What Does Airway Resistance Tell Us About Lung Function?

David A Kaminsky MD

Spirometry is considered the primary method to detect the air flow limitation associated with obstructive lung disease. However, air flow limitation is the end-result of many factors that contribute to obstructive lung disease. One of these factors is increased airway resistance. Airway resistance is traditionally measured by relating air flow and driving pressure using body plethysmography, thus deriving airway resistance (R_{aw}), specific airway resistance (sR_{aw}), and specific airway conductance (sG_{aw}). Other methods to measure airway resistance include the forced oscillation technique (FOT), which allows calculation of respiratory system resistance (R_{RS}) and reactance (X_{RS}), and the interrupter technique, which allows calculation of interrupter resistance (R_{int}). An advantage of these other methods is that they may be easier to perform than spirometry, making them particularly suited to patients who cannot perform spirometry, such as young children, patients with neuromuscular disorders, or patients on mechanical ventilation. Since spirometry also requires a deep inhalation, which can alter airway resistance, these alternative methods may provide more sensitive measures of airway resistance. Furthermore, the FOT provides unique information about lung mechanics that is not available from analysis using spirometry, body plethysmography, or the interrupter technique. However, it is unclear whether any of these measures of airway resistance contribute clinically important information to the traditional measures derived from spirometry (FEV_1, FVC, and FEV_1/FVC). The purpose of this paper is to review the physiology and methodology of these measures of airway resistance, and then focus on their clinical utility in relation to each other and to spirometry. *Key words: airway resistance; forced oscillation; interrupter technique; body plethysmography; spirometry.* [Respir Care 2012;57(1):85–96. © 2012 Daedalus Enterprises]

Dr Kaminsky is affiliated with the Department of Pulmonary Disease and Critical Care Medicine, University of Vermont College of Medicine, Burlington, Vermont.

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Correspondence: David A Kaminsky MD, Pulmonary Disease and Critical Care Medicine, University of Vermont College of Medicine, Given D-213, 89 Beaumont Avenue, Burlington VT 05405. E-mail: david.kaminsky@uvm.edu.

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Introduction

Spirometry is considered the gold standard method to measure air flow limitation. However, since air flow limitation occurs in part due to increased airway resistance, it makes sense that measuring airway resistance directly may provide additional information. Traditionally, airway resistance has been measured by relating air flow and driving pressure through the use of body plethysmography, thus deriving airway resistance (R_{aw}), specific airway resistance (sR_{aw}), and specific airway conductance (sG_{aw}).[1-4] Other methods to measure airway resistance, which require less cumbersome equipment and less patient technique and cooperation, are the forced oscillation technique (FOT),[5-7] which allows calculation of respiratory system resistance (R_{RS}) and reactance (X_{RS}), and the interrupter technique, which allows calculation of interrupter resistance (R_{int}).[8-11] All of these methods may be used clinically, but a major question is whether they add anything to the traditional measures derived from spirometry (FEV_1, FVC, and FEV_1/FVC). The purpose of this paper is to review the physiology and methodology of each of these measures of airway resistance, and then focus on their clinical utility in relation to each other and to spirometry.

Physiology

Resistance to air flow in the lung is determined by measuring the pressure difference across the airways and dividing this difference by the flow. When flow is laminar through a rigid tube, the pressure difference is related to the characteristics of the tube and the gas through the Poiseuille equation (Fig. 1A):

$$\Delta P = 8l\mu\dot{V}/\pi r^4 \quad (1)$$

where l = the length of the tube, μ = gas viscosity, $\dot{V}$ = flow, and r = the radius of the tube. Since resistance is $\Delta P/\dot{V}$, this equation highlights key points about resistance under laminar flow conditions: resistance is related inversely to flow and directly to the length of the tube, varies inversely with the 4th power of the radius of the tube, and varies with the viscosity of the gas. When flow is turbulent, the Poiseuille equation is modified

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

where ρ = gas density (see Fig. 1B). This equation now illustrates that under turbulent conditions, resistance varies with gas density, not viscosity, and is no longer linearly related to flow.[12]

In the human lung, laminar and turbulent flow both contribute to air flow, thus resulting in a mathematically

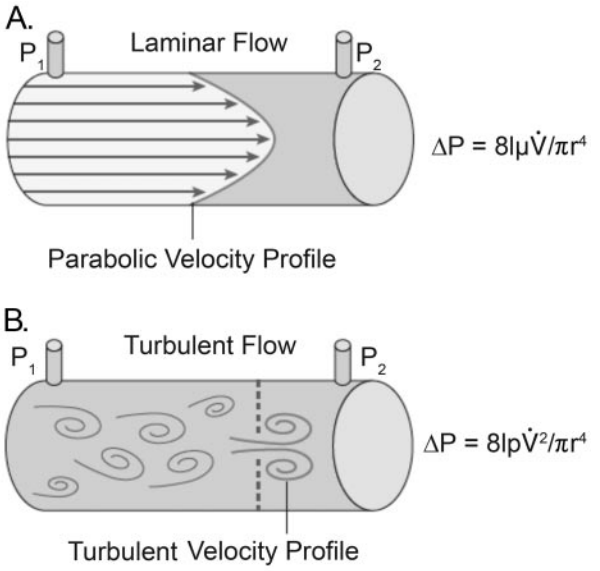

Fig. 1. A: Illustration of laminar flow through a rigid tube, where the pressure difference is related to the characteristics of the tube and the gas through the Poiseuille equation: $\Delta P = 8l\mu\dot{V}/\pi r^4$. B: Illustration of turbulent flow through a rigid tube, where the Poiseuille equation is modified to $\Delta P = 8l\rho\dot{V}^2/\pi r^4$. (From Reference 12, with permission.)

complex relationship between airway geometry, flow, and gas composition. In addition, the airways are flexible, not collapsible, so flow limitation occurs based on wave speed theory and the development of choke points.[13] Finally, the airways are connected in both series and parallel, so that total airway resistances must be added in a reciprocal fashion:

$$1/Rtotal = 1/R1 + 1/R2 + \ldots + 1/Rn \quad (3)$$

Modeling total airway resistance reveals that, based on total cross sectional areas at each airway generation, airway resistance initially falls from the trachea to generation 4, then rises again in generations 5–8, before falling off dramatically in subsequent generations[12] (Fig. 2). At breathing frequencies, small airways (< 2 mm in diameter) account for only 10% of total airway resistance,[14-16] with the remainder arising from the viscoelastic properties of the lung parenchymal tissue (40%) and flow resistance in the larger airways (50%).[17]

Measurement of Airway Resistance by Body Plethysmography

If one considers the lung as a simple, linear model made up of a rigid tube attached to a flexible parenchymal compartment, then the pressure required to move air into and

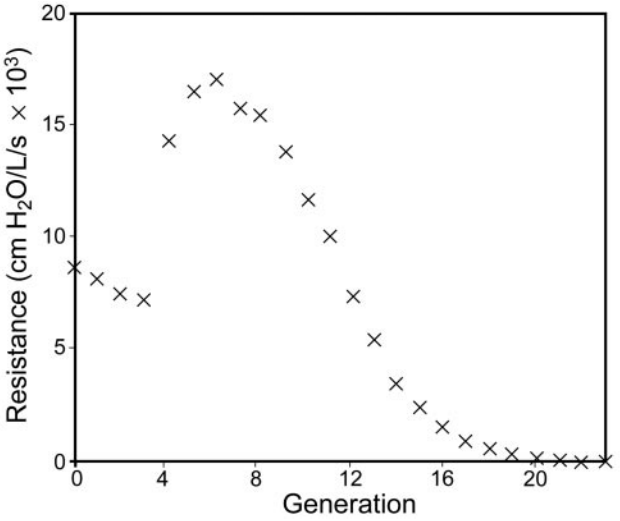

Fig. 2. Relationship of total airway resistance to airway generation. Computational modeling reveals that, based on total cross sectional areas at each airway generation, airway resistance initially falls from the trachea to generation 4, then rises again in generations 5–8, before falling off dramatically in subsequent generations. (From Reference 12, with permission.)

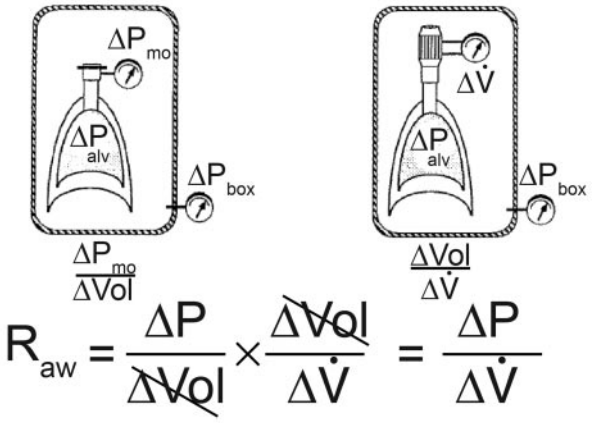

Fig. 3. Relationship of mouth pressure (P_{mo}) and box pressure (P_{box}) by body plethysmography under closed-loop panting conditions (left) and open-loop panting conditions (right). Under conditions of no-flow (left), mouth pressure would approximate alveolar pressure, so the relationship of alveolar pressure to change in lung volume (as determined by change in box pressure) is measured. When the shutter is opened (right), the relationship between flow and lung volume (change in box pressure) is measured. Airway resistance (R_{aw}) is calculated as the change in alveolar pressure (P_{alv}) divided by flow, which is derived by multiplying the slope of the closed shutter maneuver and the inverse slope of the open shutter maneuver, with the lung volume terms cancelling out. (From Reference 3, with permission.)

out of the model can be expressed as the equation of motion for the system:

$$P = EV + R\dot{V} + I\ddot{V} \quad (4)$$

where P = pressure, V = volume, $\dot{V}$ = flow, $\ddot{V}$ = acceleration, and the constants E, R, and I, representing elastance, resistance, and inertance, respectively, determine the mechanical properties of the system. One could theoretically measure resistance if volume fluctuations are kept very low (EV term approaches zero). The $I\ddot{V}$ term would already be negligible at breathing frequencies up to ~8 Hz. Thus, $P = R\dot{V}$, which we commonly recognize as the gas pressure-flow relationship analogous to Ohm's law. In 1956, Dubois and colleagues published their description of a method to measure airway resistance using body plethysmography, which essentially applied this simplified equation of motion under conditions of low breathing volume.[18] The rapid shallow panting maneuver involved in the airway resistance measurement would also optimize the signal-to-noise ratio and increase the accuracy of measurement by: minimizing thermal shifts and gas exchange; reducing glottic obstruction of the airway; minimizing flow turbulence and gas compression; and maintaining a relatively stable lung volume.[1,18] To calculate resistance one needed to know flow and alveolar pressure; the former could be measured directly, but the latter could not. What Dubois realized was that under conditions of no-flow, mouth pressure would approximate alveolar pressure, and so he related flow to no-flow conditions to derive the relationship of pressure to flow, and hence resistance[19] (Fig. 3).

An important technical factor that must be considered in measuring airway resistance by body plethysmography is deciding where to draw the slope of $\dot{V}$ versus box pressure, since different slopes can be drawn from the same flow-pressure loop when the loop has a complex configuration.[1,20] For loops used in conjunction with thoracic gas volume (TGV) to derive R_{aw}, 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. Other slopes that can be drawn when calculating sR_{aw} (see below) include connecting the points of maximal flow ($sR_{aw\text{-}total}$), connecting the points of maximal volume shift ($sR_{aw\text{-}MaxVol}$), or connecting the mid-volumes at +0.5 L/s and −0.5 L/s ($sR_{aw\text{-}Mid}$). In the case of both R_{aw} and sR_{aw}, there may be circumstances where resistance is differentiated between inspiration and expiration. For example, Ingenito and colleagues demonstrated that patients undergoing lung-volume-reduction surgery for emphysema who had less elevated inspiratory resistance were the ones more likely to demonstrate an increase in FEV_1 following surgery[21] (Fig. 4). They speculated that this was because these patients were more likely to have more severe emphysema, which would lead to dynamic airway collapse from loss of parenchymal tethering. Reducing lung volume via surgery in such patients is thought to improve elastic recoil.

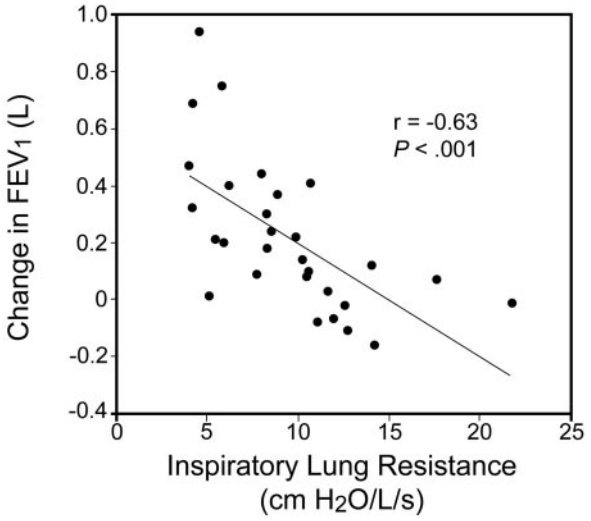

Fig. 4. Relationship between change in FEV_1 following surgery versus inspiratory lung resistance at baseline in patients undergoing lung-volume-reduction surgery. The lower the resistance, the more the FEV_1 improved after surgery. (From Reference 21, with permission.)

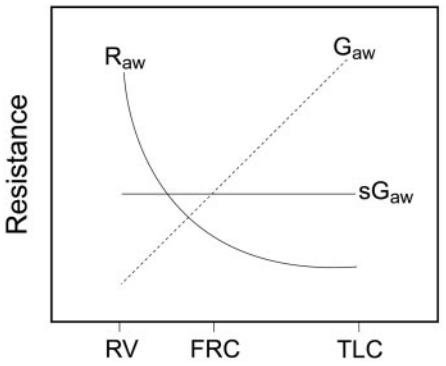

Fig. 5. Relationship between airway resistance (R_{aw}) and lung volume, the reciprocal of R_{aw} (conductance of the airways [G_{aw}]) and lung volume, and G_{aw}/TGV (thoracic gas volume) (specific airway conductance [sG_{aw}]) and lung volume. Notice that only sG_{aw} is independent of lung volume. RV = residual volume. FRC = functional residual capacity. TLC = total lung capacity. (From Reference 3, with permission.)

Airway resistance as measured by body plethysmography is usually expressed as R_{aw}. Since R_{aw} varies with lung volume, and lung volume may vary under different experimental conditions or different times of measurement, R_{aw} is usually corrected for lung volume by expressing it as sR_{aw} or sG_{aw}. When measured in conjunction with TGV (from a closed shutter maneuver), the reciprocal of R_{aw}, G_{aw}, is divided by the TGV at which the measurement was made to derive sG_{aw}, which now expresses R_{aw} independent of lung volume (Fig. 5). Thus, sG_{aw} is a stable measure that can be used in serial studies of R_{aw}. The increased sensitivity of sG_{aw} for airway resistance compared to FEV_1 is especially useful in pharmacologic studies that involve normal healthy subjects.[4] However, sG_{aw} is less reproducible, making repeated measurements important to determine an accurate mean value, and there are limited studies establishing normal values.[4] It should be noted that in patients with airways disease such as asthma, the assumption of mouth pressure equal to alveolar pressure at zero flow may not hold true, and in fact TGV may be overestimated.[22] This, in turn, would alter the calculation and accuracy of sG_{aw}.

In children, the closed shutter maneuver may be difficult to achieve, so TGV cannot be measured. Instead, flow is related to the small shifts in lung volume that occur during tidal breathing to derive sR_{aw}.[1,2,20,23,24] Mathematically, the relationship between pressure and flow during panting and its relationship to TGV (ie, R_{aw}) is equivalent to dividing sR_{aw} by TGV, so $R_{aw} = sR_{aw}/TGV$, or $sR_{aw} = R_{aw} \times TGV$.[2,20] This latter expression reveals that sR_{aw} reflects not only R_{aw} but also lung volume, and is not a resistance per se, but rather a form of work (pressure $\times$ volume).[2,20] Thus, sR_{aw} reflects the work related to changes in lung volume while overcoming a fixed resistance, while R_{aw} reflects the pressure related to air flow. Because sR_{aw} encompasses lung volume, and R_{aw} and lung volume vary inversely, sR_{aw} is relatively stable with respect to changes in lung volume (ie, as lung volume decreases, R_{aw} increases, so the product sR_{aw} remains the same, and vice versa). In this way, sR_{aw} is similar to sG_{aw} because it takes into account lung volume. However, sG_{aw} reflects only R_{aw}, whereas sR_{aw} reflects both R_{aw} and lung volume. This may be illustrated by considering an obstructed patient with hyperinflation versus an obstructed patient without hyperinflation.[2] In the former, R_{aw} is elevated and sR_{aw} is increased (increased work to move air through a higher lung volume), but the increased TGV associated with hyperinflation corrects conductance back to normal (normal sG_{aw}). In the latter, R_{aw} is increased and sR_{aw} is increased (increased work to move air through an increased resistance), but sG_{aw} is reduced (elevated R_{aw} is not reduced by altered lung volume).

Clinical Utility of sR_{aw} and sG_{aw}

Due to geometric considerations, whereby the total cross sectional area of the airways decreases dramatically as one moves from the periphery to the central regions of the lung, any measure of overall airway resistance, like sG_{aw}, will be very sensitive to central airway pathology but less sensitive to peripheral changes. Thus, sG_{aw} may pick up changes in large central airways that may be missed by spirometry. Indeed, sG_{aw} has been shown to be sensitive to upper airway involvement in vocal cord dysfunction[25] and vocal cord paralysis.[26] However, this is not necessarily true in all cases, as one study has shown that sG_{aw} was

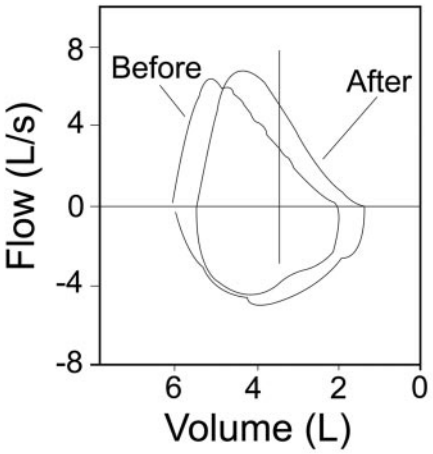

Fig. 6. The phenomenon of an isovolume shift is illustrated by plotting flow-volume loops before and after bronchodilator on an absolute volume scale. At isovolume (vertical line), flow is increased in the post-bronchodilator, compared to the pre-bronchodilator, loop, despite no change in FEV_1 or FVC.

more sensitive than FEV_1 in bronchiolitis obliterans syndrome, a disease confined to the lung periphery. This may relate to the loss of sensitivity of FEV_1 due to the deep inhalation involved (see below).[27]

Theoretically sG_{aw} should be sensitive to changes in resistance anywhere along the airway, whereas FEV_1 will be sensitive to only those changes occurring upstream from the choke point.[28] Thus, depending on the location of airway narrowing or dilation in response to a bronchoconstrictor or bronchodilator, the FEV_1 may change without significant change in sG_{aw}, or vice versa.[28] In the case of airway narrowing, hyperinflation might result. Smith and colleagues found that spirometry alone failed to find bronchodilator reversibility in 15% of patients with suspected reversible airway obstruction and clinical responses to bronchodilator, but that these patients could be identified by changes in sG_{aw} or TGV or isovolume maximal flow[29] (Fig. 6). These results suggest that the patients involved were responding to bronchodilator by changes in lung volume-related parameters but not changes in spirometry. Since these patients had clinical improvement, such volume-related changes are clinically relevant.

Another factor to consider in differentiating sG_{aw} from FEV_1 is the deep breath necessarily associated with performing spirometry, but not part of the sG_{aw} measure. Healthy subjects and those with mild asthma tend to bronchodilate after a deep inhalation, so mild bronchoconstriction could be masked by the bronchodilating effects of measuring FEV_1, but should still be evident by sG_{aw}.[30] This would make sG_{aw} a more sensitive test to detect air-flow limitation, especially in mildly obstructed patients. Many studies have investigated the relative response in FEV_1 versus sG_{aw} during bronchial challenge tests. In 1983, Dehaut and colleagues demonstrated that the PC_{40} (provocational concentration that produces a 40% decrease) in sG_{aw} was more sensitive than the PC_{20} FEV_1 at detecting bronchoconstriction to inhaled histamine, but the PC_{20} was a more reproducible measure (coefficient of variation = 2.6% vs 10%).[31] Goldstein and colleagues have shown that adding non-FEV_1 parameters, such as sG_{aw}, to FEV_1 during a methacholine challenge test increases the sensitivity of the test, although most of the increase was due to addition of FVC and the forced expiratory flow during the middle half of the FVC maneuver ($FEF_{25–75}$).[32]

Recently, Khalid and colleagues questioned the 40% cutoff for positivity of the PC sG_{aw} during methacholine challenge.[33] Based simply on comparing the PC_{20} FEV_1 with the change in sG_{aw} at that level in patients with suspected asthma, they found that the mean change in sG_{aw} was 56%. Further analysis by receiver-operator characteristic curves suggested that the optimal cutoff was a change of 52%. While this is only slightly higher than the currently accepted 40% change, it does suggest that a slightly higher cutoff may be more appropriate by enhancing the predicative value of the test. The cost of a test with such high sensitivity is typically loss of specificity. Indeed, many years ago Fish and colleagues demonstrated that sG_{aw} was less specific at distinguishing normal from asthmatic subjects than FEV_1.[34] The authors proposed that the airways hyper-responsiveness that characterizes asthma might be less a reflection of intrinsic increased responsiveness of the airways than an impaired ability to bronchodilate their constricted airways.[35]

Another study demonstrated that when the methacholine challenge test was negative, small changes in FEV_1, but not in sG_{aw}, were predictive of future development of asthma, suggesting again that the FEV_1 is a more specific measure for asthma.[36] When Parker and colleagues compared patients who responded to methacholine with changes in sG_{aw}, but not in FEV_1, to those who responded by FEV_1 only, they found that such patients had smaller lung volumes, higher FEV, and higher $FEF_{25–75}$/FVC, indicative of relatively larger airway to lung size, a mismatch referred to as lung dysanapsis.[37] Patients with lung dysanapsis with smaller airway to lung size (lower $FEF_{25–75}$) have been found to be more hyper-responsive than those without in the Normative Aging Study.[38] Thus, comparing responses in FEV_1 and sG_{aw} may lend insight into the basic physical relationship between airway size and lung size.

As mentioned above, sR_{aw} is commonly used in children but is rarely used in adults.[39] Details regarding techniques of measurement, quality control, and interpretation are available in recent, excellent reviews.[20,23,24,40] sR_{aw} has been measured in children as young as 2 years old, and has been used in assessment of bronchodilators and response to methacholine, histamine, and cold air.[24] Other studies have included measuring the effects of short- and long-

acting bronchodilators, inhaled corticosteroids, and leukotriene receptor antagonists in asthmatic children.[20] Serial measurements have been made in children with cystic fibrosis and demonstrated more consistent abnormalities than either FOT or R_{int}.[41] Since sR_{aw} is primarily used in children, normative data are mainly limited to pediatrics.[20,23,24,40] As most of the children involved in these studies would likely not have been able to perform reliable spirometry, using sR_{aw} as a measure of airways disease is a valuable tool in pediatric lung disease.

Measurement of Airway Resistance by the Forced Oscillation Technique

Another non-spirometric method to measure airway resistance is the FOT. First described by Dubois in 1956,[42] the FOT involves applying a forced perturbation of flow at the mouth and measuring the resulting pressure.[5-7] This occurs while the subject continues to breathe quietly. The applied flow is typically either pseudorandom in nature, meaning composed of many, typically mutually prime, frequencies, or truly random, as generated by a mechanical impulse. In both cases, the ratio of pressure measured to flow applied is analyzed across the frequency domain by fast Fourier transformation to arrive at a complex number known as the impedance of the respiratory system (Z_{RS}). Impedance encompasses all the forces that hinder air flow into and out of the lung, and thus include the resistance, elastance, and inertance of the system. The component of Z_{RS} in-phase with flow is the real component, respiratory system resistance (R_{RS}), and this reflects the energy dissipated due to resistive losses. The components of Z_{RS} out-of-phase with flow make up the imaginary component, respiratory system reactance (X_{RS}). The reactance, in turn, is made up of out-of-phase lagging flow, which is elastance, and out-of-phase leading flow, which is inertance; both of these components reflect energy storage. When plotted against frequency, Z_{RS} demonstrates a relatively frequency-independent resistance in healthy subjects, except at the very lowest frequencies (< 1 Hz), where negative frequency dependence occurs. This is thought to reflect tissue viscoelastic properties in healthy subjects, while there is increased frequency dependence of resistance due to mechanical inhomogeneities in subjects with obstructive diseases like asthma or COPD.[43] Reactance is frequency-dependent in all subjects, but enhanced in those with obstructive lung disease, where reactance values are more negative. Where the X_{RS} curve crosses zero, the elastance and inertance values are equal and opposite, and the frequency at which this occurs is the resonant frequency. With increasing degrees of obstruction, the X_{RS} curve is shifted to the right, the resonant frequency is increased, and the area under the X_{RS} curve (AX) is increased.[5] Impedance data at breathing frequencies reveal a substantial contribution of tissue viscoelastance to total respiratory resistance. In general, lower frequency data (< 5 Hz) reflect the more peripheral regions of the lung, while higher frequency data (> 8 Hz) are most representative of the larger, central airways.[43]

Unlike R_{aw} measured by body plethysmography, the resistance measured by the FOT represents total respiratory system resistance, and thus contains contributions from both the lung and chest wall. At 6 Hz, R_{RS} by the FOT is very comparable to R_{aw}, but slightly higher due to contributions from the chest wall.[44,45] At higher frequencies, R_{RS} by the FOT tends to underestimate R_{aw}, especially at higher R_{aw} values, likely due to shunting of flow into the upper airways (ie, cheeks, floor of mouth).[44,45] Since the FOT is performed during tidal breathing, no deep breaths are involved that might interfere with measurement. Because of this, R_{RS} by the FOT is highly sensitive to changes in bronchial tone, but is less specific for asthma or other unique disease states.

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 (eg, ventilated patients, paralyzed patients). There is only one commercially available FOT system in the United States, called the impulse oscillometry system. This device uses an impulse of flow made up of random frequencies and amplitudes to compute R_{RS} and X_{RS}. Compared to the traditional FOT using pseudorandom noise, resistance measured by the impulse oscillometry system tends to overestimate R_{RS} by the FOT at lower frequencies, and R_{aw} at all frequencies, likely due to non-linearities involved in measurement.[45] The R_{RS} by the impulse oscillometry system and the FOT agree well at higher frequencies (25 Hz).[45]

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 impulse oscillometry system resistance than for FEV_1[46]; and measuring the severity of obstruction in asthma and COPD[47,48] (Fig. 7). Methacholine-induced dyspnea is significantly associated with changes in R_{RS} and X_{RS} at 5 Hz (R5 and X5, respectively), but not changes in FEV_1, suggesting that these FOT measures are more sensitive to symptoms.[49] However, Houghton and colleagues have shown that the most sensitive method varies between healthy and asthmatic subjects, and with the degree of severity in asthma.[50] A statistical analysis found that some FOT parameters, including R5, are more sensitive than FEV_1 in detecting bronchodilation in asthmatic subjects.[51]

Since the FOT requires no patient cooperation or technique, it can be applied widely in many clinical settings. Indeed, the FOT is well suited to studies in children, the elderly, and any patients who cannot perform spirometry,

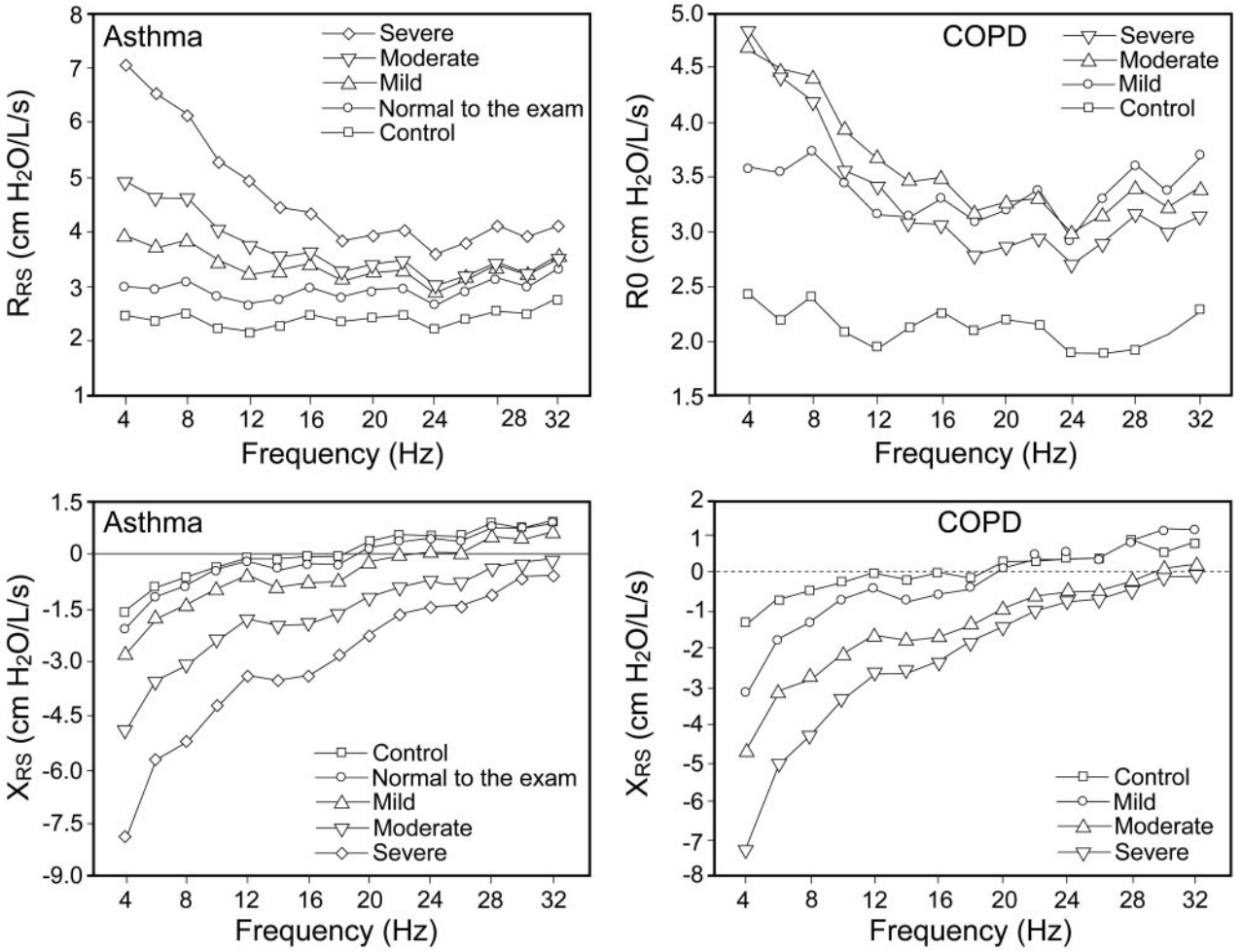

Fig. 7. Impedance data from patients with asthma (left) and COPD (right) according to severity of underlying disease. Notice the consistent relationship between diseases of the changes in respiratory system resistance (R_{RS}) and respiratory system reactance (X_{RS}) with increasing severity. In both cases, as severity increases, R_{RS} rises and becomes more frequency dependent, especially at lower frequencies ($< \sim 16$ Hz), and X_{RS} falls to more negative values, with an increase in the resonant frequency (point at which X_{RS} crosses zero). (Left from Reference 47, with permission. Right from Reference 48, with permission.)

such as those with neuromuscular disease or on mechanical ventilation.[6] For example, only impulse oscillometry bronchodilator responses, and not responses measured by FEV_1, were able to distinguish 4-year-old children at risk for persistent asthma participating in the Childhood Asthma Prevention Study.[52] A similar finding was seen in a cohort of children form Belgium.[53] 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.[6] In all these situations, measuring FOT resistance will lend insight into the presence and severity of obstructive disease.

More studies are also focusing on the X_{RS} component of Z_{RS}, which may yield different information related to the elastic properties of the lung. In some cases increased X_{RS} may be related to reduced lung volume due to airway closure. Indeed, Walker and colleagues showed that in moderate to severe COPD, the fall in FEV_1 with methacholine was more closely related to a fall in X_{RS} than a rise in R_{RS}, and this occurred in association with a decrease in inspiratory capacity, suggesting that airway closure was the main response to methacholine.[54] Asthmatics had a smaller change in lung volume and a larger change in R_{RS}, suggesting more of an airway response in asthmatics. In other cases the increase in X_{RS} is thought to represent an artifact of central airway shunting, which occurs under conditions of extreme peripheral airway resistance, leading to shunting of forced flow into the more central airways.[55] Reactance has been noted to differentiate mild air-flow obstruction before changes in R_{RS} occur[56] and may detect flow limitation in patients with COPD.[57] Also in COPD, Kolsum and colleagues have shown that R5, X5, and resonant frequency were significantly associated with FEV_1, sG_{aw}, total lung capacity, RV, and inspiratory ca-

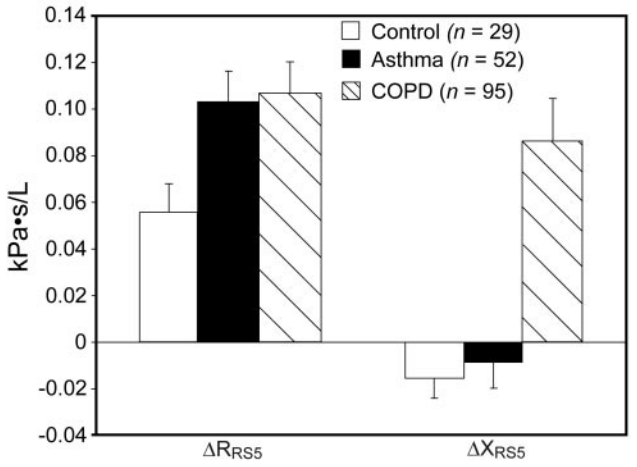

Fig. 8. Comparison of change in respiratory system resistance at 5 Hz (R_{RS5}) and respiratory system reactance at 5 Hz (X_{RS5}) between inspiration and expiration in healthy control subjects, and subjects with asthma and COPD. Notice that only the patients with COPD had significant differences in X_{RS5} between inspiration and expiration, differentiating them from both control subjects and subjects with asthma. (From Reference 63, with permission.)

pacity, with the strongest associations between X5 and resonant frequency and FEV_1, and X5 and resonant frequency and sG_{aw}.[58] A recent study in pediatric asthma has shown that only reactance area (AX) continues to improve after the initial 12 weeks of therapy with inhaled fluticasone during a 48-week total study.[59] The authors speculate that this might reflect ongoing improvement in small airway function in these patients. Two studies from Japan note that X_{RS} relates more closely with quality of life measures than FEV_1 in both patients with asthma[60] and COPD.[61]

One of the benefits of the FOT is that one can separately measure inspiratory from expiratory parameters. Using this technique, Paredi and colleagues have shown that while whole breath impulse oscillometry could not differentiate patients with asthma and COPD, patients with COPD had higher mean expiratory X5 than those with asthma, which they thought might be due to enhanced dynamic airway narrowing on expiration in these patients.[62] Another study has shown that in comparing FOT in patients with asthma and COPD, only patients with COPD show a significant difference in X_{RS} between inspiration and expiration[63] (Fig. 8). The authors speculate that the same process of dynamic airway narrowing on expiration due to loss of recoil in COPD may explain this phenomenon. Interestingly, this theory mirrors the concept suggested by Ingenito and colleagues, mentioned above, that describes the relationship between outcomes from LVRS and inspiratory resistance.[21] High inspiratory resistance may not only reflect differences in underlying physiology, but may relate to the pathogenesis of airway inflammation[64] and acute lung injury.[65]

The methodology and analysis of FOT data are complex. The European Respiratory Society has published guidelines on methodology in 2003,[6] but there have been no updates since then. In general, the repeatability of the technique is similar to R_{aw} from body plethysmography and interrupter resistance (see below). The correlation with spirometry is highly variable, in part because of the deep breath involved in spirometry, and in part due to the differing mechanics assessed by the two techniques.[5] The FOT is subject to strong influence by upper airway shunting, and this must be carefully controlled. Interestingly, the FOT does not yield distinctive data in patients with restrictive lung disease.[6] Many regression equations are now available, but they each come from different populations and use different devices and techniques, so their applicability is limited.[6]

The FOT is used commonly in research, from clinical studies to basic studies of lung mechanics. For example, Kaczka and colleagues have described the association of more severe asthma with increasing frequency dependence of elastance, thought to be due to more severe peripheral airway resistance causing shunting of flow back into central airways.[55] In a different study, Kaminsky and colleagues have uniquely demonstrated hyper-responsiveness of the lung periphery in participants with asthma using the FOT.[66] Because interpretation of Z_{RS} depends on lung models, the technique yields information in relation to such models, and therefore is also limited by the properties of the model in use.[67]

Measurement of Airway Resistance by the Interrupter Technique

A third method to noninvasively measure airway resistance, used primarily in children, is the interrupter technique.[8,9,11,68,69] The concept here is similar to that used in body plethysmography, in that the alveolar pressure is estimated by mouth pressure during transient occlusion of flow. In this case, flow is occluded intermittently during spontaneous breathing, and the mouth pressure recorded immediately after the occlusion is related to the air flow measured immediately before the occlusion to calculate resistance. The display of data is unique and is important for monitoring for quality. During expiration, initially there is a sharp increase in pressure, reflecting central airway resistance, followed by rapid, damped oscillations of pressure, and finally a slowly rising steady pressure thought to be due to tissue viscoelasticity[9,11,69] (Fig. 9).

The pressure used for calculation of R_{int} is ideally immediately after occlusion, but in reality is back extrapolated to 15 ms after occlusion based on the slope of pressure between 30 and 70 ms after occlusion. Like the FOT,

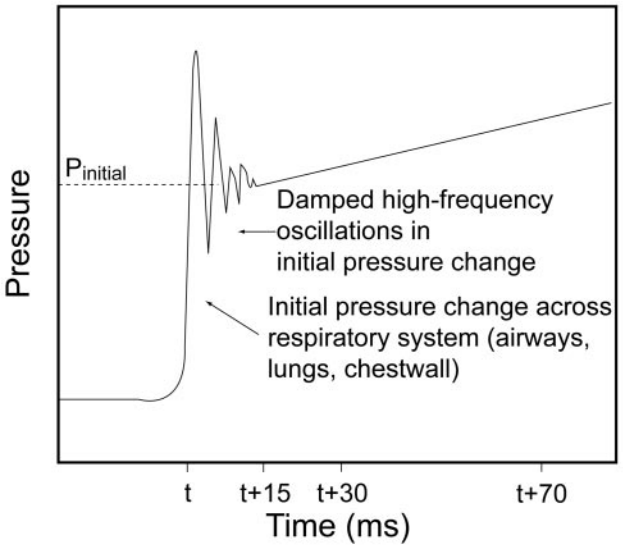

Fig. 9. Pressure versus time during an interrupter maneuver during expiration. At time 0 the airway is transiently occluded, resulting in an abrupt spike in pressure, reflecting the initial pressure change across the respiratory system. The pressure then oscillates briefly before slowly climbing as pressure rises from viscoelastic properties and gas redistribution in the lung. By convention, a common method to calculate interrupter resistance (R_{int}) is to take the pressure at +15 ms determined by back extrapolation from t+30 and t+70 ms, and divide this pressure by the flow immediately before the occlusion. (From Reference 69, with permission.)

numerous technical factors are important, such as reducing upper airway shunt by firm support of the cheeks and floor of mouth, timing of valve closure, taking the mean or median of repeated values, and use of a face mask or a mouthpiece.[8,68-70] Also, similar to the body plethysmography technique, the assumption of equilibration between mouth and alveolar pressure at zero flow may not hold true in patients with substantial airway heterogeneities. Because it is noninvasive and performed during normal breathing, the technique is especially suitable for use in young children, and has been demonstrated feasible in children as young as 2 years old. The intra-subject coefficient of variation is similar to that of FOT (5–15%). There is a small group of reference equations that derive from pediatric studies.[69]

Clinically, R_{int} has been used in discriminating between different phenotypes of wheezy children and between healthy children and children with asthma.[69] In the latter group, a correlation coefficient of 0.73 was found for baseline values of spirometry and R_{int}.[71] R_{int} has been used in conjunction with other measures to evaluate bronchodilator response in asthmatic children. As to discriminating capacity, R_{aw}, R5, R_{int}, and X5 were found to be useful, with positive predictive values of 84%, 74%, 82%, and 76%, respectively.[72] The interrupter technique has also been used to evaluate the response to cold air inhalation, inhaled fluticasone,[73] and oral montelukast therapy.[74] One issue with the interrupter technique is determining the best cutoff for bronchoconstrictor response. In adults, Sundblad and colleagues have shown that a 20% change in FEV_1 following methacholine corresponds to different levels of change of G_{aw} (reciprocal of R_{int}) determined by the interrupter technique, depending on the underlying degree of bronchial responsiveness, in this case, to a 39% change in G_{aw} in all subjects, but a 66% change in less responsive subjects and a 27% change in more responsive subjects.[75] Thus, the range of cutoff of a positive test varies widely, depending on the nature of the underlying bronchial responsiveness.

Comparing sR_{aw}, FOT, and R_{int}

There are limited studies directly comparing the above indices, and by their nature, appear mainly in children. Even though all 3 measures are based on differing mechanical principles, in general all show consistent changes in relation to disease state or response to bronchodilator or bronchoconstrictor. These measures tend to be more sensitive to detection of bronchodilation and bronchoconstriction than FEV_1, with one study demonstrating that R_{aw} was more sensitive than FOT and R_{int} in detecting bronchoconstriction in normal subjects.[44] Technical factors are critical in deriving robust measurements, with special attention given to reducing thermal artifact in sR_{aw} measures, and upper airway shunting in FOT and R_{int}. In children, all 3 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 3 measures are commonly abnormal in young children with asthma, but none appear to associate with clinical outcomes assessed 3 years later.[76] sG_{aw}, FOT, and R_{int} allow differentiation of inspiratory and expiratory resistance, and the dynamic looping of resistance and flow, as seen by the sR_{aw} and FOT methods, may yield important information about laryngeal narrowing, a common occurrence during testing. The FOT uniquely also provides information about frequency dependence and reactance, which yield additional insight into peripheral airway mechanics and inhomogeneities.[5,7,43] A summary of the specific measurement properties of FEV_1 in comparison to sR_{aw}, sG_{aw}, FOT-R, and R_{int} is shown in Table 1.

Summary

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

Table 1. Characteristics of Different Lung Function Tests Related to Airway Resistance

	Spirometry (FEV_1)	Plethysmography (sR_{aw}, sG_{aw})	R_{int}	FOT (R_{RS})
Patient cooperation/effort	+++	++	+	+
Involves deep inhalation	+++	–	–	–
Adjusts for lung volume	–	+	–	–
Intra-subject variability (coefficient of variation)[5,6,31,44,69,77,78]	3–5%	8–13%	5–15%	5–15%
Sensitivity to airway location				
Central	+	++	+++	+++
Peripheral	++	+	+	+++
Cutoff for bronchodilator/ bronchoconstrictor[6,20,24,69,78,79]	12/20%	25/40%	35%/3SDw	40/50%
Insight into mechanics	+	+	+	+++
	Global, nonspecific	R_{aw}, TGV	Lung + chest wall	Lung + chest wall
Standardized methodology	+++	++	+	++
Reference equations[2,6,10,69,78]	+++	++	++ (pediatric)	++

+ to +++ = Yes, with increasing strength or prevalence of feature
– = No
sR_{aw} = specific airway resistance
sG_{aw} = specific airway conductance
R_{int} = interrupter resistance
FOT = forced oscillation technique
R_{RS} = respiratory system resistance
SDw = within-subject standard deviation
TGV= thoracic gas volume

cooperation and skill; it involves a deep breath, which can alter underlying airway resistance; and it provides limited insight into lung mechanics. For patients who cannot perform spirometry, measuring airway resistance with sR_{aw}, FOT, or R_{int} remain important options. Measuring sR_{aw} by body plethysmography involves bulky equipment that does not allow portable measurement, and it provides an index that reflects both R_{aw} and lung volume. In adults, sG_{aw} is typically used, and provides a sensitive measure of airway caliber. However, due to high sensitivity, it has poor specificity for asthma or other unique disease states. The FOT is easy to perform, but the equipment is sophisticated and the method is very sensitive to upper airway shunting. Nevertheless, the FOT provides unique information related to lung mechanics, information that is not available by any other noninvasive technique. Measuring R_{int} also involves important technical issues and upper airway shunt, 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. As with all clinical tests, interfacing the physiological data with the clinical picture is critical to properly using the information in the care of the patient.

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Discussion

Pichurko: I thank Dr Kaminsky for his comments, and his interests certainly overlap with my own. I wish to recognize my mentor Dr Roland Ingram, who guided me through an investigation and its publication[1] on volume history as a determinant of expiratory flow in asthma. I believe this is an important issue in the performance of spirometry during bronchoprovocation. Two and a half decades of directing 6 pulmonary function laboratories has taught me that unrecognized volume history effects are an important and typically unrecognized source of error in bronchoprovocation studies.

Dr Kaminsky was kind enough to display a methacholine provocation dose-response slide representing one patient's experience. This is admittedly an extreme one, but it highlights a point. This was my patient who asked to be tested at another hospital where she was employed. She returned afterward describing a scenario that is represented on the posted slide. Essentially, afterinhaling a relatively low concentration of methacholine, she felt tight and reported this to the technician. The tech responded as apparentlyinstructed, "I'm sorry but I'm obligated to keep giving you drug, because you have not yet declined the required amount." So, despite her reported and worsening chest tightness and distress, the only end point recognized by the testing lab was a 20% drop in FEV_1. Thus, the test subject was given 2 additional doses, ultimately declining in FEV_1 63% from baseline. She tuned cyanotic and was emergently transported to the emergency department, where she just barely escaped intubation.

While there is understandably a lot of discussion about excessive sensitivities and false positive methacholine responses, I am equally concerned about false negatives. These occur due to the bronchodilating effects of deep inhalation to total lung capacity that accompanies all spirometric testing. This serves to mitigate or even reverse the constrictor response in mild and

some moderate asthmatic subjects, which are precisely the people we send for methacholine bronchoprovocation. I would make the case that this may be more consequential than false positives, as it produces apparently negative results in asthmatic individuals, allowing these individuals at risk for bronchospastic events to be reassured by the test results and to go undiagnosed and untreated. Thus, their asthma goes unnoticed.

If I had 3 wishes to be granted, the third wish would be that every lab performing methacholine provocation would be equipped to perform spirometry and also R_{aw}. I do think that 40% is a little bit low. We observe 50% increase in R_{aw} as threshold. Certainly, every pulmonary function lab medical director should have a discussion with their technicians and inform them of the confounding dilating effects of deep inhalation that limit the accuracy of spirometry and may expose the test subject to risk.

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Ruppel: I'd like to follow up on that. We also do R_{aw} and conductance in conjunction with bronchial challenge, and we don't have the technologist stop when they observe a 50% decrease in conductance. We use conventional criteria and look for the change in FEV_1. Would you consider that a reasonable thing to do, or are we unduly putting the patients at risk?

Pichurko: There's a third signal that we use. We call it sustained chest tightness. This refers to the patient's report of progressive chest tightness lasting at least 2 minutes, sometimes combined with auscultation by the therapist to determine that air flow is reduced. Of the 3 lines of evidence (PC_{20} FEV_1, PC_{50} R_{aw}, and sustained chest tightness), we use 2 to conclude the study. That assures that at least one threshold airway measurement is exceeded, but that we don't ignore clinical evidence of sustained and progressive patient distress. This has improved test accuracy, but also recognizes the subject's safety.

Kaminsky: We do the same thing. If we get to 8 mg and they're coughing or have tightness, even though they haven't reached FEV_1 criteria, but they've reach conductance criteria by that point, I stop the test.

Busse: To go back to your first slide, I don't think what you presented was atypical. I'm not a pulmonary physiologist, but many times I'll have people coming in who complain of shortness of breath and use medications without relief. I'll begin the measurement of R_{aw}, and they are abnormal even though lung functions tend to be really quite normal.

We began our discussion this morning talking about phenotypes, and asthma is a very broad definition and it may not encompass all things that have altered physiology. And we don't have good data, necessarily, on people who have just increases in R_{aw}. We don't test them under various conditions, nor do we necessarily test them after we've given them medications like inhaled corticosteroids. This is certainly not the usual approach to patients who come in with symptoms compatible with asthma. In patients who have symptoms of asthma but largely normal lung function, vocal cord dysfunction is a high probability. These individuals have an inspiratory loop cutoff. Addressing these patients requires going through an appropriate differential diagnosis and matching the lung function abnormalities to the clinical picture.

Kaminsky: I would agree with you, but in this case the symptoms were very responsive to the inhaler, and I don't know if that was a placebo effect or real. But we did document physiology that at least helps us understand and be convinced that the medicine is doing some good. I will say there's a decent literature from the 1970s and 1980s looking at this different response to bronchodilator and bronchoconstrictor in the central airways versus peripheral airways. Nobody knows quite what to make of that, and it's a hot topic now because we're all interested in giving these small particle HFA [hydrofluoroalkane] solution steroids that penetrate deeper, but we don't know the ultimate clinical effect. I think there is something phenotypically different between asthmatics in particular who have disease location in different parts of their lung. Like you say, we just don't understand a lot about it yet.

Busse: Right, we don't know what part of the tree they're on: the beginning part of the tree or somewhere else. It's amazing how long these things have been around and how little sophistication we have in knowing what to do with the data.

Coates: When I finished my training, I thought I knew what cystic fibrosis was, and I thought I knew what asthma was. And now I'm looking at retirement, with cystic fibrosis being defined with a range between sterility in males with no lung disease and no gastrointestinal disease and the full-blown syndrome with severe bronchiectasis and malnutrition. We still know it's all related to the same protein, but variations in expression and type of the defect change the presentation dramatically. I think asthma has become way more complicated. The lung has very few tricks up its sleeve, and reversible bronchospasm is one of those tricks. Hence, reversible bronchospasm may have manifestations that we may later come to understand as several different disease processes. Hence, I'm not surprised that we keep seeing very different types of expressions of asthma while we actually may be looking at different diseases that we just haven't sorted out yet.

Kaminsky: I agree, and that's why some are calling asthma a syndrome as opposed to a disease: because it encompasses facets of different types of symptoms, airway dysfunction, inflammation, and so on.

Rundell:* You mentioned you measure R_{aw} as well as FEV_1 during methacholine challenges. Do you do that all the time?

Kaminsky: Yes.

Rundell: Do you do other challenges? Exercise challenge or eucapnic voluntary hyperventilation?

Kaminsky: We do exercise challenge with the treadmill, and we only do spirometry during that challenge. It's physically located in a different room than the body box, and the rooms are always going concurrently, so it makes it hard to do.

Rundell: Now, have you found that you see the changes in the R_{aw} before you see changes in the FEV_1?

Kaminsky: In terms of the methacholine testing?

Rundell: Yeah.

Kaminsky: It's highly variable. I can't say I've seen a specific pattern that's consistent.

Hess:† If I can take the discussion into the ICU just for a few minutes, which I guess is fair because I heard you say you just came off service in the unit.

Kaminsky: And I mentioned a mechanical ventilator in here, too!

Hess: Not uncommonly, when we intubate a patient with obstructive lung disease, we'll use volume control ventilation, set the flow to 60 L/min, 1 L/s, measure the peak pressure, the plateau pressure, determine the R_{aw}, and, anecdotally, we think that information is useful and sometimes we follow it serially over time. Is that a worthwhile thing to do? Do you do that in your practice? We can't take the body box into the ICU.

Kaminsky: The answer is yes, I think it is worthwhile, and we do that in our practice. We don't follow R_{aw} per se, but I look at the difference between peak and plateau pressure as a surrogate for respiratory system resistance. In obstructed patients this is also a valuable way to teach our fellows and residents. When we're giving bronchodilator therapy, one way we know the patient is getting better is their peak pressures are coming down, the difference in peak and plateau pressure is narrowing, and presumably the patient is moving better air. But as we've been saying the whole conference, it's not just one factor: that's one of many we're looking at. Yes, I use that as part of the monitoring of these patients.

Hnatiuk: When you said you use 2 of the 3 measures to stop the bronchoprovocation test, do you deem that positive then?

Kaminsky: Yes. I don't use 2 of our 3 specifically, like Bo [Pichurko], but for us the clinical impression still overrides everything. If the patient is coughing or tight, no matter what the values are, the technologist will try to get a body box measurement and spirometry at that point in time. Then, if either criteria are met, FEV_1 or conductance, we will stop. If the patient is asymptomatic, we'll go up to 16 mg, and we still continue to look for both responses.

One of my jobs as pulmonary-function-testing director is to be available if they have any questions, and it's not uncommon for me to run up to the lab and take a look at someone in the midst of their challenge to try and help the techs determine if it's safe to go on or not. We try to put the clinical response to methacholine together with both aspects of physiology.

Enright: Do you then take the response to albuterol (the ability to quickly reverse the bronchospasm) into account when interpreting the results?

Kaminsky: I take it into consideration, but it's not the primary thing we look at. As I've said before, I've never seen a patient not reverse. Sometimes we have to give another 2 puffs. Typically we give 2, but sometimes it takes 4. Once we used ipratropium thinking cholinergic/anticholinergic, and that got the patient out of their methacholine tightness. We like to see the FEV_1 come back within 10% of baseline before we discharge the patient.

Salzman: I'm not sure I was hearing the 2 of you correctly about this. You're saying that you stopped the test for safety reasons, even if you haven't dropped the FEV_1, if you have symptoms, such as wheezing and coughing. Are you saying you call the test positive with just subjective end points?

Kaminsky: No, I won't call the test positive with just subjective end points. We like to see one of those 2 objective criteria being met in addition to symptoms, but I'll make a comment in my report that the patient did develop wheezing and tightness and they did not meet the "official" ATS/ERS criteria for positive response. Then, and I'm not fudging on this, I'll say this needs to be put into the clinical context. If that was my patient, it's still someone I might put on a 6-week trial of inhaled corticosteroids and see how they do.

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* Kenneth W Rundell PhD, Pharmaxis, Exton, Pennsylvania.
† Dean R Hess PhD RRT FAARC, Respiratory Care Services, Massachusetts General Hospital, Boston, Massachusetts, and Editor in Chief, RESPIRATORY CARE.

Pichurko: Similarly, I would require exceeding the diagnostic threshold for at least one of those objective measures before concluding the provocation study. The additional support of patient symptomatology serves to validate the objective measure.

Coates: Didn't we talk this morning about the idea that the methacholine challenge test was a good test to rule out asthma? So, within what you just said, how do we fit that?

Kaminsky: To me, a negative test is someone who goes up to 16 and flies through it, and there are no changes physiologically, and they have no discomfort. I don't think they have asthma if they respond that way.

Busse: Well, one could argue the other way. Allan, I think we've defined the positive response to methacholine for what we consider to be the classical, clinical asthma, haven't we? You wonder if we've been overly constrictive on what we're calling a positive test as far as the disease is concerned. Like you said, when I began work 35 years, ago I really felt like I knew a lot about asthma, and as time has gone on, my understanding of the ambiguities has increased. I think we need to open things up a little bit and look at these various characterizations and responses to tests to give us some ideas about abnormalities in functions and what they really mean.

Coates: No disagreement about that, because I am coughing and wheezing even though my PC_{20} is greater than 10.

Kaminsky: We have these arbitrary cutoffs. This [showing an additional slide of a series of flow-volume loops during a methacholine challenge that illustrates progressive truncation of inspiratory flow] is a patient who responded to methacholine with vocal cord dysfunction. The FEV_1 didn't change a bit. The conductance did change, as you would imagine, because R_{aw} elevated due to closure of the cords. This is a nice example of someone who almost had no symptoms: she kind of got a little cough and a little discomfort. I think we have to take all the information together in making our clinical judgments. But if everything goes smoothly, at least at that point in time, I would consider it a negative challenge and I think it has a high specificity in that case.

Rundell: One last question. You're doing full FVC maneuvers then, during your methacholine challenge? With R_{aw}?

Kaminsky: Yes, and we do the 5 deep breaths method.

Rundell: Do you train these patients before you test them, for 6 weeks or so? It seems that this would be very fatiguing for the patient and quite time consuming. With the Aridol bronchial challenge test, we used only FEV_1 maneuvers after the baseline spirometry FVC maneuver, and with the methacholine test we (and others) prefer the FEV_1 maneuver because of patient fatigue.[1]

1. Pearlman D. A phase III multicenter study to demonstrate the sensitivity and specificity of Aridol (mannitol) challenge to predict bronchial hyper-responsiveness as manifested by a positive exercise challenge in subjects presenting with signs and symptoms suggestive of asthma but without a definitive diagnosis. http://clinicaltrials.gov/ct2/show/NCT00252291. *Accessed September 26, 2011.*