Respiratory System Dynamics

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Abstract

While static mechanical forces govern resting lung volumes, dynamic forces determine tidal breathing, airflow, and changes in airflow and lung volume during normal and abnormal breathing. This section will examine the mechanisms, measurement methodology, and interpretation of the dynamic changes in airflow and lung volume that occur in health and disease. We will first examine how the total work of breathing can be described by the parameters of the equation of motion, which determine the pressure required to move air into and out of the lung. This will include a detailed description of airflow characteristics and airway resistance. Next, we will review the changes in pressure and flow that determine maximal forced inspiration and expiration, which result in the maximal flow–volume loop and the clinically important forced expired volume in 1 second. We will also assess the mechanisms and interpretation of bronchodilator responsiveness, dynamic hyperinflation, and airways hyperresponsiveness.

Keywords

- work of breathing
- airway resistance
- flow–volume loop
- airflow limitation
- bronchodilator responsiveness
- dynamic hyperinflation
- airway hyperresponsiveness
- methacholine challenge

The following section will explore the ways in which dynamic forces influence respiratory function, and how that function is measured. Specifically, we will examine the work of breathing as related to quiet, tidal breathing, determinants of airway resistance, the physiology of forced exhalation and airflow limitation, the response of flow and volume to inhaled bronchodilator administration, dynamic hyperinflation, and airways hyperresponsiveness.

Work of Breathing

During quiet breathing the inspiratory muscles are activated to raise intrathoracic volume, which decreases pleural pressure, increases transmural (alveolar minus pleural) pressure, and ultimately expands the alveoli outward from functional residual capacity (FRC). Since lung recoil is inward and chest wall recoil is outward at FRC, the work of the inspiratory muscles is mainly necessary to overcome increasing lung recoil as the lung expands to end-inspiratory lung volume. At the end of inspiration, the inspiratory muscles relax, and the passive recoil of the lung draws the lung and chest wall back toward FRC. The total work required to perform quiet, tidal breathing can be depicted by a Campbell Diagram, which displays the volume versus pressure (intrapleural) relationship, with the area of the inscribed inspiratory and expiratory loop equaling the total work involved (►**Fig. 1**).[1] The work can be broken down into its individual components related to resistive work due to the friction of moving gas through the airways and elastic work necessary to overcome the elastic forces of the lung parenchyma and chest wall. The Campbell Diagram illustrates how resistive work is increased in patients with increased airway resistance (e.g., obstructive lung disease), and elastic work is increased in patients with reduced lung compliance (e.g., restrictive lung disease). It is

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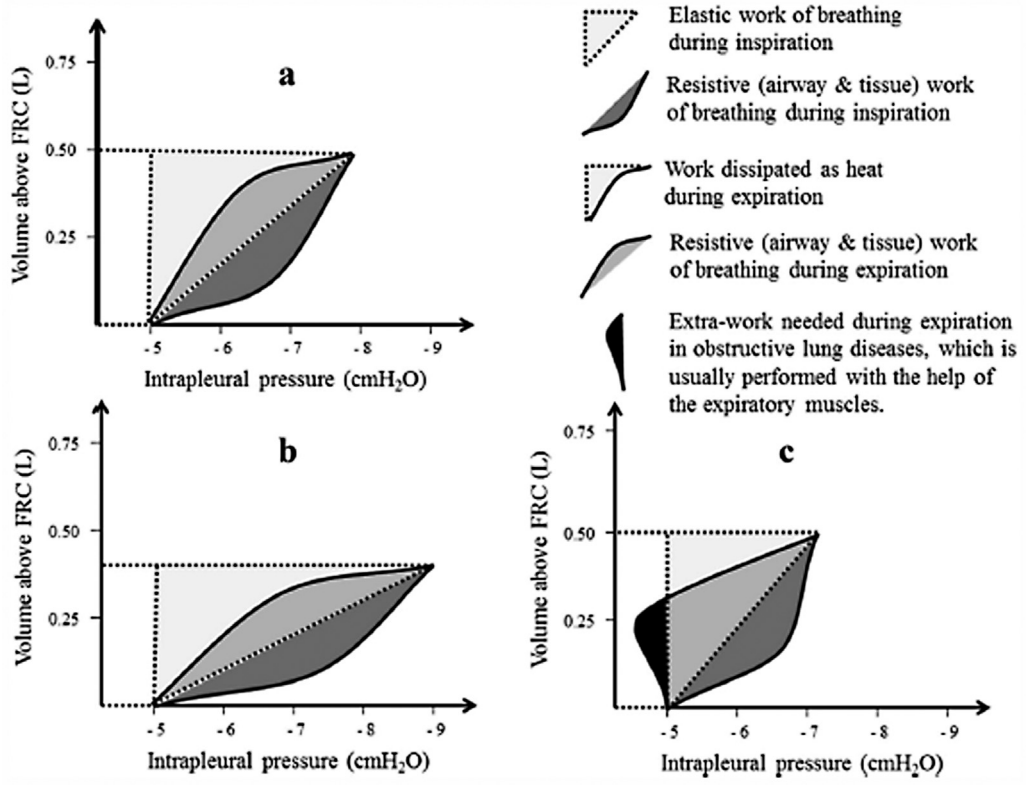

Fig. 1 Work of breathing in a healthy person (**A**) Compared with a person with increased lung elastance (**B**) or increased airway resistance (**C**). Notice for the person with increased elastance (**B**), the static, elastic work of breathing (area inscribed by diagonal dotted line) is increased as seen by the reduced slope of Volume versus Pressure, indicating decreased compliance, but there is relatively normal resistive work of breathing on both inspiration and expiration. Notice for the person with increased airway resistance (**C**), static, elastic work of breathing is normal (normal slope of volume vs. pressure), but there is increased resistive work during expiration due to airway narrowing from airflow obstruction. FRC, functional residual capacity. Reproduced with permission from Lufti 2017.[1]

also useful for assessing the contribution of intrinsic positive end-expiratory pressure to work of breathing in patients with obstructive lung disease.[2]

Let us examine each of the components of work separately, using the equation of motion describing the lung in its most simplified form, an inflatable balloon on a rigid pipe to represent a single compartment, linear system.[3] The equation of motion states that the pressure (P) necessary to move air into and out of the lung is determined by the sum of the associated forces involved, which include airway resistance (R), lung parenchymal elastance (E), and gas inertance (I):

$$P = E\Delta V + R\Delta\dot{V} + I\Delta\ddot{V}$$

where ΔV = change in lung volume, $_{\Delta}\dot{V}$=airflow, and $_{\Delta}\ddot{V}$ = gas acceleration. Airway resistance refers to the frictional forces that develop when air moves by bulk flow through the pipe. Elastance is the reciprocal of compliance and refers to the stiffness of the lung parenchyma that must overcome to expand the alveoli. Inertance is the force developed by the acceleration of the mass of gas within the system as it moves from mouth to alveoli and back again.

To accomplish airflow, a driving pressure must be provided to overcome airway resistance, which is related to pressure and flow as described by analogy to Ohm's law

$$R = \Delta P/\Delta\dot{V}.$$

Air flows in two general patterns: laminar, when the pathways of airflow are parallel to the side wall of the flow conduit, and turbulent, when airflow pathways are random and chaotic (►**Fig. 2**). Whether air flows in either of these patterns is described empirically by the Reynold's number (Re)

$$Re = \frac{\rho v d}{\mu}$$

where ρ = density, v = velocity, d = diameter, μ = viscosity

When Re < 2,000, airflow tends to be laminar, and when Re > 2,000 it is more likely to be turbulent. Under laminar conditions, the pressure required to achieve flow is described by Poiseuille' law

$$\Delta P = [8l\mu\dot{V}]/\pi r^4.$$

When flow is turbulent, the pressure required to achieve flow is greater (now $\Delta P \propto \dot{V}^2$ and gas density (ρ), rather than viscosity), which results in a higher work of breathing.[4]

$$\Delta P = [8l\rho(\dot{V}^2)]/\pi r^4.$$

Since laminar versus turbulent flow is related to the Reynold's number, laminar flow can be enhanced by either slower airflow, larger airways, or less dense or more viscous gas. When patients with asthma or chronic obstructive

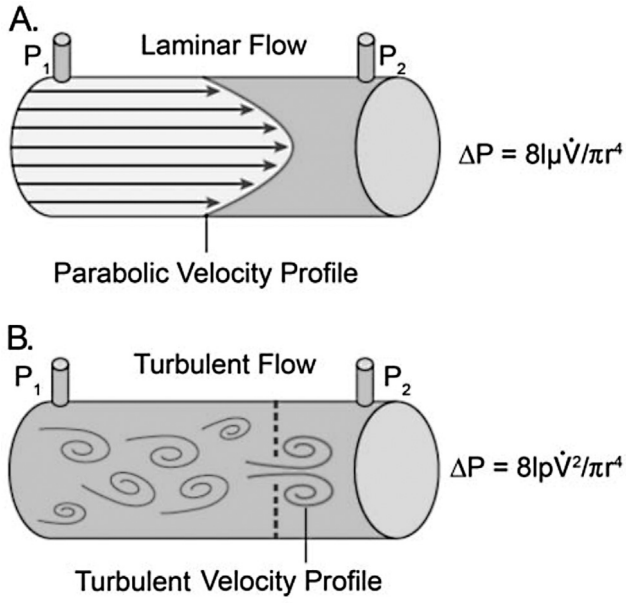

Fig. 2 The difference between laminar (**A**) and turbulent (**B**) flow. Notice that the change in pressure required to drive flow when flow is laminar is directly proportional to length (*l*), viscosity (μ), and flow $\Delta P \propto \dot{V}^2$, and inversely proportional to radius (*r*) to the fourth power, whereas for turbulent flow, pressure is proportional to similar parameters except density (ρ) instead of viscosity, and the square of flow ($\dot{V}^2$) rather than directly to flow. Reproduced with permission from Bossé et al 2010.[4]

pulmonary disease (COPD) are struggling to breathe due to excessively turbulent airflow, the work of breathing can be reduced by dilating the airways with inhaled bronchodilators. One could also provide a gas with less density or more viscosity than air, such as the mixture of helium and oxygen (heliox), although this is not commonly used and is of uncertain clinical benefit.[5] Slower airflow is achieved by breathing at lower respiratory frequency, so for the same minute ventilation, a patient with obstructive lung disease will minimize their work of breathing by breathing at a low respiratory rate and a higher tidal volume (►**Fig. 3**).

The airways are arranged in a complex, branching system of series and parallel airways such that total airway resistance (R_{tot}) is the sum of the reciprocals of the resistances of each parallel pathway:

$$\frac{1}{R_{tot}} = \frac{1}{R_1} + \frac{1}{R_2} + \cdots \frac{1}{R_n}$$

where R_n = resistance of airway at the nth generation.

While airway diameter quickly decreases moving distally, the total cross-sectional area increases exponentially, resulting in the highest total airway resistance between the fourth and eighth generation of airways and less as one moves more distally (►**Fig. 4**). This concept is important in explaining why overall changes in airway resistance are very sensitive to changes in central airway diameter but markedly less sensitive to changes in peripheral airway diameter. It is estimated that at rest, the lung periphery only accounts for 10% of total airway resistance, explaining why this area is difficult to

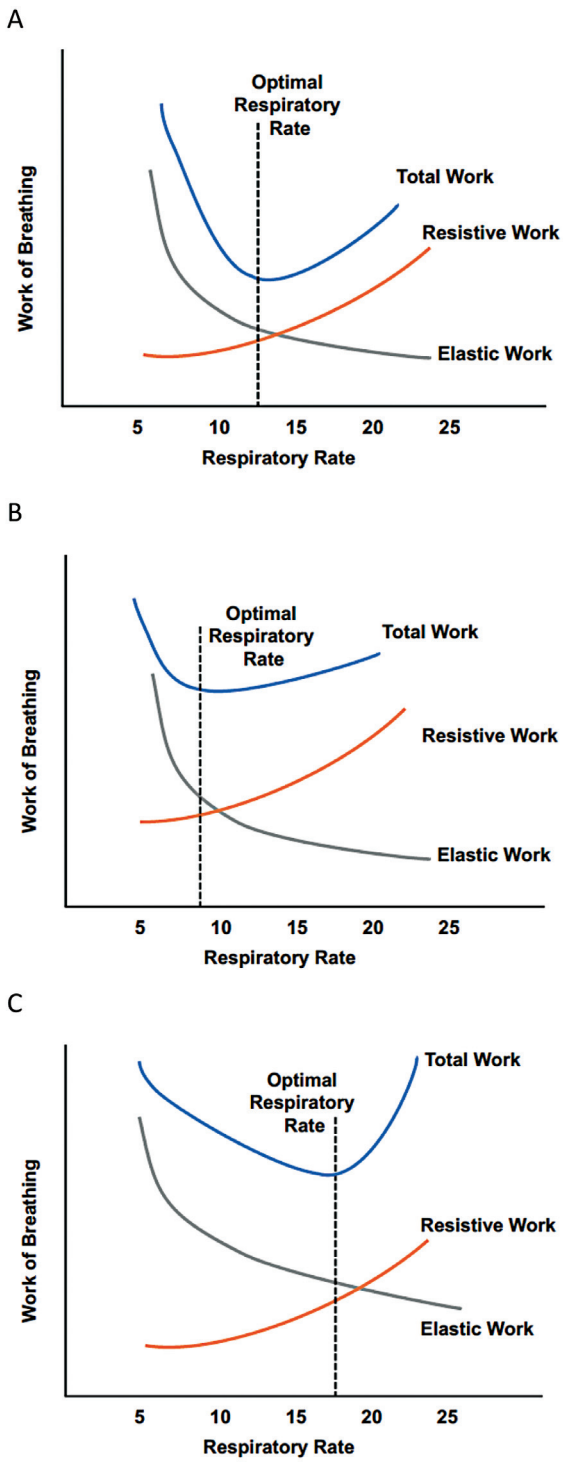

Fig. 3 Illustration of how optimal respiratory rate is determined by minimizing work of breathing. Three situations are shown: normal resistance and elastance (**A**), increased airway resistance (**B**), or increased elastance (**C**). For a given minute ventilation, elastic work increases at lower respiratory rates because larger tidal volumes, and hence lung stretch, are necessary. Likewise, airflow work is the highest at higher respiratory rates because airway resistance varies with airflow velocity. Adding together elastic and resistive work produces the total work curve. Notice how a person with increased airway resistance will adopt a lower respiratory rate (and higher tidal volume), whereas a person with increased elastance will adopt a higher respiratory rate (and consequently lower tidal volume) than a person with normal mechanics.

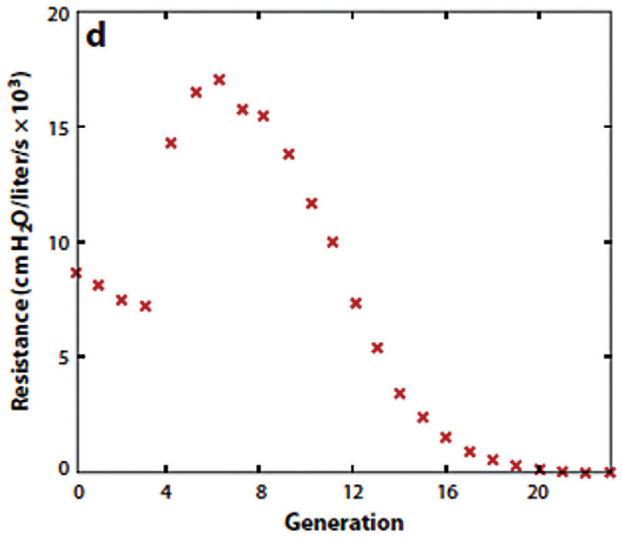

Fig. 4 Total airway resistance as a function of location within the airway tree as designated by airway generation. Notice that the highest resistance occurs at the segmental bronchial level (generations 4–8) and resistance falls with subsequent airway generations. Reproduced with permission from Bossé et al 2010.[4]

detect by conventional spirometry and hence dubbed "the quiet zone."[6]

Since airway resistance is highly dependent on airway diameter, lung volume plays a key role in determining airway resistance because of the mechanical linkage of the airway wall to its surrounding lung parenchyma, known as airway–parenchymal interdependence.[7] Thus, as lung volume increases, so will airway diameter, which will greatly reduce airway resistance (►**Fig. 5**). Other factors that influence airway resistance by altering airway diameter, such as airway smooth muscle (ASM) tone, airway wall thickness and geometry, and airway inflammation, are discussed in the section on airway hyperresponsiveness.

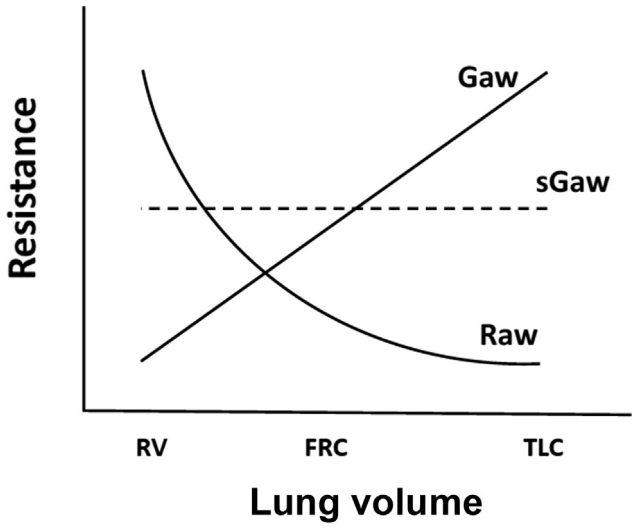

Fig. 5 Dependence of airway resistance on lung volume. While airway resistance (R_{aw}) varies inversely and hyperbolically with lung volume, its reciprocal, airway conductance (G_{aw}) varies linearly and directly with lung volume. Dividing G_{aw} by the volume at which it is measured results in specific G_{aw} (sG_{aw}), which is independent of lung volume. FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity.

Airway resistance (R_{aw}) can be measured by several methods.[8] In the pulmonary function laboratory, R_{aw} is commonly measured during body plethysmography by relating mouth pressure to airflow via

$$R_{aw} = \frac{P_{mouth}}{P_{box}} x \frac{P_{box}}{Flow}.$$

Because of its important dependence on lung volume, R_{aw} is adjusted to lung volume by expressing it as its reciprocal, airway conductance (G_{aw}), divided by the lung volume at which it was measured to arrive at specific G_{aw} or sG_{aw} (►**Fig. 5**).

Respiratory system resistance can also be determined by oscillometry. Oscillometry, also known as the forced oscillation technique, involves having an individual breathe passively while a superimposed oscillatory flow of air is applied to the mouth. The resulting pressure oscillations measured at the mouth in response to the superimposed "forced" oscillatory flow are recorded and related in time to the applied oscillatory signal. Pressure in phase with flow reflects respiratory system resistance, whereas pressure out of phase with flow represents respiratory system reactance (the sum of elastance and inertance of the respiratory system). Conventionally, the flow signal is applied across a frequency range of ~5 to 40 Hz. At 5 Hz and greater, respiratory system resistance is predominantly comprised of airway resistance.[9]

A second important component of the work of breathing is the compliance of the lung and chest wall (usually described by its reciprocal, elastance, in the equation of motion). The elastic forces of these respiratory system components are discussed in the preceding chapter. Based on the Campbell diagram, one can see that there is substantially more pressure required to achieve a given lung volume when elastance is high (e.g., in idiopathic pulmonary fibrosis [IPF]) than when it is low (e.g., in emphysema; ►**Fig. 1**). There is no direct treatment that relieves the high elastance of lung tissue in diseases like IPF, so patients will try to minimize their work of breathing by breathing at a lower tidal volume (less lung stretch), therefore requiring a higher respiratory rate to achieve the same minute ventilation (►**Fig. 3**).

The third component of the equation of motion is inertance, related primarily to the acceleration of the gas column with the central airways.[10] Since this does not significantly contribute to increased work of breathing until relatively high frequencies (>12 Hz), inertance is usually not considered clinically important.

Physiology of the Flow–Volume Loop and Forced Expiratory Airflow

Flow–Volume Loop

The fundamental measure that characterizes lung function is the forced expiratory volume in 1 second (FEV_1). Surprisingly, this seemingly arbitrary assessment of lung function is highly reproducible, defines airflow obstruction (when related to the total amount of air exhaled, the forced vital

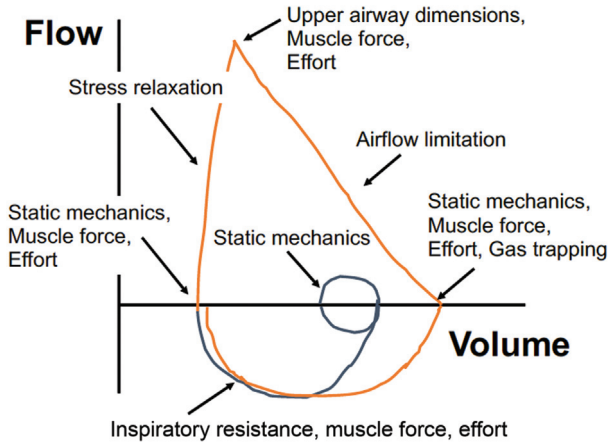

Fig. 6 Mechanical events involved in determining the key components of the maximal flow–volume loop. See text for details.

capacity, FVC, by the ratio FEV_1/FVC),[11] tracks disease severity, control, and progression over time, and is independently related to important patient outcomes such as symptoms, quality of life, and mortality.[12–15] FEV_1 is measured by spirometry, which requires a person to breathe on a mouthpiece, take in a full deep breath of air, and then, without hesitation, blast the air out as hard and as fast as they can until their lung empties. The FEV_1 is measured as the volume expired in the first second of an acceptable forced expiratory maneuver. The details of measuring and interpreting spirometry are discussed below, but before discussing these details, one must understand the physiological determinants of FEV_1 and FVC (►**Fig. 6**).

To achieve an acceptable FVC, an individual must be able to inspire fully to total lung capacity (TLC). This full, deep inspiration (DI) requires proper motivation and effort on the part of the individual, as well as sufficient inspiratory muscle strength and patency of the upper airway to achieve full deep inflation.[16] Once at TLC, the individual must blast the air out as hard and fast as possible, and this, once again, requires proper motivation and effort, sufficient muscle strength, and normal patency of the upper airway. Furthermore, it is important that there be no hesitation prior to the start of exhalation because of the tendency of the elastic elements in the lung to relax when held in distension, a property called "stress relaxation" that reduces the elastic recoil force of the exhalation and hence the resulting maximal flow.[17] As the lung empties, the volume of the lung decreases, and the airways diminish in size. In addition, the force of exhalation causes airway compression along the compliant, intrathoracic airways, resulting in airway narrowing. The end result is the development of expiratory flow limitation within the airways.

Expiratory flow limitation indicates that maximal expiratory flow is governed by the physical interactions of the compressible airway and the surrounding pleural pressure. Maximal flow is effort independent, because as more effort is applied, more airway narrowing takes place, limiting enhanced airflow. Expiratory flow limitation during forced exhalation has been described by two different but interrelated mechanisms. A simple view is the development of the equal pressure point (EPP), which is the location along the airway where the inside and outside pressures are equal and opposite (►**Fig. 7**).[18,19] From the EPP toward the mouth, the airway pressure is less than surrounding pleural pressure and so the airway wall will buckle and continue to narrow as flow approaches the mouth. The independent forces governing maximal flow ($\dot{V}_{max}$) in the collapsible airway are the elastic recoil of the lung (P_{el}) and the resistance of the airways upstream (i.e., toward the alveoli) from the EPP (R_{us}).[18]

$$\dot{V}_{max} = \frac{P_{el}}{R_{us}}.$$

As can be seen by this equation, maximal flow is reduced by loss of elastic recoil (lower P_{el}), such as seen in emphysema, or increase in (upstream) airway resistance (higher R_{us}), such as seen in asthma. As forced exhalation proceeds and the lung empties, the EPP will migrate deeper and deeper

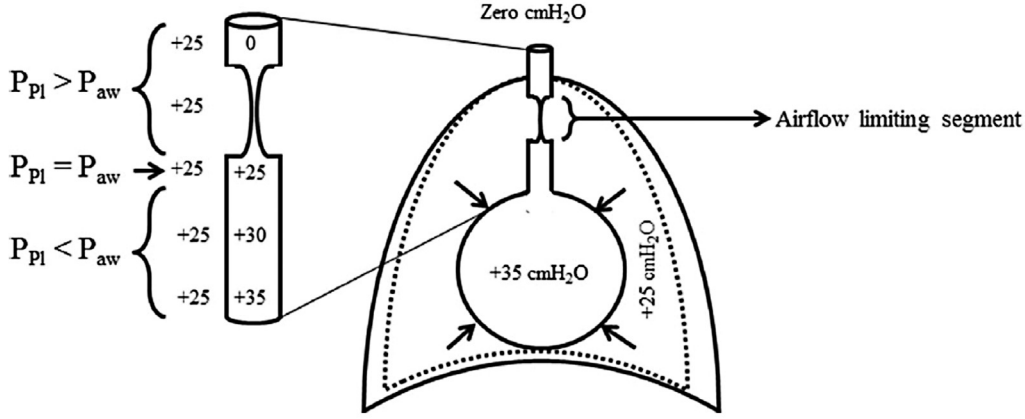

Fig. 7 Illustration of the equal pressure point (EPP) concept explaining expiratory airflow limitation. During forced exhalation, pleural pressure (P_{pl}) is positive (+25 cm H_2O), which together with lung elastic recoil (+10 cm H_2O) results in a markedly positive intra-alveolar pressure (+35 cm H_2O) well above atmospheric pressure. This results in expiratory airflow. The pressure within the airway (P_{aw}) drops from intra-alveolar to atmospheric and somewhere along the way becomes equal to the surrounding pleural pressure (the EPP), around 25 cm H_2O . At this point and beyond toward the mouth, the flexible airway will narrow, limiting airflow. Reproduced with permission from Lufti 2017.[1]

into the lung as the elastic recoil of the lung drops and the surrounding pleural pressure more quickly exceeds inside airway pressure.

While the EPP mechanism explains expiratory flow limitation on the basis of the viscous properties of a gas flowing through a collapsible tube, another mechanism explains airflow limitation on the basis of "wave speed" theory,[20] which depends on the density of the gas and airway collapsability.[21] By this mechanism, the flow ($\dot{V}$) of air through a collapsible tube can never exceed the speed at which a pressure wave can propagate through the wall of the tube, regardless of the driving force (alveolar pressure minus mouth pressure = atmospheric pressure, or zero) behind it. This theory of flow limitation is dependent on the cross-sectional area of the airways (A), the collapsibility of the airway under pressure (dP/dA), and density of the gas (ρ);

$$\dot{V}\,\max = A\sqrt{\frac{A}{\rho}\left(\frac{dP}{dA}\right)}.$$

This formula indicates that maximal flow ($\dot{V}_{max}$) varies (1) directly with the area (A) of the tube, such that narrowing of the tube results in reduced flow (as occurs in asthma); (2) directly with the stiffness (dP/dA) of the tube, such that a more collapsible (less stiff) tube results in reduced flow (as occurs in emphysema); and (3) inversely with the density of the gas. The latter effect is exemplified by the higher peak expiratory flow (PEF) in patients with status asthmaticus when breathing a mixture of helium and oxygen that has a lower density than air.[22] During pressure wave propagation, the sides of the tube oscillate inward and outward to accommodate the wave, and at some point the amplitude of the inward oscillation would approach the radius of the tube such that the two inner sides would meet, causing a choke point that would limit flow.[21] This is somewhat analogous to the EPP explained above.

Once airflow has diminished and no further lung volume is expired, the lung has reached residual volume (RV). As the name indicates, the lung is not empty of all air; instead, a residual amount of air remains. The volume at which this occurs is determined by the maximal strength and effort provided during exhalation as well as chest wall compliance, because the muscle force to reduce lung volume must overcome increasing outward chest wall recoil. In addition, as airways narrow at lower lung volume, some will narrow to the point of closure or near closure before the communicating distal airspace has fully emptied, resulting in trapped gas that contributes to the RV.[23]

Measurement of Airflow and Vital Capacity by Spirometry

Methodology of Measuring Spirometry

Technical details for performance of spirometry were initially developed in 1979[24] have been updated several times since[25–27] with most up-to-date version published jointly by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 2019.[28] Electronic spirometers

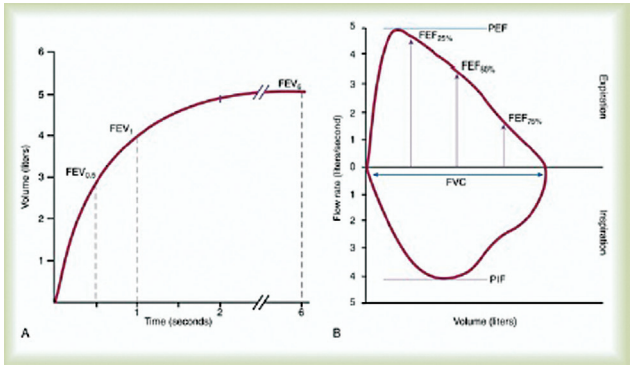

Fig. 8 (**A**) Maximal forced expiratory spirogram (volume time curve). Volume (L) is on the vertical axis and time (sec) on the horizontal axis. (**B**) Expiratory and inspiratory flow–volume curve. Flow rate (L/s) is on the vertical axis and volume (L) on the horizontal axis. Expiration and inspiration above and below the horizontal axis respectively. $FEF_{y\%}$, forced expiratory flow at y-percentage of the expired vital capacity; FEV_x, forced expiratory volume at x seconds; FVC, forced vital capacity; PEF, peak expiratory flow; PIF, peak inspiratory flow. Reproduced with permission from Douse.[29]

produce both a volume–time and a flow–volume curve (►**Fig. 8**).[28] Values obtained from the spirogram include the FEV_1, the FVC, and the forced expired flow between 25 and 75% of the FEV ($FEF_{25-75\%}$).[28] Additional values include the $FEV_{0.75}$ used in children under 6 years of age and the FEV_6, which can be used as a surrogate for FVC.[28] The FEV_3/FEV_6 ratio has also been studied.[28] From the flow–volume curve PEF and FEF at 25, 50, and 75% of vital capacity can be obtained.

Interpretation of Spirometry

Obstruction

Airflow obstruction is identified by a reduced FEV_1/FVC ratio and its severity by the degree of FEV_1 reduction. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has recommended a fixed ratio of <0.7 to define obstruction,[30] but, since this is markedly age-dependent (falling with age),[31] the preferred approach is to use the lower limit of normal defined as the fifth percentile,[11] 1.645 standard deviation below the Global Lung Initiative (GLI) predicted values.[32] Schemes for quantification of severity of obstruction over the last 2 decades[11,29,32,33] are summarized in ►**Table 1**. The current ATS/ERS recommendation discourages use of FEV_1% predicted to grade severity and instead recommends using *z*-scores below the predicted FEV_1,[11] −1.645 to −2.5 mild, −2.5 to −4 moderate, and > −4 severe obstruction.[11] Disproportionate reduction of flows in the latter part of expiration (e.g., $FEF_{25-75\%}$, $FEF_{75\%}$) may signify distal airway obstruction.[33] The shape of the flow–volume curve can suggest intra- or extrathoracic variable obstruction or fixed obstruction.[33] Even though obstruction is typically characterized by a reduction in FEV_1 in the presence of a low FEV_1/FVC, obstruction may also result in a reduction in FVC from hyperinflation (see below).[23]

Table 1 Definitions and categorization of airflow obstruction using the FEV_1 and the FEV_1/FVC ratio

	Pauwels 2001[30] Ratio < 0.7	Pellegrino 2005[33] Ratio < LLN[a]	Quanjer 2014[34] Ratio < LLN	Stanojevic 2022[11] Ratio < LLN
Obstruction: severity classification	FEV_1 (% predicted)	FEV_1 (% predicted)	FEV_1 (*z*-score)	FEV_1 (*z*-score)
Mild	>80%	>70%	< −2	−1.65 to −2.5
Moderate	50–80%	60–70%	−2 to −2.5	−2.5 to −4
Moderate–severe		50–60%	−2.5 to −3	
Severe	30–50%	35–50%	−3 to −4	> −4
Very severe	<30%	<35%	> −4	

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.
[a]LLN = lower limit of normal (5th percentile or *z*-score = − 1.645).

Restriction

Nonobstructive reduction in both FEV_1 and FVC (i.e., with a normal FEV_1/FVC) raises the possibility of restriction; measurements of lung volume are required to confirm this as restriction is defined by a low TLC.[11] While restriction is typically thought of in association with parenchymal lung disease causing reduced lung compliance, it may also be seen in any process that reduces TLC, such as space-occupying extrapulmonary disease (e.g., pleural effusion), reduced compliance of the chest wall (e.g., obesity, kyphoscoliosis), or neuromuscular disease resulting in muscle weakness (e.g., amyotrophic lateral sclerosis). Once pulmonary restriction is confirmed, the FVC is commonly used to monitor disease status.

Bronchodilator Response

A bronchodilator response is often tested at the time of spirometry to determine whether there might be significant ASM constriction contributing to airway narrowing. Because of the acute response being investigated, short-acting β agonists (SABA's) are the standard bronchodilator agent used. The mechanism of action of a β-agonist bronchodilator is related to stimulation of β2 adrenergic receptors on ASM resulting in smooth muscle relaxation. Other mechanisms may also be operative. For example, the very act of taking a deep breath may result in some bronchodilation by direct relaxation of ASM.[35] In addition, another action of β-agonists is stimulation of surfactant,[36] which could result in reduced airway fluid surface tension allowing airway widening. Interestingly, a deep breath is also a potent stimulus for surfactant secretion,[37] so taking a deep inhalation of SABA may have dual bronchodilator actions. The bronchodilator response allows faster and better lung emptying, resulting in a lower end-expiratory lung volume and less hyperinflation, as well as reduced gas trapping, both of which may have profound consequences for improvement in symptoms of shortness of breath.[38]

Bronchodilator response is assessed by repeat determination of FEV_1 and FVC 15 minutes following administration of a bronchodilator. While the choice of agent and dose is optional, a suggestion is salbutamol (albuterol) 100 µg 4 puffs.[33] Significant bronchodilator improvement was previously defined as a 12% and 200-mL increase in FEV_1 and/or FVC from baseline.[33] The ATS/ERS currently recommends that to minimize age and sex differences, a significant response is an increase in FEV1 or FVC of more than 10% of their respective predicted values.[11] This defines significant difference from normal but provides minimal distinction between different types of airway disease.[11] It is recommended against assessing bronchodilator response at various points in the FVC ($FEF_{25-75\%}$, $FEF_{50\%}$, $FEF_{75\%}$, etc.)[11] since they will be measured at different absolute lung volumes.[28,39,40] Of note, a bronchodilator response may also be defined by other criteria related to FEV_1 or FVC or changes in lung volumes[41] as well as changes in oscillatory resistance or reactance.[9]

Dynamic Hyperinflation

When airflow obstruction is present, a fundamental problem is insufficient time for full exhalation because expiratory flow is reduced. This may lead to a situation of incomplete lung emptying prior to the next inhalation, resulting in hyperinflation.[23] Another mechanism of hyperinflation is persistent inspiratory muscle activity during what would otherwise be a normal, passive exhalation through an open glottis. In this situation, FRC may not return to its fully relaxed level, resulting in hyperinflation.[42] If hyperinflation occurs during exercise or other reasons for increased ventilation, progressive elevation of end-expiratory lung volume may occur. This process is known as "dynamic hyperinflation" and is related to the degree of flow limitation as well as the time available for exhalation (►**Fig. 9**). Dynamic hyperinflation can also occur at rest during exacerbation of underlying disease such as COPD.[43] Dynamic hyperinflation results in severe dyspnea due to progressive flattening of the diaphragms and expansion of the chest, resulting in decreased mechanical advantage of the respiratory muscles. Progressive lung volume expansion also results in an increased work of breathing as the respiratory system now sits at a flatter position on its pressure–volume curve.[43] It also raises FRC to such a point that inspiratory capacity (IC) decreases, resulting in severe dyspnea.[44] The work of breathing is also increased because the respiratory muscles must generate enough inspiratory pressure to overcome any trapped, residual positive pressure within areas of gas trapping, similar to autopeep described in mechanical

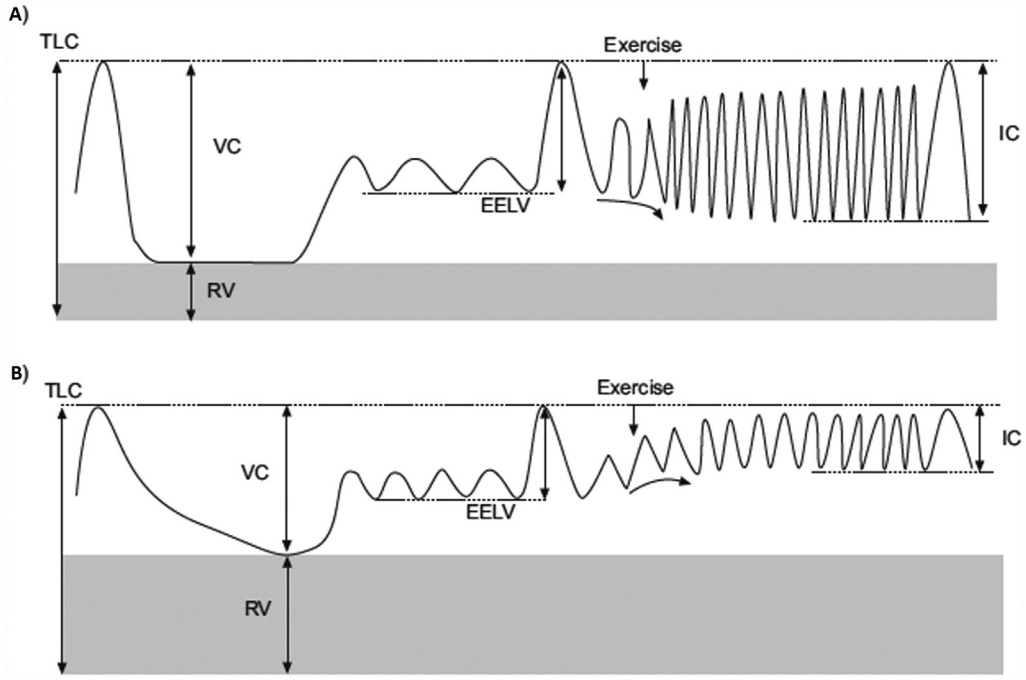

Fig. 9 Dynamic hyperinflation. Shown are typical volume versus time tracings in a healthy person (**A**) and a person with airflow obstruction (**B**), as they do a slow vital capacity maneuver (VC), breathe quietly at rest with end-expiratory lung volume (EELV) at functional residual capacity (FRC), and then take in a full deep inspiration (inspiratory capacity, IC) to total lung capacity (TLC). Exercise then starts as shown by the vertical downward arrow. In the healthy person, the IC during exercise becomes progressively larger as the EELV drops toward residual volume (RV) and the end-inspiratory lung volume rises toward TLC. In a person with airflow obstruction, who already starts off with a higher RV and EELV (FRC) at rest, limited time for exhalation only allows the IC to increase in the direction of TLC, not decrease toward RV, resulting in progressive elevation of the EELV, or dynamic hyperinflation. Reproduced with permission from O'Donnel DE.[45]

ventilation. Dynamic hyperinflation may also result in impaired gas exchange, since it is an uneven process resulting in more heterogeneous matching of ventilation and perfusion.[46] In addition, dynamic hyperinflation has been shown to have hemodynamic consequences since venous return through the pressurized, hyperinflated thoracic cavity may be compromised and result in reduced cardiac function and increased pulmonary artery pressures, further contributing to dyspnea.[46] Dynamic hyperinflation can be assessed using spirometry by tracking changes in IC before and after exercise.[47]

Airway Hyperresponsiveness

Airway hyperresponsiveness (AHR) refers to the increased sensitivity and response of the ASM to constrict following exposure to a stimulus. It is considered a defining feature of asthma, although AHR can also be observed in patients following upper respiratory tract infection (particularly due to viral causes), and in those with COPD,[48] cystic fibrosis,[49] and cardiac disease.[50]

The dual nature of increased sensitivity and response to a stimulus was first demonstrated in asthma by Woolcock et al,[51] who administered increasing doses of a bronchoconstrictor to healthy people and individuals with asthma and observed that AHR was characterized by both increased sensitivity (leftward shift in the dose–response curve) and increased maximal response. AHR is diagnosed when a lower dose of agonist causes a prespecified response, such as a 20% fall in FEV_1 when methacholine is the agonist.[52] Similarly, the fall in FEV_1 can be plotted on a linear dose axis to calculate the dose–response slope, providing a measure of AHR in all subjects, and not just those whose response meets the prespecified threshold.[53]

Mechanisms of Airway Hyperresponsiveness

Multiple mechanisms are implicated in the phenomenon of AHR (►**Fig. 10**).[54] Alterations in ASM function may result in increased contractile force[55,56] or speed.[57] Airway remodeling may result in increased airway wall thickness and thus geometric enhancement of any degree of ASM contraction on airway narrowing.[58,59] Airway remodeling may also disrupt the mechanical linkage of the airway wall to the surrounding lung parenchyma, reducing the tethering of the airway wall (airway–parenchymal interdependence) and thus enabling enhanced airway narrowing for any degree of ASM contraction.[60] The mechanical linkage of the airway to surrounding lung parenchyma is critical to understanding the effects of deep inflation and lung volume on ASM tone and AHR.[7] In health, periodic DI's result in stretch of ASM and cause bronchodilation.[7] DI's may also protect against subsequent bronchoconstriction.[61] In asthma, external ASM loads are thought to be decreased because of peribronchial inflammation and edema, which serve to uncouple the airway wall

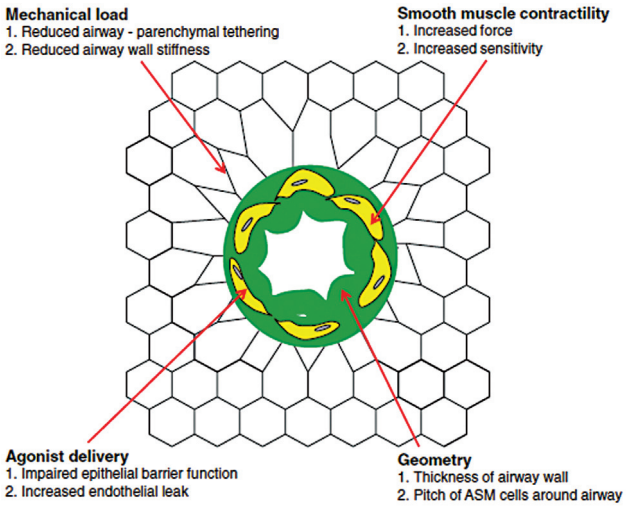

Fig. 10 Mechanisms involved in airways hyperresponsiveness (AHR). Shown is a theoretical cross-section of an airway embedded in its surrounding parenchymal alveolar attachments. Major factors involved in AHR include altered airway smooth muscle (ASM) mechanical load or contractility, changes in airway wall geometry, and changes in agonist delivery. Not shown is the variability in subsequent regional airflow resulting in ventilation heterogeneity, which may also predispose to AHR. Reproduced with persmission from Bates.[62]

from the surrounding alveolar tethering units, a phenomenon referred to as loss of interdependence.[60] Loss of interdependence not only allows the ASM to constrict more for a given force, but also uncouples the airway wall from the lung parenchyma such that the airways dilate less in response to a DI. DI bronchoprotection is also lost in asthma,[63] which is thought to be a primary cause of AHR.

Resting lung volume can also play a role in determining AHR. Healthy individuals can develop AHR by voluntary breathing at low lung volume, lying supine, or increasing the external load on the chest wall, all of which result in a low volume state that can increase AHR.[64–66] Three mechanisms are thought to contribute. First, breathing at low lung volume may allow ASM to adapt to a shorter length thereby generating increased force and greater airway narrowing.[67] Second, a reduction in FRC would reduce the outward tethering forces exerted on the airways by the lung parenchyma,[68] allowing the airways to narrow more in response to a bronchoconstricting stimulus. Third, both voluntary low lung volume breathing[69] and chest wall strapping increase ventilation heterogeneity,[66] which computational modeling predicts would predispose to localized and exaggerated airway closure upon ASM stimulation[70] (see discussion of ventilation heterogeneity as a mechanism of AHR below). Indeed, chest wall strapping leads to exaggerated airway closure during bronchial challenge.[71]

Other mechanisms of AHR are also described. Since the airway epithelium acts as a barrier between the outside environment and the ASM underneath, any disruption in the airway epithelium may allow easier and quicker access of inhaled bronchoconstricting agents (e.g., methacholine) to the ASM, resulting in AHR.[72] Changes in environmental conditions at the airway epithelium surface, particularly low humidity, may result in local water loss and increased airway surface fluid osmolarity, triggering the release of bronchoconstricting mediators like histamine and cysteinyl leukotrienes from airway mast cells;[73] this is thought to be the primary stimulus for AHR in response to exercise. Even ventilation heterogeneity has been shown to contribute to AHR[74] and enhance AHR.[75] Computational modeling predicts that a positive feedback mechanism may develop that allows a small degree of induced bronchoconstriction on a heterogeneously narrowed airway tree to result in an "avalanche" effect of airway narrowing and closure throughout the tree.[70]

Table 2 PD_{20}[a] diagnostic cut points

Classification	PD_{20}[a] (μg)[b]	Comparable English-Wright 2-min tidal breathing PC_{20}[c] (mg/mL)
Normal	>400	>16
Borderline AHR	>100–≤400	>4–≤16
Mild AHR	>25–≤100	>1–≤4
Moderate AHR	>6–≤25	>0.25–≤1
Marked AHR	≤6	≤0.25

Abbreviations: AHR, airway hyperresponsiveness; FEV1, forced expiratory volume in 1 second.
[a]PD_{20} = provocative dose causing a 20% fall in FEV1.
[b]PD_{20} after taking into account evaporation if a jet nebulizer is used.
[c]PC_{20} = provocative concentration causing a 20% fall in FEV1.

Methodology of Measuring Airway Hyperresponsiveness

AHR may be measured by either direct or indirect airway challenge. In direct challenges, agents such as methacholine are administered that act directly on ASM to cause bronchoconstriction. Increasing doses of inhaled methacholine are administered in a standardized fashion to determine the provocative dose that causes a 20% fall in FEV_1 (PD_{20}-FEV_1, ►**Table 2**).[52] If the PD_{20}-FEV_1 < 100 μg, AHR is defined, whereas a PD_{20}-FEV_1 > 400 μg is considered normal (no AHR). PD_{20}-FEV_1 values between 100 and 400 μg are considered borderline. Due to the bronchodilating effect of a deep inhalation, it is recommended that methacholine challenge be performed using tidal breathing rather than 5 deep breaths to avoid overestimating the PD_{20}-FEV_1, which may miss mild AHR (►**Fig. 11**).[52] Indirect challenges involve inhalation of agents that act secondarily on ASM and thus mimic the more natural condition of asthma.[71] Common indirect challenges include exercise and mannitol, both of which result in ASM constriction through an osmotic stimulus as described above; standardized protocols for each have been published.[71] Differential features comparing indirect and direct challenges are summarized in ►**Table 3**. Indirect challenges reflect airway inflammation, whereas direct challenges reflect ASM function. Therefore, direct challenges are thought to be more sensitive but less specific for asthma, so are useful for ruling out asthma at the time of testing,

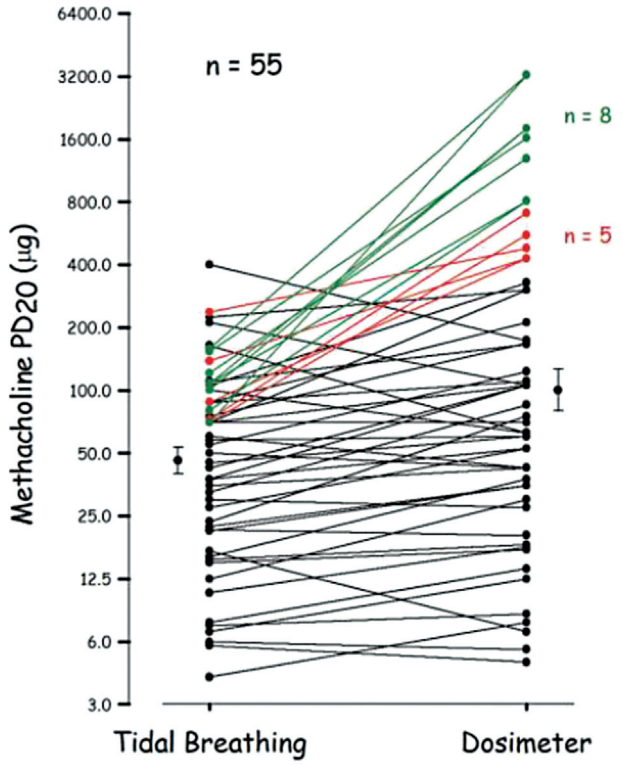

Fig. 11 Comparison of methacholine provocation dose causing a 20% FEV_1 fall (PD_{20}) performed in 55 asthmatics by the two allegedly equivalent methods outlined by the American Thoracic Society document in 2000 (Crapo et al[78]). The 2-minute tidal breathing PD_{20} is shown on the left and the deep inhalation dosimeter PD_{20} is shown on the right (both on a log scale). The geometric mean tidal breathing PD_{20} is 45 µg and the dosimeter PD_{20} 103 µg ($p < 0.00001$). The eight participants in green had dosimeter PD_{20}s between 800 and 3,200 µg and the five in red values between 400 and 800 µg. Reproduced in modified form (PC_{20} in mg/mL replaced with PD_{20} in µg) from Cockcroft and Davis.[79]

whereas indirect challenges are more specific but less sensitive for asthma.[76,77]

Conclusion

This chapter has highlighted the dynamics of the respiratory system. We need to understand the underlying principles governing airway resistance, lung elastance, and airflow to understand the events and work associated with tidal breathing. Likewise, a full appreciation of FEV_1 requires understanding the concept of airflow limitation during forced exhalation through collapsible airways. Important aspects of altered airflow and its consequences include bronchodilator responsiveness, dynamic hyperinflation, and airway hyperresponsiveness.

Conflict of Interest
None declared.

Acknowledgment
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Table 3 Comparison of direct and indirect challenges

	Direct challenge e.g., methacholine	Indirect challenge e.g., mannitol
Muscle function	++++	++
Airway calibre	++++	±
Inflammation	Nil to ++	++++
Dose required	Low	Higher (1,000-fold)
Deep inhalations	Bronchoprotection	No effect
Refractory period	±	++++
Cromolyn inhibition	Nil	++++
Diagnostic sensitivity	High	Low
Diagnostic specificity	Low to moderate	High
Diagnostic value	Rule out	Rule in

Notes: + to ++++ = less to more highly associated.
± = equivocal.

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