Chapter 7
Breathing In and Out: Airway Resistance

David A. Kaminsky and Jason H. T. Bates

7.1 Introduction

In order to fully appreciate the complexities of pulmonary airflow, one must consider all of the pressures necessary to move air into and out of the lung. These pressures are required to overcome the elastic stiffness of the lung and chest wall, the frictional resistance to airflow offered by the airways and parenchymal tissues, and the inertia of the gas within the central airways. Considering the respiratory system as a single expansible unit served by a single airway conduit, these pressures add to give the so-called equation of motion:

$$P(t) = EV(t) + R\dot{V}(t) + I\ddot{V}(t) \tag{7.1}$$

where P is the total pressure across the respiratory system, V is the volume of gas in the lungs (referenced to some initial volume, usually functional residual capacity – FRC), $\dot{V}$ is flow entering the airways, and $\ddot{V}$ is volume acceleration. The constants E, R, and I are termed elastance, resistance, and inertance, respectively. This chapter will focus on the component of R that is due to flow of air through the pulmonary airways. This component, known as airway resistance, can be measured in several different ways and is of major clinical significance.

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7.2 What Is Resistance?

By definition, resistance, R, is the pressure required to produce a unit flow through a system. It is convention in the field of lung function measurement to express pressure in units of cmH_2O and gas flow in liters per second (L/s). The unit of resistance is thus $cmH_2O/L/s$, or $cmH_2O.s/L$. The resistance of a conduit, or tube, is simply the difference in pressure, ΔP, between the two ends of the conduit divided by the flow through it. That is,

$$R = \frac{\Delta P}{\dot{V}} \tag{7.2}$$

R is thus a measure of function, but it can be related to structure: a high value of R is indicative of a long and/or narrow conduit, and vice versa. The precise link between structure and function reflected in R depends on many factors, but under certain ideal circumstances this link can be stated in relatively straightforward mathematical terms based on the laws of physics.

Qualitatively, there are two steady flow situations that are important to understand. When flow is sufficiently low, the flow streamlines, observable from the behavior of a very thin stream of smoke injected into the flow at some point, move along parallel with the bulk flow in an orderly fashion. This is known as *laminar flow* (Fig. 7.1a). At the other extreme, when flow is sufficiently rapid, the streamlines cannot be visualized at all because the injected smoke stream immediately swirls around to quickly encompass the entire diameter of the tube. This is known as *turbulent flow* (Fig. 7.1b). Most real flow situations are neither perfectly laminar nor completely turbulent, but rather sit within a transition region between these two extremes. Nevertheless, it is useful to consider how R is linked to tube geometry under the ideal condition of laminar flow through a rigid cylindrical conduit, because here it is possible to derive an equation for R from first physical principles. The result is known as the Poiseuille equation given by

$$\Delta P = 8\mu L\dot{V} / \pi r^4 \tag{7.3}$$

where L is the length of the conduit, μ is gas viscosity, and r is the radius of the conduit. An equivalently precise formula for turbulent flow does not exist, but empirically R still varies inversely with r to the fourth power and linearly with l, similar to Eq. 7.3. An important difference between laminar and turbulent flow, however, is that while R is constant during laminar flow, as shown by Eq. 7.3, R increases roughly linearly with increasing flow when flow is turbulent. Also, whereas R is proportional to the viscosity of the gas when flow is laminar, R is determined by the density of the gas when flow is turbulent.

Of course, airflow through the pulmonary airways is not precisely steady because it reverses direction with every breath. In addition, the airways themselves are not perfectly rigid or perfectly cylindrical, and they branch frequently over a range of

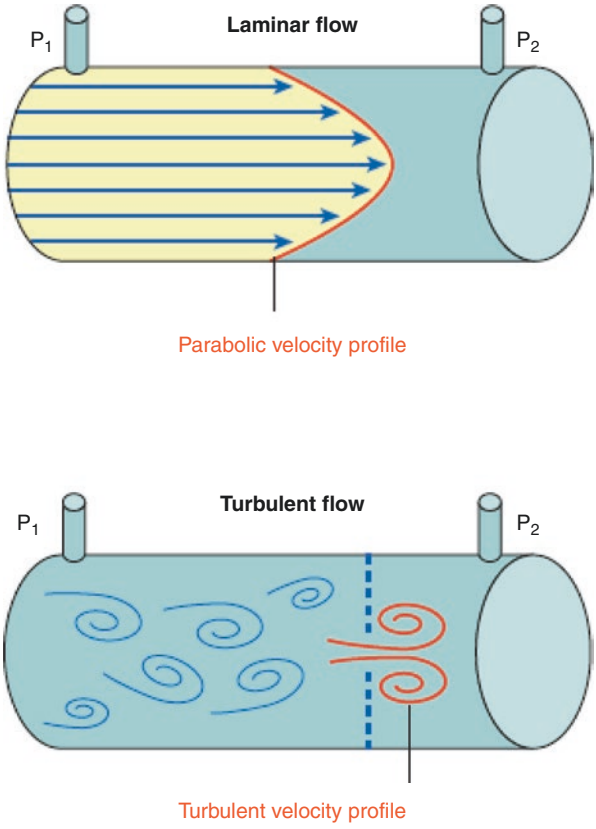


Fig. 7.1 (**a**) Illustration of laminar flow through a rigid tube, where the resistance to flow is constant with flow. (**b**) Illustration of turbulent flow through a rigid tube, where the resistance to flow varies roughly linearly with flow. (From Bossé, Riesenfeld, Paré, and Irvin 2010, with permission from Annual Review of Physiology)

angles, so the flow through them is neither laminar nor turbulent. Accordingly, the relationship between Raw and flow can only be stated empirically. An expression that has been widely used in pulmonary physiology and medicine is the so-called Rohrer equation

$$\text{Raw} = K_1 + K_2\dot{V} \tag{7.4}$$

where K_1 and K_2 are constants that have no particular physical interpretation but nevertheless serve as useful empirical quantifiers of airway pressure-flow characteristics.

Thus, to the extent that the pulmonary airways can be viewed as behaving like a single conduit, the above discussion provides an understanding of the key factors that influence airway resistance, Raw. Most importantly, it illustrates the incredibly powerful effect of airway radius on function; if airway radius decreases by 50%, for example, then Raw increases by 16 times!

Of course, the airways are not a single conduit, but rather comprise a branching tree structure that can be viewed as having multiple generations from the trachea

(generation 1) down to the terminal bronchioles (roughly generation 23, although this varies considerably because the airway tree branches asymmetrically). As generation number increases, the diameters of the airway branches decrease. However, the total airway cross-sectional area increases dramatically beyond about generation 6. Thus, even though the resistance of a single airway branch at generation n may be high, the airway branches become so numerous as generation number increases that this offsets the increase in individual branch resistance. This can be seen from the formula for the total resistance of many airway branches in parallel. If Raw_n is the contribution to Raw from all m branches of generation n, and Rn_1, Rn_2, …, Rn_n are the resistances of the m individual branches, then

$$\frac{1}{\mathrm{Raw}_n} = \frac{1}{\mathrm{Raw}_1} + \frac{1}{\mathrm{Raw}_2} + \ldots + \frac{1}{\mathrm{Raw}_n} \tag{7.5}$$

The result of this is that the distal airways in a normal lung make a negligible contribution to overall Raw, a phenomenon that has led to the lung periphery being termed the *silent zone*.

Total respiratory resistance (Rrs) includes not only Raw but also the resistance of the chest wall (Rcw) and the resistance of the lung tissues (Rti). Rcw and Rti arise from dissipative processes within the chest wall and lung tissues themselves as a result of frictional interactions between their constituents. At normal breathing frequencies (10–12 bpm), Rti contributes about 40% to total Rrs, while Rcw is negligible. The component of Raw due to the large central airways accounts for roughly 50% of Rrs, while the small airways (< 2 mm in diameter) account for only about 10% because of their very large combined cross-sectional area.

Airflow is determined by airway resistance in normal lungs at the modest flows associated with breathing at rest. However, during maximally forced expiration or in severe obstructive disease, flow is limited by dynamic airway collapse, which itself is strongly influenced by transpulmonary pressure. During the resulting flow limitation (see Chap. 6), the conventional concept of resistance as developed above does not apply.

7.3 The Importance of Lung Volume

The relationship of Raw to the fourth power of radius reflects the critical importance of the caliber of an airway on the ease with which air can move through it. Accordingly, the factors that are most important for increasing Raw are those that cause radius to decrease. These factors include transpulmonary pressure (Ptp), airway smooth muscle contraction, airway inflammation and mucus secretion that may either thicken the airway wall or partially occlude the airway lumen, and dynamic airway compression. Of these, Ptp is particularly potent because of its effect on the ability of the airway smooth muscle to shorten when stimulated. Ptp is transmitted

across the intrapulmonary airway walls by the alveolar walls that are attached to their outside borders. These alveolar walls exert an outward tethering effect on the airway wall that opposes smooth muscle shortening and hence limits the degree to which the airways can narrow. Ptp decreases with decreasing lung volume, which results in increased airway narrowing from smooth muscle constriction, with an inverse dependence on volume that becomes particularly strong as volume descends below normal FRC. Conversely, at high lung volumes, the radial traction from tethering increases, and a greater opposing load is presented to airway smooth muscle, which reduces airway narrowing from smooth muscle constriction. For this reason, increasing Ptp through a deep lung inflation is one of the most effective ways of reversing bronchoconstriction in normal lungs. Interestingly, bronchoconstriction becomes worse after a deep inflation in some asthmatic subjects, but the reasons for this remain controversial and poorly understood.

Lung volume is often altered in disease and thus has a direct effect on Raw. For example, in obstructive disease, airway closure and hyperinflation may raise FRC and thus reduce Raw. In restrictive lung disease, patients breathing at low lung volumes may have increased Raw, but if associated with increased elastic recoil of the lung parenchyma, such as in pulmonary fibrosis, any tendency for Raw to increase is offset by increased radial traction of the surrounding lung. Of note, obesity commonly results in increased Raw due to the reduced lung volumes that result from mass loading by the adipose tissues of the chest wall and abdomen. Any such reduction in volume has the potential to substantially increase airways responsiveness, which may at least partly explain why asthma is so common in obese individuals.

7.4 Measurement of Airway Resistance by Body Plethysmography

Traditionally, airway resistance has been measured by relating airflow and driving pressure through the use of body plethysmography, providing measures of Raw, specific airway resistance (sRaw), and specific airway conductance. In 1956, Dubois and colleagues described the plethysmographic method that we still use today. The principle of measuring Raw through body plethysmography is based on *Boyle's law*, which expresses how the pressure in a gas is related to the amount by which its volume has been compressed (see Chap. 3).

To calculate airway resistance, one needs to know flow and alveolar pressure; the former can be measured directly, but the latter cannot. What Dubois realized was that under conditions of no-flow, mouth pressure would approximate alveolar pressure. Therefore, resistance is calculated by combining two measurements: one of flow vs. box pressure, and the other of mouth pressure vs. box pressure (from which TGV is measured, see Chap. 3) (Fig. 7.2). In this way, flow vs. mouth pressure (as a surrogate for alveolar pressure) can be inferred at equal box pressures, allowing the calculation of airway resistance, Raw. For a more detailed explanation, see the Appendix A.

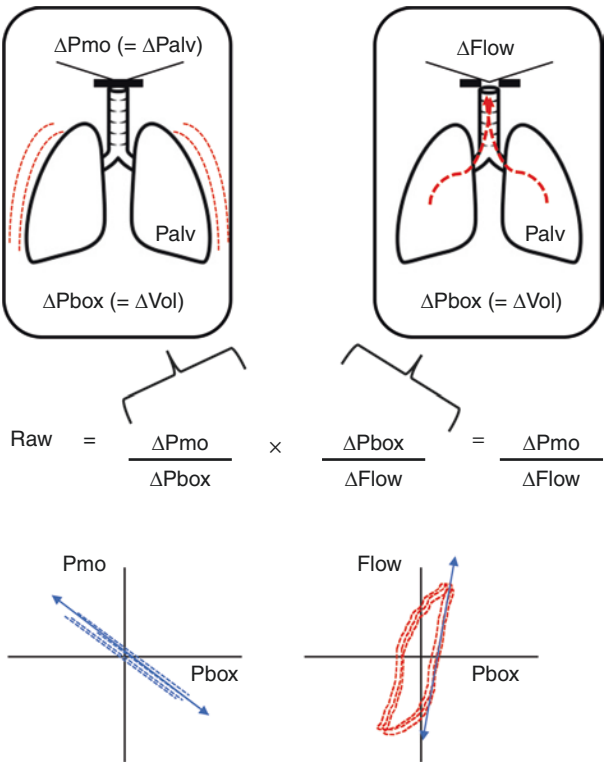


Fig. 7.2 Relationship of mouth pressure and box pressure by body plethysmography under closed-loop panting conditions (left) and open-loop panting conditions (right). Under conditions of no-flow (left), mouth pressure (P_{mo}) would approximate alveolar pressure (P_{alv}), so the relationship of alveolar pressure to change in lung volume (Vol) (as determined by change in box pressure, P_{box}) is measured. When the shutter is opened (right), the relationship between flow and lung volume (change in box pressure) is measured. Airway resistance (Raw) is calculated as the change in alveolar pressure ($\sim P_{mo}$) divided by flow, which is derived by multiplying the slope of the closed-shutter maneuver (bottom left) and the inverse slope of the open-shutter maneuver (bottom right), with the P_{box} (volume) terms canceling out

A few technical details are important to keep in mind. During the measurement of flow vs. box pressure, the patient breaths with rapid, shallow panting breaths through the circuit at a frequency of 1.5–2.5 Hz (90–150 breaths per minute) for 1–2 s (Fig. 7.3). The rapid shallow panting is designed to optimize the signal-to-noise ratio and increase the accuracy of measurement by (1) minimizing thermal shifts and gas exchange, (2) maintaining glottic opening, (3) minimizing flow turbulence and gas compression, and (4) ensuring a measureable difference between P_A and Pao. During the measurement of mouth pressure vs. box pressure, a shutter is closed occluding the mouthpiece, and the patient is asked to pant at a rate of 0.5–1.0 Hz (30–60 breaths per minute) for 1–2 s (Fig. 7.3). This relatively slower rate is meant to allow adequate time for equilibration of mouth and alveolar pressure.

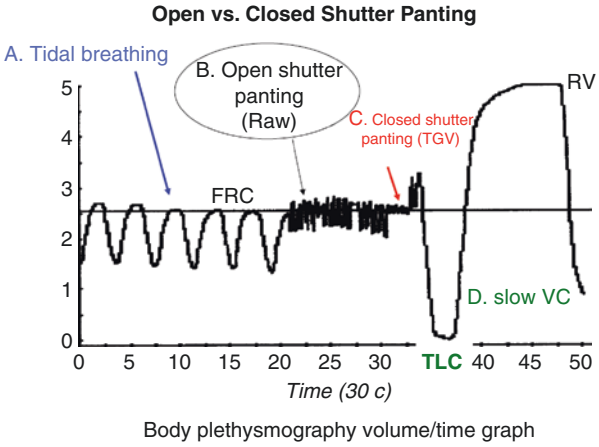


Fig. 7.3 Tracing of volume vs. time in a patient having Raw measured. Following tidal breathing (A), there is a brief period of open-shutter panting (B), followed immediately by closed-shutter panting (C). Patient then typically performs a slow vital capacity maneuver (D)

Once the open- and closed-shutter panting maneuvers are complete, the slope of the relationship between mouth pressure and box pressure is determined. The slope is conventionally taken at the transition between the end of inspiration and the beginning of expiration between +0.5 and − 0.5 L/s flow (Fig. 7.4). This low flow range is chosen to mimic the normal range of flow during quiet breathing and ensure that flow is mostly laminar to allow the principles of Poiseuille's law to apply. However, measuring the slope may be difficult because of the potentially complicated configurations of these curves. Multiple technical issues can influence the shape and size of the open-panting loops (Fig. 7.5). Airway resistance as measured by body plethysmography is usually expressed as Raw defined by Eq. 7.6. However, Raw varies inversely with lung volume because bigger airways have a smaller resistance than smaller airways. Consequently, Raw is usually normalized to lung volume to become *specific airway resistance*, sRaw, defined as

$$\text{sRaw} = \text{Raw} \times V_{\text{TG}} \tag{7.6}$$

or its inverse known as *specific airway conductance*, sGaw (Fig. 7.7)

$$\text{sGaw} = \frac{1}{\text{sRaw}} \tag{7.7}$$

Both sRaw and sGaw are thus independent of changes in lung volume that may occur between different measurement conditions in a given subject and so are useful for studies involving serial measurements of lung function separated by significant time intervals. The increased sensitivity of sGaw for airway resistance compared to FEV1 is especially useful in pharmacological studies that involve normal healthy

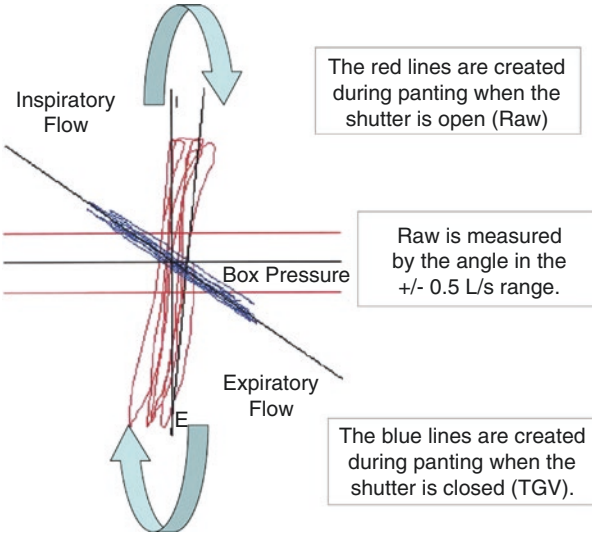


Fig. 7.4 Close-up of open- and closed-shutter panting loops. Open-shutter panting is shown in red, and the loops move clockwise during shallow panting including inspiration (positive *y*-axis) and expiration (negative *y*-axis). The slope of flow vs. box pressure (angled black line) is conventionally measured at the end of the inspiratory loop between +0.5 and − 0.5 L/S (horizontal red lines). Closed-shutter panting is shown in blue where the *y*-axis is now mouth pressure and the *x*-axis remains box pressure

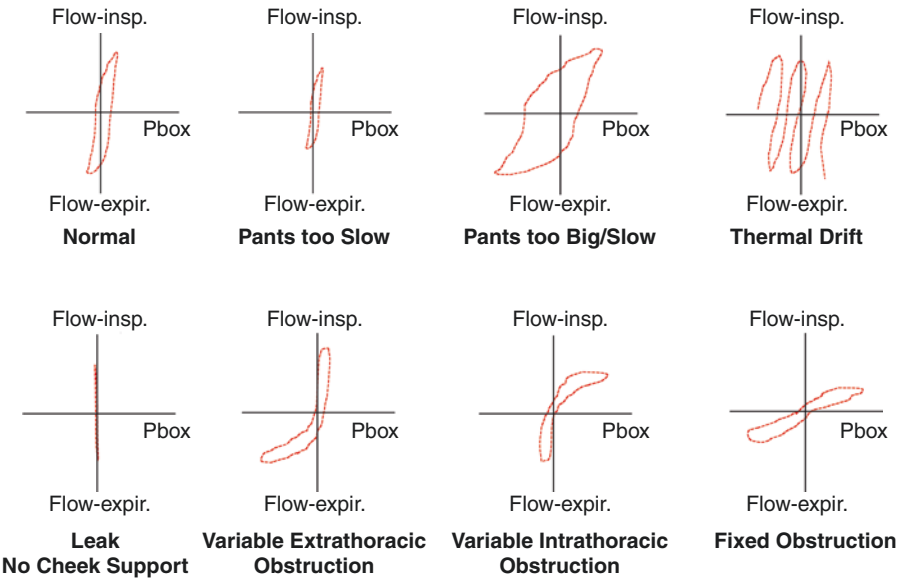


Fig. 7.5 Examples of normal and abnormal open-shutter loops, plotted on *y*-axis of inspiratory (negative *y*-axis) vs. expiratory flow (positive *y*-axis) versus *x*-axis of box pressure (P_{box})

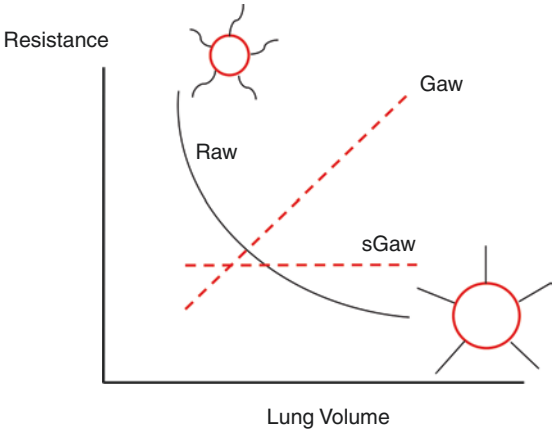


Fig. 7.6 Relationship between Raw and lung volume (hyperbolic), with increased tethering of airways (circles) resulting in increased airway diameter and lower Raw at higher lung volumes. Notice the relationship of the reciprocal of Raw (Gaw) to lung volume (linear, but still dependent on lung volume) and Gaw/TGV (sGaw) to lung volume (horizontal, independent of lung volume)

subjects. However, sGaw is less reproducible than FEV1, and thus it must be measured repeatedly to determine an accurate mean value. Furthermore, there are limited studies establishing normal values for sGaw.

In children, the closed-shutter panting maneuver may be difficult to achieve, so V_{TG} cannot be measured. Instead, flow is related to the small shifts in box pressure (which correspond to changes in lung volume) that occur during tidal breathing to determine sRaw directly, which is calculated as flow divided by changes in box pressure. Multiple different slopes of the flow versus box pressure relationship may be measured, each of which results in a different value of sRaw. The exact slope used in the calculation of sRaw should be specified in the reporting of the results.

7.5 Clinical Utility of sRaw and sGaw

Because the total cross-sectional area of the airways decreases dramatically as one moves from the peripheral to the central regions of the lung, any measure of overall airway resistance, such as sGaw, will be very sensitive to central airway pathology but less sensitive to peripheral changes. Thus, sGaw may pick up changes in large central airways that may be missed by spirometry. Indeed, sGaw has been shown to be sensitive to upper airway involvement in vocal cord dysfunction and vocal cord paralysis. However, sGaw may also be more sensitive to peripheral airway involvement as well, such as what occurs in bronchiolitis obliterans syndrome. This may relate to the loss of sensitivity of FEV1 due to the deep inhalation involved (see below).

Theoretically, sGaw should be sensitive to changes in resistance anywhere along the airway tree, whereas FEV1 will be sensitive to only those changes occurring upstream from the equal pressure point (see Chap. 6). Thus, depending on the location of airway narrowing or dilation in response to a bronchoconstrictor or bronchodilator, FEV1 may change without a significant change in sGaw, and vice versa

(see cases illustrated in Figs. 7.7 and 7.8). In the case of airway narrowing, hyperinflation might result. Spirometry alone may fail to find bronchodilator reversibility in 15% of patients with suspected reversible airway obstruction and clinical responses to bronchodilator, but these patients may be identified by changes in sGaw or V_{TG} or isovolume maximal flow. These results suggest that the patients involved were responding to bronchodilator by changes in clinically relevant lung function parameters related to volume, but not changes in spirometry.

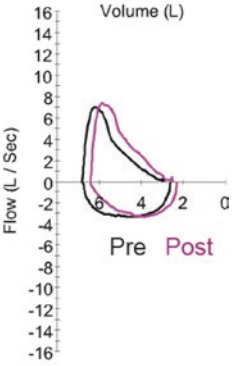
Another factor to consider in differentiating sGaw from FEV1 is the deep breath necessarily associated with performing spirometry, but which is not part of the procedure involved in measuring sGaw. Healthy subjects and those with mild asthma tend to bronchodilate after a deep inhalation. Therefore, mild bronchoconstriction could be masked by the bronchodilating effects of measuring FEV1 but should still be evident in sGaw. This would make sGaw a more sensitive test to detect airflow limitation, especially in mildly obstructed patients. Many studies have investigated the relative response in FEV1 versus sGaw during bronchial challenge tests. For example, the provocative concentration causing a 40% drop in sGaw (PC40 sGaw) was found to be more sensitive than the PC20 FEV1 at detecting bronchoconstric-

Gender: Male Age: 62 years Race: Caucasian

Height: 175 cm. Weight: 99 kg. BMI: 32 (kg/m²)

Clinical Notes: dyspnea on exertion

	Pre-Bronchodilator			Post-Bronchodilator			
Spirometry	**Best**	**%Pred**	**LLN**	**Best**	**%Pred**	**Change**	**%Change**
FVC (L)	3.96	87	3.59	3.92	87	-0.04	0
FEV1 (L)	2.94	87	2.61	3.12	92	+0.18	+5
FEV/FVC	0.74		0.65	0.80			
Lung Volumes	**Actual**	**%Pred**		**Actual**	**%Pred**	**Change**	**%Change**
TLC (L)	7.30	107		6.93	102	-0.37	-5
FRC (L)	3.14	88		2.82	79	-0.32	-10
RV (L)	2.88	128		2.47	110	-0.41	-14
Airway Resistance	**Actual**	**%Pred**		**Actual**	**%Pred**	**Change**	**%Change**
Raw (cm H20/L/s)	2.31	159		1.20	82	-1.11	-37
sGaw (1/cmH20-s)	0.14	70		0.25	124	+0.11	+79



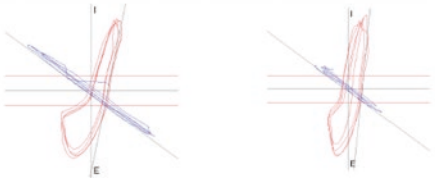


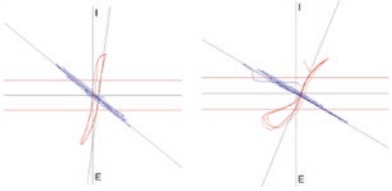
Fig. 7.7 Example of pulmonary function tests performed at baseline and after bronchodilator. Notice that despite no change in FEV1 or FVC after bronchodilator, there has been a 79% increase in sGaw, which was clinically associated with improvement in dyspnea on exertion. Interestingly, there was also a slight drop in FRC and RV, suggesting a beneficial lung volume response to bronchodilator as well

Gender: Male Age: 33 years Race: Caucasian

Height: 173 cm. Weight: 84 kg. BMI: 28 (kg/m²)

Clinical Notes: intermittent cough, shortness of breath

	Diluent			Post-Methacholine (4 mg/ml)	
Spirometry	**Best**	**%Pred**	**LLN**	**Best**	**%Change**
FVC (L)	4.92	94	4.21	4.59	-6
FEV1 (L)	3.77	95	3.14	3.30	-12
FEV/FVC	0.77		0.67	0.72	
Lung Volumes	**Actual**	**%Pred**		**Actual**	**%Change**
TLC (L)	7.34	100		7.56	+3
FRC (L)	2.99	78		3.75	+25
RV (L)	2.23	100		2.86	+28
Airway Resistance	**Actual**	**%Pred**		**Actual**	**%Change**
Raw (cm H20/L/s)	1.65	113		3.82	+131
sGaw (1/cmH20-s)	0.18	90		0.06	-67



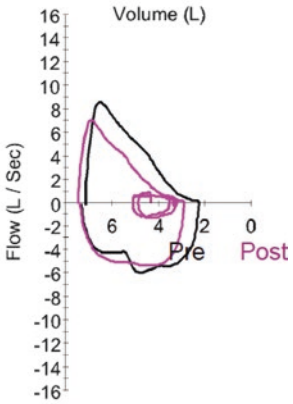


Fig. 7.8 Example of pulmonary function tests performed at baseline and at 4 mg/ml of methacholine during a methacholine challenge test. Notice that despite no significant change in FEV1 at 4 mg/ml (i.e., >/= 20% drop), there has been a substantial decrease in sGaw, which was associated with symptoms of chest tightness and shortness of breath. In addition, there was an increase in FRC and RV, suggesting the development of hyperinflation as well

tion to inhaled histamine, but the PC20 was a more reproducible measure (coefficient of variation = 2.6% vs. 10%). Indeed, combining non-FEV1 parameters, such as sGaw, with FEV1 during a methacholine challenge test increases the sensitivity of the test. Recently, a receiver-operator characteristic analysis demonstrated that the optimal cutoff for change in sGaw corresponding to a 20% fall in FEV1 was 52%. However, the cost of a test with high sensitivity is typically loss of specificity. Indeed, many years ago sGaw was shown to be less specific than FEV1 at distinguishing normal from asthmatic subjects. Another study demonstrated that when the methacholine challenge test was negative, small changes in FEV1 but not in sGaw were predictive of future development of asthma, suggesting again that the FEV1 is a more specific measure for asthma. The differences in response of sGaw versus FEV1 may also reflect underlying differences in anatomy. For example, patients who responded to methacholine with changes in sGaw but not in FEV1 were found to have smaller lung volumes, higher FEV1, and higher FEF25–75/FVC, compared to patients who responded by FEV1 only, indicative of relatively larger airway to lung size, a mismatch referred to as lung dysanapsis. Patients with smaller airway to lung size (lower FEF25–75/FVC) have been found to be more

hyperresponsive than those with larger airways in the Normative Aging Study. Thus, comparing responses in FEV1 and sGaw may lend insight into the basic physical relationship between airway size and lung size.

sRaw is commonly used in children and is sometimes used in adults. Details regarding techniques of measurement, quality control, and interpretation are available in recent, excellent reviews. sRaw has been measured in children as young as 2 years old and has been used in the assessment of bronchodilators and responses to methacholine, histamine, and cold air. Other studies have included measuring the effects of short- and long-acting bronchodilators, inhaled corticosteroids, and leukotriene receptor antagonists in asthmatic children. Serial measurements have been made in children with cystic fibrosis and have demonstrated more consistent abnormalities than either FOT or Rint. Since sRaw is primarily used in children, normative data are mainly limited to pediatrics. As most of the children involved in these studies would likely not have been able to perform reliable spirometry, using sRaw as a measure of airways disease is a valuable tool in pediatric lung disease.

In the case of both Raw and sRaw, there may be circumstances where it is useful to differentiate resistance between inspiration and expiration. For example, inspiratory resistance was shown to be inversely associated with changes in FEV1 in patients following lung volume reduction surgery for emphysema. This may be due to patients with less elevated inspiratory resistance having more predominant emphysema rather than intrinsic airway disease. Since lung volume reduction surgery is thought to work, in part, by removing emphysema and improving elastic recoil, these findings suggest that patients with more emphysema are more likely to have less elevated inspiratory resistance and show improvement following surgery.

7.6 Measurement of Airway Resistance by the Forced Oscillation Technique (FOT)

Although body plethysmography remains a gold standard method for measuring Raw, its use requires patient cooperation and some rather cumbersome equipment that is typically only found in hospital pulmonary function laboratories. These limitations are avoided to a large extent by the forced oscillation technique (FOT) that measures the *impedance* of the respiratory system (Zrs) from which a measure of Raw can be derived, and a related method known as the interrupter technique that provides an interrupter resistance (Rint) approximating Raw.

The FOT was first described by Dubois in 1956 and involves applying controlled oscillations in flow to the lungs via the mouth, while the resulting pressure oscillations at the same location are measured (Fig. 7.9). These oscillations are typically applied while the patient continues to breathe quietly, although they can also be applied during a brief period of apnea. A variety of different oscillatory flow signals have been used for the FOT including white noise, sums of individual sine waves (referred to as composite signals), and trains of brief square pulses. All such signals have the property that they contain multiple frequency components, which allows

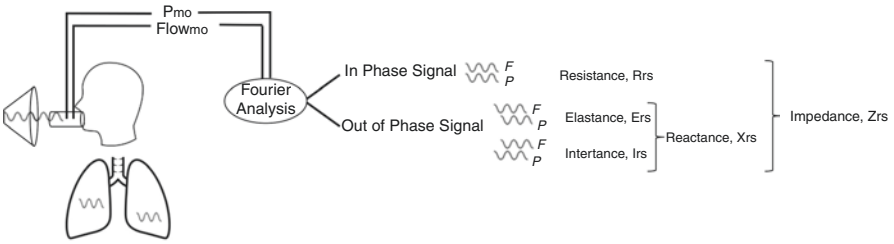


Fig. 7.9 Basic illustration of the forced oscillation technique. The patient breathes through a mouthpiece through which a forced oscillatory flow is produced and transmitted into the airways and lungs. Flow (*F*) and pressure (*P*) are recorded at the mouth and processed in the Fourier domain to produce a complex function of frequency (i.e., one having both real and imaginary parts). This function is known as respiratory system impedance (Zrs). The component of *P* that is in phase with *F* reflects energy dissipation and gives rise to the real part of Zrs, which is known as respiratory system resistance (Rrs). The component of *P* that is out of phase with *F* reflects energy storage and gives rise to the imaginary part of Zrs, which is known as respiratory system reactance (Xrs). The out-of-phase component of *P* is itself composed of two parts; one lags *F* by 90° and reflects the elastic stiffness of the respiratory tissues, while the other leads *F* by 90° and reflects respiratory system inertia

Zrs to be determined simultaneous at each of the frequencies using the fast Fourier transform algorithm. Zrs is thus a function of frequency, *f*, written as Zrs(*f*). In fact, Zrs(*f*) is a *complex function* of frequency, which means it consists of two independent components, a *real part* and an *imaginary part*. The real part is commonly known as *resistance*, Rrs(*f*), while the imaginary part is known as *reactance*, Xrs(*f*). Rrs(*f*) determines how much of the measured pressure oscillations are in phase with the applied oscillations in flow and reflects resistance of the respiratory system. Xrs(*f*) determines how much of the measured pressure oscillations are out of phase with flow and reflects the elastance (*E*) (flow leads pressure) and inertance (*I*) (flow lags pressure) of the system.

During the measurement of Zrs(*f*) by the FOT, an individual sits and breathes quietly on a mouthpiece while wearing a noseclip and supporting the cheeks and floor of the mouth with their hands, similar to the method used in body plethysmography. Once steady tidal breathing is established, the forced oscillations in flow are applied on top of the breathing pattern. Most FOT systems collect oscillatory pressure and flow data for periods of about 16 s of measurement, after which the patient is free to come off the mouthpiece. The pressure, flow, and volume measurements obtained are then processed to produce calculations of Rrs(*f*) and Xrs(*f*) as well as any derivatives of these quantities, such as resonant frequency (f_{res}) and area under the reactance curve (A_X); see below. Subjects may be asked to repeat a FOT measurement 3 to 5 times to provide average values for the final PFT Lab report. For additional interpretation of Zrs(*f*)by the FOT, see the Appendix A.

Rrs(*f*) has a marked negative dependence on *f* below about 2 Hz in normal lungs due to the viscoelastic properties of the respiratory tissues. In obstructive diseases, such as asthma and COPD, Rrs(*f*) becomes elevated due to the decrease in airway caliber (Fig. 7.10). In addition, the negative frequency dependence of Rrs(*f*) often becomes accentuated and may extend well above 2 Hz due to mechanical heteroge-

neities in regional ventilation throughout the lung. These heterogeneities can be distributed in a parallel fashion to different distal lung regions. Alternatively, they can reflect a serial distribution of ventilation where the flow entering the airway opening first enters a proximal compliant compartment, representing the upper and possibly central airways, from which it then moves on through the distal airways to an alveolar compartment. Serial heterogeneity is more likely, on purely physiological grounds, to explain frequency dependence in Rrs(f) above about 5 Hz, in which case Rrs(f) above 5 Hz likely reflects central airways and closely parallels Raw as measured by body plethysmography. Meanwhile, parallel heterogeneity is more likely to be relevant below 5 Hz, in which case Rrs(f) below 5 Hz can be thought of as pertaining to the distal airways. Xrs(f) takes a negative hyperbolic form at low frequencies but then becomes linear as it crosses zero at f_{res}, which is about 8–10 Hz in a normal adult subject. Xrs (f) can be thought of as an overall measure of respiratory system stiffness, in which below f_{res} is dominated by the elastance of the system (due to actual lung stiffness, loss of lung volume, or airway heterogeneities) and above

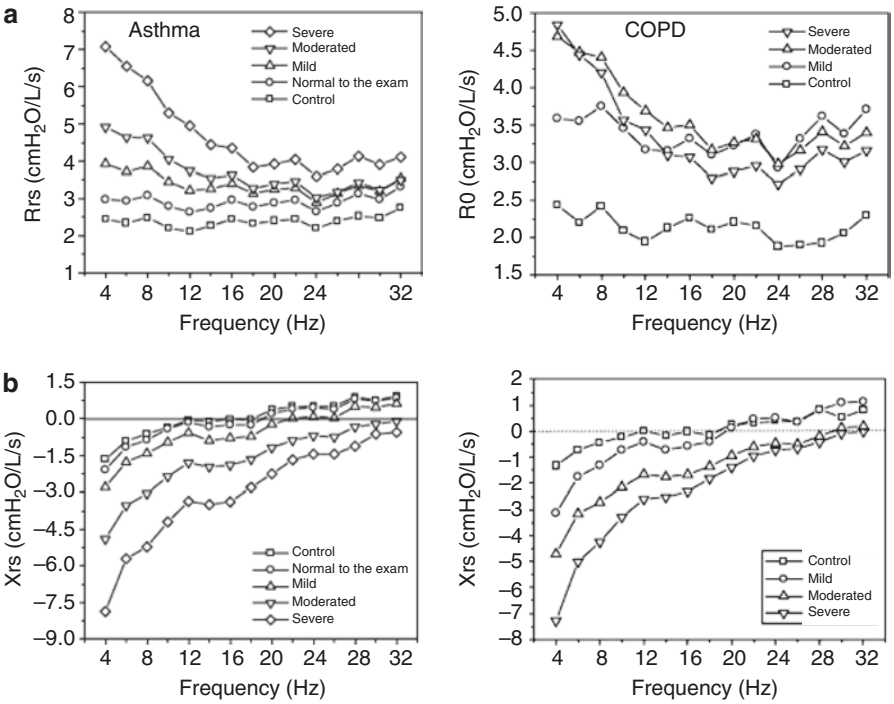


Fig. 7.10 Impedance data from patients with asthma (left) and COPD (right) according to severity of underlying disease. Notice the consistent relationship between diseases of the changes in Rrs and Xrs with increasing severity. In both cases, as severity increases, Rrs rises and becomes more frequency dependent, especially at lower frequencies (< ~16 Hz), and Xrs falls to more negative values, with an increase in the resonant frequency (point at which Xrs crosses zero). (Left = From Cavalcanti 2006, with permission from Elsevier. Right = From DiMango 2006, with permission from Elsevier)

f_{res} is dominated by inertance of the airway gas. Xrs becomes more negative with severity of obstructive disease. As a result, the area under Xrs(*f*) below f_{res}, denoted A_X, also increases and thus serves as a robust, empirical measure of overall respiratory system elastance.

Unlike Raw measured by body plethysmography, Rrs(*f*) measured by the FOT represents total respiratory system resistance and thus contains contributions from both the lung and chest wall. At low frequencies (i.e., <5Hz), Rrs(*f*) is very comparable to Raw but slightly higher due to contributions from the chest wall. At higher frequencies, Rrs(*f*) tends to underestimate Raw, likely due to shunting of flow into the upper airways (i.e., cheeks, floor of mouth). There is no direct comparison that can be made between either Rrs(*f*) or Raw and FEV1 since these quantities reflect different physical phenomena. Nevertheless, both Rrs(*f*) and *Raw* have an important advantage over FEV1 in that they do not involve the subject taking a deep breath, which can reverse any bronchoconstriction that is induced by standard challenge test with a bronchial agonist. Because of this, Rrs(*f*) is highly sensitive to changes in bronchial tone, but it is not particularly specific for asthma or other unique disease states.

7.7 Clinical Utility of FOT

The FOT has become popular because of its ease of administration. It requires minimal subject cooperation and is thus suitable for use in children and any patient who cannot cooperate or manage spirometry (e.g., ventilated patients, paralyzed patients, elderly). The FOT has been used in many applications, including differentiating healthy from obstructed patients in COPD and asthma; detecting bronchoconstriction, which occurs at lower doses of methacholine for Rrs(*f*) than for FEV1; measuring the severity of obstruction in asthma and COPD (Fig. 7.10); detecting early smoking-related changes in lung mechanics in smokers with normal spirometry; and assessing respiratory mechanics in patient with obesity. Methacholine-induced dyspnea is significantly associated with changes in Rrs(5) and Xrs(5), sometimes referred to as R5 and X5, respectively, but not with changes in FEV1, suggesting that these FOT measures are more sensitive to symptoms. However, the most sensitive measurement method varies between healthy and asthmatic subjects and with the degree of severity in asthma.

Since the FOT requires no patient cooperation or technique, it can be applied widely in many clinical settings. For example, only FOT bronchodilator responses, and not responses measured by FEV1, were able to distinguish 4-year-old children at risk for persistent asthma participating in the Childhood Asthma Prevention Study. A similar finding was seen in a cohort of children from Belgium. The FOT has yielded insight into the mechanism of wheezing in infants. It also has unique application in studies of sleep and patients on mechanical ventilation, where the oscillatory signal can be applied on top of tidal breathing. The use of FOT in ventilated and critically ill patients has provided insight into lung derecruitment, paren-

chymal overdistention, and expiratory flow limitation and has the potential to optimize ventilator settings.

Recent studies are tending to focus more on Xrs(*f*), as opposed to Rrs(*f*), since Xrs(*f*) yields information specifically related to the elastic properties of the lung, and these properties often change dramatically in lung disease. In particular, the magnitude of Xrs(*f*) increases in proportion to the amount of lung volume that is lost via atelectasis or closure of small airways. Indeed, in patients with moderate to severe COPD, the fall in FEV1 with methacholine was more closely related to Xrs(*f*) becoming more negative rather than Rrs(*f*) increasing. This occurred in association with a decrease in inspiratory capacity, suggesting that airway closure was the main response to methacholine. Asthmatics had a smaller change in lung volume and a larger change in Rrs(*f*), suggesting they had more of an airway response. In other cases, increases in the magnitude of Xrs(*f*) are thought to be a consequence of the shunting of forced flow into the more central airways that can occur with a sufficient degree of peripheral airway constriction. Xrs(*f*) has been noted to signal mild airflow obstruction before changes in Rrs(*f*) occur and may detect flow limitation in patients with COPD. Also in COPD, there are strong associations between Xrs(5) and resonant frequency and FEV1 and Xrs(5) and f_{res} and sGaw. A recent study in pediatric asthma has shown that only A_X continues to improve after the initial 12 weeks of therapy with inhaled fluticasone during a 48-week total study, perhaps reflecting ongoing improvement in small airway function. Two studies from Japan note that Xrs(*f*) relates more closely with quality of life measures than FEV1 in patients with both asthma and COPD.

One of the benefits of the FOT is that one can separately measure inspiratory from expiratory parameters. While whole-breath FOT may not differentiate patients with asthma and COPD, patients with COPD may have a higher mean expiratory Xrs(5) than patients with asthma, which may be due to enhanced dynamic airway narrowing on expiration in these patients. In comparing FOT in patients with asthma and COPD, only patients with COPD show a significant difference in Xrs(*f*) between inspiration and expiration, which again may relate to dynamic airway narrowing on expiration due to loss of recoil in COPD.

The European Respiratory Society published guidelines on FOT methodology in 2003, and new guidelines are currently being developed. In general, the repeatability of the technique is similar to Raw from body plethysmography and Rint from the interrupter technique (see below). The correlation with spirometry is highly variable, in part because of the deep breath involved in spirometry and also due to the differing mechanics assessed by the two techniques. The FOT is subject to strong influence by upper airway shunting, and this must be carefully controlled. Many regression equations are now available, but they each come from different populations and use different devices and techniques, so their applicability is limited. Recently, normative reference values and bronchodilator responses have been published from healthy people using five different devices.

The FOT is used commonly in research, from clinical studies in human subjects to basic studies of lung mechanics in experimental animal models. For example,

severe asthma is associated with increasing frequency dependence of elastance, thought to be due to more severe peripheral airway resistance causing shunting of flow back into central airways. The FOT applied through the wedged bronchoscope has allowed demonstration of airway hyperresponsiveness of the lung periphery in asthmatics. It must be remembered, however, that the interpretation of Zrs(*f*) depends on mathematical models of the lung, so the physiological information it yields depends on the particular model that is invoked.

7.8 Measurement of Airway Resistance by the Interrupter Technique

A third method to noninvasively measure airway resistance, used primarily in children, is the interrupter technique. The concept here is similar to that used in body plethysmography in the sense that alveolar pressure is estimated from mouth pressure during transient occlusion of the airway opening during which flow, and thus the resistive pressure drop along the airways, is zero. The interrupter technique also shares a formal similarity with the FOT in the sense that it involves an analysis between pressure-flow relationships recorded at the mouth while mouth flow is manipulated by the measuring system; small-amplitude oscillations are forced into the lungs in the case of the FOT, while with the interrupter technique, mouth flow is forced to go from some finite value to zero in a very short period of time by a shutter that closes within a few milliseconds.

Interrupter resistance (Rint) is determined by measuring the difference in mouth pressure immediately after (Ppost) relative to immediately before (Ppre) a rapid interruption of flow at the mouth and then dividing this pressure difference by the flow ($\dot{V}$pre) measured immediately prior to the interruption. That is,

$$\text{Rint} = \frac{\text{Post} - \text{Ppre}}{\dot{V}\text{pre}} \tag{7.8}$$

It is important that the flow be interrupted extremely abruptly, within a few milliseconds, or Rint may be significantly underestimated due to passage of flow past the interrupter value while it is closing. Also, immediately upon occlusion, mouth pressure invariably exhibits rapid damped oscillations due to inertive effects in the respiratory system followed by a slow pressure transient due to tissue viscoelasticity plus any ventilation heterogeneities that might be present (Fig. 7.11). The oscillations obscure Ppost, and by the time the oscillations have decayed away, the subsequent pressure transient is at a different level, so Ppost is estimated by back-extrapolating the transient through the oscillations to the point in time when the occlusion took place (different systems have different algorithms for exactly how this is done, depending on how fast their interruption shutters close). Accordingly, the value of Rint one obtains depends on a variety of technical matters, including whether a facemask or mouthpiece is used. Typically, several repeat measurements are made and the mean or median is reported.

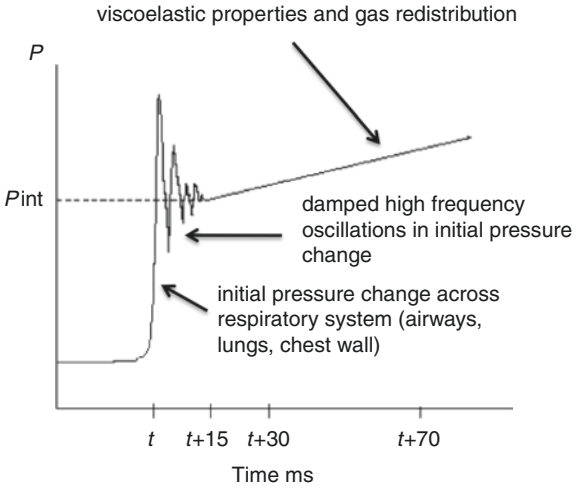


Fig. 7.11 Pressure vs. time during an interrupter maneuver during expiration. At $t = 0$, the airway is transiently occluded, resulting in an abrupt spike in pressure reflecting the initial pressure change across the respiratory system. The pressure then oscillates briefly before slowly climbing as pressure rises from viscoelastic properties and gas redistribution in the lung. By convention, a common method to calculate interrupter resistance (Rint) is to take the pressure at $t + 15$ ms determined by back extrapolation from $t + 30$ and $t + 70$ ms and divide this pressure by the flow immediately before the occlusion. (Adapted from Kooi 2006, with permission from Elsevier)

Animal studies have shown that Rint provides a measure of the flow resistance of the pulmonary airways when the chest is open but includes a contribution from the chest wall in the intact respiratory system, but this applies only when the lung is normal and functionally quite homogeneous. In obstructive pulmonary disease, as with body plethysmography, the assumption of rapid equilibration between mouth and alveolar pressures at zero mouth flow may not hold up very well, which can lead to difficulties in determining the value of Ppost. Nevertheless, because it is noninvasive and performed during normal breathing, the interrupter technique is especially suitable for use in young children and has been demonstrated feasible in children as young as 2 years old. The intrasubject coefficient of variation is similar to that of FOT (5–15%). There is a small group of reference equations that derives from pediatric studies.

7.9 Clinical Utility of Rint

Clinically, Rint has been used in discriminating between different phenotypes of wheezy children and between healthy children and children with asthma. In children with asthma, a correlation coefficient of 0.73 was found for baseline values of spirometry and Rint. Rint has also been used in conjunction with other measures to evaluate bronchodilator response in asthmatic children. In order of discriminating capacity, Raw, R5, Rint, and X5 were found to be useful with positive predictive values of 84%, 74%, 82%, and 76% respectively. The interrupter technique has also

been used to assess the response to cold air inhalation, inhaled fluticasone, and oral montelukast therapy. An important issue with the interrupter technique has been deciding on the best cutoff for a bronchoconstrictor response. In adults, a 20% change in FEV1 following methacholine corresponds to different levels of change of Gaw (the reciprocal of Rint) determined by the interrupter technique, depending on the underlying degree of bronchial responsiveness.

7.10 Comparing sRaw, Rrs(*f*), and Rint

The limited studies directly comparing sRaw, Rrs(*f*), and Rint appear mainly in children. Even though these three measures of resistance are based on somewhat differing mechanical principles, all show consistent changes in relation to disease state or response to bronchodilator or bronchoconstrictor. Furthermore, these measures tend to be more sensitive to bronchodilation and bronchoconstriction than FEV1, with one study demonstrating that Raw was more sensitive than Rrs(*f*) and Rint in detecting bronchoconstriction in normal subjects. Technical factors are critical in achieving valid results, with special attention given to reducing thermal artifact in sRaw, and upper airway shunting in Rrs(*f*) and Rint. All three measures have shown higher values in children with asthma, but there is no clear agreement on cutoffs for abnormal values. This is especially important because even healthy children demonstrate reduced resistance in response to bronchodilators when using these highly sensitive measures. All three measures are commonly abnormal in young children with asthma, but none appear to associate with clinical outcomes assessed 3 years later. sGaw, Rrs(*f*), and Rint allow differentiation of inspiratory and expiratory resistance, and the dynamic looping of resistance and flow with use of sRaw and Rrs(*f*) may yield important information about laryngeal narrowing, a common occurrence during testing. Rrs(*f*) also provides information about frequency dependence, which yields additional insight into peripheral airway mechanics and inhomogeneities. In addition, the FOT and the interrupter technique provide information about the elastic properties of the respiratory system. A summary of the specific measurement properties of FEV1 in comparison with sRaw, sGaw, Rrs(*f*), and Rint is shown in Table 7.1.

7.11 Conclusions

Spirometry remains the gold standard pulmonary function test for determining the presence and severity of airflow limitation. However, spirometry has some key limitations: it is effort dependent and requires patient cooperation and skill, it involves a deep breath that can alter underlying airway resistance, and it provides limited insight into the link between lung structure and function. For subjects who cannot perform spirometry, measuring airway resistance by plethysmography, the FOT, and the interrupter technique remain important options. Measuring sRaw by body plethysmography involves bulky equipment that does not allow portable

Table 7.1 Characteristics of different lung function tests related to airway resistance

	Spiro (FEV1)	Pleth (sRaw, sGaw)	Rint	FOT (Rrs)
Requires patient cooperation/effort	+++	+++	+	+
Involves deep inhalation	+++	–	–	–
Adjusts for lung volume	–	++	–	–
Intrasubject variability (CV)	3–5%	8–13%	5–15%	5–15%
Sensitivity to airway location				
Central	+	++	+++	+++
Peripheral	++	+	+	+++
Cutoff for bronchodilator/ bronchoconstrictor responses	12/20%	25/40%	35%/3SDw	40/50%
Provides insight into respiratory system mechanics	+ Global, non-specific	+ sRaw: Raw, TGV sGaw: Raw	+ Lung + chest wall	+++ Lung + chest wall
Standardized methodology available	+++	++	+	++
Reference equations available	+++	++	++ (peds)	++

Abbreviations: *Spiro* spirometry, *FEV1* forced expiratory volume in 1 s, *Pleth* plethysmography, *sRaw* specific airway resistance, *sGaw* specific airway conductance, *Rint* interrupter resistance, *FOT* forced oscillation technique, *Rrs* respiratory system resistance, *SDw* within subject standard deviation, *TGV* thoracic gas volume, *Peds* pediatrics
"+" to "+++" = Yes, with increasing strength or prevalence of feature
"–" = No

measurement, and it provides an index that reflects both airway resistance and lung volume. In adults, sGaw is typically used to provide a sensitive measure of airway caliber. However, due to high sensitivity, sGaw has poor specificity for asthma or other unique disease states. The FOT is easy to perform with newly available commercial devices, but the method is very sensitive to upper airway shunting. Nevertheless, the FOT provides unique information related to lung mechanics that is not available by other noninvasive techniques. Measuring Rint also presents important technical issues including the upper airway shunt problem but is well-tolerated by very young children. There are no data comparing the clinical utility of these various measures head to head with each other and with spirometry, but measures of airway resistance may provide important physiological information that contributes to the care of the patient.

Appendix A

More Detailed Analysis of Raw by Body Plethysmography

To measure Raw by body plethysmography, one first needs to measure thoracic gas volume (TGV). During panting against an occluded mouthpiece ("closed-shutter panting"), a pressure transducer in the mouthpiece measures the changes in airway opening pressure (ΔPao) that occur with each breathing effort. As Dubois realized, because there is no airflow along the airways during this maneuver, ΔPao must equal the change in alveolar pressure that results in small changes in V_{TG} due to gas compression. At the same time, another pressure transducer measures the pressure changes within the plethysmograph (ΔPpleth). The changes in Ppleth occur because the air around the subject in the plethysmograph becomes cyclically compressed and decompressed as the subject decompresses and compresses, respectively, the air in their lungs as they try to breathe. In fact, the amounts by which V_{TG} and the gas in the plethysmograph change are always equal and opposite, so by knowing the compressibility of the air around the subject (which can be accurately estimated from the geometry of the plethysmograph and the weight of the subject), one can estimate from ΔPpleth what this volume change, ΔV, is. Boyle's law then states that

$$\frac{\text{Atm}}{V_{\text{TG}-\Delta V}} = \frac{\text{Atm} + \Delta Pao}{V_{\text{TG}}} \tag{7.9}$$

where Atm is atmospheric pressure. The only quantity in Eq. 7.6 that is not known is V_{TG}, so it can be solved for explicitly.

With V_{TG} in hand, one proceeds to measure Raw by having the subject breathe freely from the plethysmograph through a pneumotachograph so that mouth flow, $\dot{V}$, is recorded. The subject wears a nose clip and supports the cheeks and floor of the mouth with their hands in order to minimize any pressure losses in the soft tissues of the mouth and throat (so-called upper airway shunting). This ensures that any pressure changes measured are due to flow of air along the lower airways and into the lungs. This flow is caused by a pressure difference between mouth pressure (Pao), which is also recorded, and alveolar pressure (P_A). P_A itself causes the gas in the lungs to be compressed, or decompressed, according to Boyle's law, so this is reflected in changes in Ppleth as described above for the measurement of V_{TG}, and thus yields the amount of gas compression, ΔV, in the lungs. However, since V_{TG} is now known, P_A (relative to Atm) can be solved for through another statement of Boyle's law, namely,

$$\frac{\text{Atm}}{V_{\text{TG}} \mp \Delta V} = \frac{\text{Atm} \pm P_{\text{A}}}{V_{\text{TG}}} \tag{7.10}$$

in which P_A is the only unknown quantity.

Finally, Raw is calculated from the defining equation for resistance,

$$\text{Raw} = \frac{\text{Pao} - P_A}{\dot{V}} \tag{7.11}$$

The difference between Ppleth and P_A during this measurement tends to be rather small, so it is necessary to have the subject breathe at a sufficient rate to make this difference measurable.

The closed-shutter panting maneuver used to measure V_{TG} is typically performed immediately after the open-shutter panting maneuver used to measure Raw, a so-called linked maneuver (Fig. 7.3). During the open-shutter panting maneuver, inspiratory and expiratory flows are plotted against Ppleth (often called *box pressure*, as in Fig. 7.4) and the slope of the relationship, S_{open}, determined. During the linked closed-shutter maneuver to measure V_{TG} (see chapter on lung volumes), inspiratory and expiratory mouth pressure is plotted against box pressure and the slope of the relationship, S_{closed}, determined. Dividing S_{open} by S_{closed} has the effect of combining Eqs. 7.9, 7.10, and 7.11 to provide Raw (Fig. 7.5).

More Detailed Interpretation of Impedance by the Forced Oscillation Technique (FOT)

Interpreting the physiological meaning of Rrs(f) and Xrs(f) must be done on the basis of some model idealization of the respiratory system. At the simplest level, one can think of the system as an elastic balloon on a flow-resistive airway, as was done above in deriving Eq. 7.1. In this case, Zrs(f) is a constant equal to R, while Xrs(f) is equal to $2\pi fI - E/2\pi f$, with E = elastance and I = inertance, as defined previously for the equation of motion of the lung. Importantly, Xrs(f) becomes zero at the so-called resonant frequency, f_{res}, when $2\pi fI - E/2\pi f$, which means that $f_{res} = \left(\sqrt{E/I}\right)/2\pi$. This model is far too simple to represent a real lung, of course, so one invariably finds that Rrs(f) and Xrs(f) exhibit dependencies on f that can only be reasonably interpreted in terms of more complex models.

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