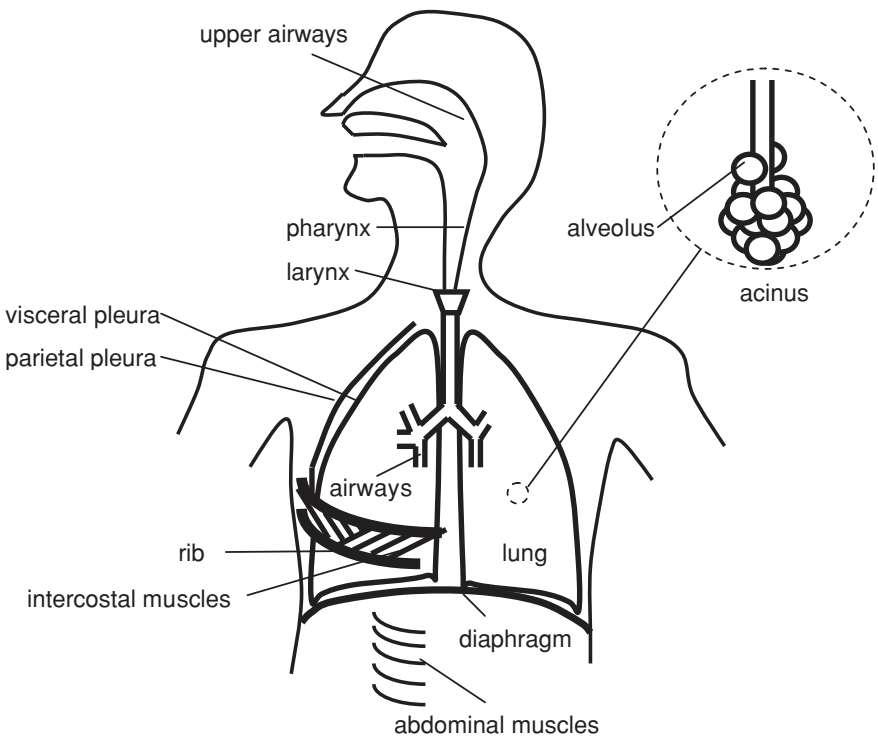

Figure 1.1 The principal mechanical components of the respiratory system. In a spontaneously breathing subject, a negative pressure is generated around the outside of the lungs by the respiratory muscles. This produces a flow of gas along the pulmonary airways in the direction of decreasing pressure.

that brings blood and gas into close juxtaposition either side of an extremely thin physical barrier deep inside the lungs. This *blood-gas barrier* is less than a micron thick, so it presents a very small impediment to the passage of gas molecules. It also has an extremely large surface area so that many gas molecules can cross it in parallel.

The enormous surface area of the blood-gas barrier is achieved by tree-like structures that geometrically amplify their cross-sections as their branches divide and become increasingly numerous. In the case of the *pulmonary airways* (Fig. 1.1), a cross-sectional area of a few square centimeters at the trunk of the tree (the *trachea*) is translated through about 23 bifurcations into an area roughly the size of a tennis court by the time the *alveoli* have been reached at the end of the most distal airway branches. A corresponding branching scheme begins with the pulmonary artery as it exits the right ventricle of the heart, and eventually leads to the myriad of pulmonary capillaries that distribute blood throughout the alveolar walls.

The transport of oxygen and carbon dioxide across the blood-gas barrier occurs solely by passive diffusion. Gases always tend to move from regions of high partial pressure to regions of low partial pressure, provided they are not physically prevented from doing so. The partial pressures of oxygen and carbon dioxide in the alveoli and the pulmonary

capillary blood normally favor movement of oxygen into the blood and carbon dioxide into the alveoli. The blood-gas barrier these gases must cross in the process is so large and so thin that sufficient numbers of gas molecules can move across it to meet the demands of life in a healthy lung. In some diseases, however, this ceases to be the case. The efficiency of gas exchange is thus tightly linked to the physical properties of the blood-gas barrier.

1.2.2 Control of breathing

Gas exchange can only take place effectively if fresh air is continually supplied to the blood-gas barrier. This is achieved through the repeated inflation and deflation of the lungs under the coordinated actions of the *respiratory muscles*, a process known as ventilation. The principal muscles of inspiration are the *diaphragm*, a sheet of muscle that separates the thorax from the abdomen, and the *intercostal muscles* that stabilize the rib cage (Fig. 1.1). When activated, the diaphragm descends and, together with the muscles of the thorax, creates a negative pressure (relative to atmospheric) around the lungs that acts to draw air into the airways. The region around the lungs in which this negative pressure acts is known as the *pleural space*, and is filled with a very thin layer of lubricating fluid that separates the outer surface of the lungs (the *visceral pleura*) from the inner surface of the rib cage (the *parietal pleura*). Expiration under resting conditions is passive; the inspiratory muscles are deactivated to allow the lungs to deflate as a result of the net elastic recoil of the lung and chest wall tissues. The increased ventilatory demands of exercise may require the use of expiratory muscles, notably those of the abdomen, to increase the rate of expiration above that produced by elastic recoil alone.

The volume of air taken into the lungs with each breath, termed the *tidal volume* (Fig. 1.2), is substantially less than the total volume that can be forcibly expired from a maximal inspiration. This total volume, called *vital capacity*, is equal to the difference between *total lung capacity* and *residual volume*, the latter defined as the volume of air left in the lungs after a maximum expiratory effort. Residual volume is substantially less than the volume of air in the lungs at the end of a normal passive expiration, termed *functional residual capacity*.

Obviously, respiration requires that the various respiratory muscles be activated in a periodic and coordinated fashion. This is the job of the *respiratory control centers* in the brainstem, which usually operate automatically but may be overridden temporarily by the higher (conscious) centers of the brain. Sensors known as *chemoreceptors* continually deliver information to the respiratory centers about how much oxygen and carbon dioxide the arterial blood is carrying. Other sensors known as *mechanoreceptors* inform the respiratory centers about the state of inflation of the lungs. The information supplied by these various sensors is used by the respiratory centers to control the actions of the respiratory muscles in order to produce a level of ventilation appropriate to the body's needs. The neural control of respiration is thus based on negative feedback, and is normally able to maintain the partial pressures of arterial oxygen and carbon dioxide within very tight bounds, even during exercise.

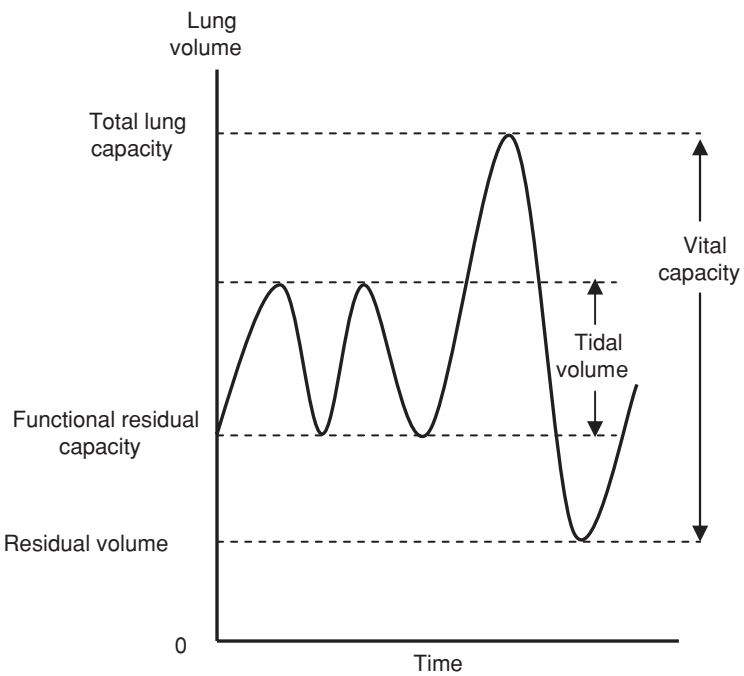

Figure 1.2 The standard subdivisions of lung volume.

1.2.3 Lung mechanics

A healthy blood-gas barrier and a functioning respiratory control system are not enough to guarantee effective gas exchange, however, unless the mechanical properties of the lung are also up to the task. These properties, basically the *flow resistance* of the airways and the *elastic recoil forces* of the lung tissues, must be successfully overcome by the respiratory muscles with each breath if fresh air is to be supplied to the blood-gas barrier. The resistance of the airway tree is determined by the internal dimensions of its various branches. The upper airways comprise the nose, mouth, and pharyngeal regions. The pulmonary airway tree starts on the other side of the vocal cords, beginning with the trachea and proceeding though a series of bifurcations to reach the *terminal bronchioles*. Each terminal bronchiole leads into an *acinus*, frequently depicted (Fig. 1.1) as something resembling a bunch of grapes (alveoli) on a set of branching twigs (the respiratory bronchioles). Exchange of gases between air and blood takes place within the acinar regions of the lung, so the acinus can be considered the basic ventilatory unit.

The conducting airways are lined with a delicate *epithelium* that partakes in numerous metabolic activities. Some of the cells in the epithelium continually secrete protective mucus that, being sticky, acts to trap inhaled particles of potentially noxious materials. The mucus and its particle prisoners are then swept up to the tracheal opening by tiny hair-like projections known as *cilia*. The cilia project into the airway lumen from specialized epithelial cells, and beat in the direction of the tracheal opening. The walls of the airways

also contain significant amounts of *smooth muscle*. In the trachea this smooth muscle exists as a continuous band along its posterior aspect, linking the open ends of cartilage horseshoes that give the trachea its mechanical stability. Contraction of the tracheal smooth muscle causes the open ends of the horseshoes to approach each other, thereby decreasing the cross-sectional area of the tracheal lumen. Smooth muscle is wrapped more or less circumferentially around the airways distal to the trachea, and extends as far down as the alveolar ducts that serve as the entrance to the gas-exchanging zone of the lung. Whether or not there is any survival advantage to having smooth muscle in our lungs is still debated, but a disease such as asthma leaves little doubt that its presence can have adverse consequences.

1.3 Pathophysiology

There are numerous diseases that can make it difficult for the lungs to do their job, one way or another. Our focus is on pathologies that involve mechanical abnormalities. These pathologies constitute a substantial fraction of the public health burden in all age groups in modern society, and are classically divided into two categories labeled *obstructive* and *restrictive*.

1.3.1 Obstructive lung disease

The archetypical example of an obstructive lung disease is *asthma*, a common syndrome that varies widely in severity. Asthma is defined on the basis of its functional characteristics. Principal among these is reversible airway obstruction, demonstrated as an improvement in lung function following treatment with drugs that relax airway smooth muscle. The definition of asthma also requires a degree of inflammatory involvement as indicated by the presence of certain types of cells in the airway secretions that are brought up by coughing. However, the mechanisms underlying the pathophysiology of asthma are still debated. Indeed, it seems very likely that asthma represents the common clinical endpoint for a number of different pathological processes. Nevertheless, persistent inflammation in the lung is involved in many cases of asthma, and the inopportune contraction of airway smooth muscle is clearly a key event in an acute asthmatic attack. As most people probably recognize, the chief characteristics of asthma are wheezing and shortness of breath. Curiously, in recent times, the incidence of asthma has increased markedly in Western nations for reasons that remain poorly understood, although prevalence seems to have leveled off over the last decade.

Another common obstructive pathology is the condition known as *chronic obstructive pulmonary disease* (COPD), which frequently follows from a lifetime of heavy smoking. This, again, is a complex disease exhibiting a spectrum of features. Prominent among these is *emphysema*, which involves the progressive destruction of the microstructure of the lung tissue. The result is a reduction in the surface area of the blood-gas barrier that in mild cases may simply limit exercise capacity, but when severe may confine a patient to complete inactivity and a dependency on supplemental oxygen. The main mechanical consequence of emphysema is a reduction in the elastic recoil of the lung tissue.

The pulmonary airways are not completely rigid. This makes them prone to collapse during vigorous expiration, even in normal individuals who exhale forcefully enough. Indeed, healthy individuals with normal abdominal and thoracic muscle strength are able, over most of the lung volume range, to exhale at a rate that cannot be exceeded despite increases in expiratory effort. This maximum exhalation rate can be determined by measuring the flow of gas leaving the mouth. The magnitude of the maximum flow during a forced expiration is reduced in both asthma and emphysema. In extreme cases, the limiting flow may even be attained during quiet breathing.

The phenomenon of *expiratory flow limitation* is exploited in the diagnosis of obstructive lung diseases because the maximum volume of gas that can be expelled from the lungs during the first second following a maximal inspiration, known as forced expiratory volume in one second (FEV_1), is reduced in these diseases. On the other hand, the total volume forcibly expelled over the course of an entire expiration, the so-called *forced vital capacity* (FVC), remains relatively unaffected in a purely obstructive disease. In other words, all the air comes out eventually, but it just takes longer than normal to do so. A graphic representation of flow limitation is provided by plotting flow against expired volume throughout the entire course of a maximal expiratory maneuver. In obstructive lung disease, the expiratory *flow-volume curve* is depressed and is frequently concave upwards compared to the normal, relatively straight curve (Fig. 1.3).

1.3.2 Restrictive lung disease

The other major class of pathologies affecting lung mechanics, the so-called restrictive diseases, is exemplified by pulmonary fibrosis. Here, aberrant deposition and organization of connective proteins, particularly collagen, leaves the lungs scarred and stiff with a reduced capacity to accommodate inspired air. A reduced inspiratory capacity is also found in situations where the *surface tension* of the liquid that lines the airways and alveoli is increased. Normally, this surface tension is maintained at low levels by the presence of *pulmonary surfactant*, a detergent-like molecule secreted by cells in the lining of the airways and alveoli. The efficacy of surfactant can be reduced by leakage of plasma fluid and proteins from the pulmonary blood vessels into the airspaces of the lung, as can occur in pneumonia or pulmonary edema. Although not usually considered a restrictive condition, fluid accumulation in the airspaces can nevertheless flood some lung regions completely, effectively shutting them down. Such events decrease the total air volume of the lung and increase its overall stiffness, causing a commensurate reduction in the organ's capacity to inspire air.

Classically, restrictive lung diseases are said to be typified by a reduction in the amount of gas that can be drawn into the lungs during a maximal inspiratory effort, while the shape of the maximum expiratory flow remains relatively normal. This produces an expiratory flow-volume curve that intersects with the normal curve over a truncated volume range (Fig. 1.3). The simple view of things is thus that obstructive and restrictive lung diseases are separable on the basis of the kinds of expiratory flow-volume curves they produce. In reality, things are not quite this simple; many lung pathologies with mechanical manifestations exhibit varying degrees of both obstructive and restrictive

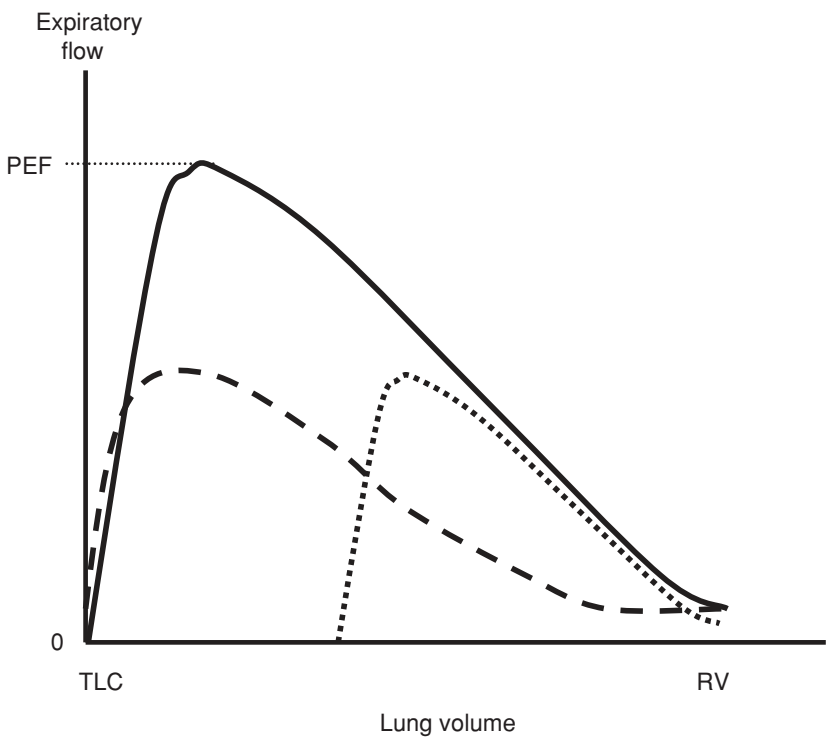

Figure 1.3 Stylized representation of forced expiratory flow-volume curves for a normal lung (solid line), an obstructed lung (dashed line), and a restricted lung (dotted line). The normal peak expiratory flow (PEF) is reduced in both pathologies, but only in the restrictive case is total lung capacity (TLC) commensurately reduced. This highly simplified diagram shows residual volume (RV) being identical in all cases, but RV is frequently increased in obstructive disease due to air becoming trapped behind airways that close as lung volume decreases.

patterns. What is certain, however, is that abnormalities in lung mechanical function accompany a wide and important range of pathologies.

1.4 How do we assess lung mechanical function?

The assessment of respiratory mechanics involves uncovering relationships between key pressures, flows, and volumes measured at appropriate sites. Accordingly, what we know about lung mechanical function is dictated by what we can measure. In this regard, the lung has long been a favorite organ of study for quantitative scientists, including mathematicians and biomedical engineers, because it is relatively easy to obtain data from it. For example, gas pressures, flows, and volumes at the mouth are readily monitored with high accuracy and temporal resolution. Controlled perturbations in these variables can be easily applied as probes to investigate the lung's internal workings. Nevertheless, most events taking place inside the lung that influence its mechanical function are not accessible by direct observation. This leaves us having

to infer what is going on from dynamic relationships observed between those limited variables that can be measured experimentally. Ideally, when we observe abnormal relationships between these variables, we would like to be able to deduce what structural abnormalities caused them.

Some inferences about the internal workings of the lung can be made by observing pressures, flows, and volumes and using a little common sense. For example, a sharp increase in peak airway pressure during mechanical ventilation likely indicates that something has suddenly impeded the flow of air into the lungs. Even though an elevated peak pressure on its own gives no information as to where the airway impediment might be, it may still prompt the anesthesiologist to check the endotracheal tube and find that it is blocked with mucus – clearly a useful outcome. Empirical quantities such as peak airway pressure, FEV_1, and FVC that are derived from measured variables may thus have great utility despite being of limited specificity.

The full inferential potential hidden inside measurements of respiratory pressures, flows, and volumes, however, is only revealed once we use them to derive quantities based on theoretical models. Perhaps the most immediate example of this is the calculation of pulmonary *airway resistance* as the ratio of the pressure drop between the proximal and distal ends of the airway tree to the air flow through it. Leaving aside for the moment the question of how one actually measures these pressures and flows, it is obvious that the calculation of airway resistance is motivated by the notion that the airway tree behaves like a single rigid conduit through which flows an incompressible fluid. This is a very simple model of what is in reality a very complicated structure. Nevertheless, this model has proven enormously useful because it allows a measure of function (resistance) to be linked to hypothetical structure (airway length and internal diameter). The concept of airway resistance is also readily accessible to the educated mind without the need for special analytical tools. Even so, it is obvious that one ought to do much better by using a model with a structure more closely resembling the anatomy of a real airway tree. As the complexity of such a model increases, however, predicting the details of its behavior rapidly exceeds the capacity of the unaided human intellect.

To break free of the constraints of human intuition in developing a quantitative understanding of lung mechanics, we must resort to the systematic construction of mathematical models. A mathematical model is a set of equations that serve both as a precise statement of our assumptions about how the lung works mechanically and as a means of exploring the consequences of those assumptions. As alluded to above, the human mind is incapable of doing either without the aid of mathematical tools except in the most trivial of cases. A state-of-the-art understanding of lung mechanics thus requires a certain familiarity with the methods of mathematical and computer modeling. This requires some effort, but is well worth the reward of enlightenment that ensues.

1.4.1 Inverse modeling

The process of trying to construct a mathematical model of a system from measurements of *inputs* to and *outputs* from the system is known as *inverse modeling* (also known as

system identification). The *parameters* of the model are evaluated by getting the model to predict the outputs from the inputs as accurately as it can. The structure of such a model is not generally known *a priori*, so it has to be determined from considerations of experimental data, prior knowledge about the structure of the system being modeled, and whatever else can be brought to bear on the issue. The modeler uses all this information to specify what the various components of the model are, and how they are to be linked together. Ideally, the structure of an inverse model should correspond in some useful way to the structure of the real system, so that when the model mimics the behavior of the system it does so in a way that is true to the internal mechanisms responsible for the behavior of the system itself.

For obvious practical reasons it is usually not possible to include every known component of a complicated system in a mathematical model. This is certainly true in the case of the lung, even if we understood in detail how each of its components works (which we don't). Therefore, the choice of model structure requires a decision about which components of the real system are important for the purpose at hand, and which components can be safely ignored. This is not a process which is readily codified. Indeed, determination of model structure is very much an art that reflects the experience and wisdom of the modeler. It is also a dynamic process; models of complex systems such as the lung are constantly being tested and refined in the light of new experimental data and knowledge.

Mathematical models do not have to be complicated to be useful. Indeed, inverse models are invariably rather simple, having few independent components and small numbers of adjustable parameters. This is a necessary consequence of the fact that such models have to be matched to experimental data, and there are usually only so many free parameters that even the most precise data can support. Inverse models of the lung, for example, do not even come close to encapsulating everything we know about the organ, yet they are still capable of mimicking many of the details of its global behavior. An example of an extremely simplistic but nevertheless intuitively acceptable model of lung mechanics consists of an elastic balloon sealed over the end of a rigid pipe; the balloon represents the expandable lung tissues while the pipe represents the pulmonary airways (Fig. 1.4). Obviously, a real lung is vastly more complicated than this simple construct, even though it still embodies much that is key to the process of ventilation.

Once the structure of an inverse model of the lung has been settled upon, the mathematical equations describing its mechanical behavior – the so-called *equations of motion* – must be derived. These equations state how pressure is related to flow and volume within each component of the model, and tell us exactly how the complete model will behave under every conceivable circumstance. The world of mathematical models is thus fundamentally different from the real world in which we breathe. In the real world we can never measure anything exactly, nor understand any system down to the last detail. By contrast, in the world of models it is possible to know everything there is to know about a particular model.

Equations of motion contain quantities known as *variables*. These represent the things that are measurable, and which usually vary with time. The variables in models of lung mechanics are typically gas pressures, flows, and volumes. Equations of motion also