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PULMONARY PHARMACOLOGY & THERAPEUTICS

Review

Clinical Application of Forced Oscillation

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SUMMARY: This review summarizes current clinical use of the forced oscillation technique (FOT) for analysis of lung function. It presents an intuitive approach to FOT pattern recognition for interpretation of results in human subjects, and the view that FOT is now well established and, clinically, eminently useful in patients with airflow obstruction. The focus of this review is on findings that relate directly to clinical utility, with less emphasis on theoretical mechanisms.

The major thrust for clinical application of FOT derives from a number of European clinical research centers. Farre and Navajas and their colleagues in Barcelona, Harf and the Lorinos and their coworkers in Paris, Peslin and Duvivier and their coworkers in Vandoeuvre-les-Nancy, Pride and coworkers in London, and Van de Woestijne, Clement, Demedts, Landser, Van Noord, and their colleagues in Leuven have essentially been responsible for clinical development of FOT over the past 25 years. Publishing space does not permit an exhaustive listing of the many contributions of these investigators, but it is intended that the present review will provide a useful infrastructure from which the reader may progress to other research citations as desired.

KEY WORDS: **Respiratory resistance, Respiratory reactance, Pulmonary function, Lung mechanics.**

SCOPE OF THIS REVIEW

The focus of this review is alluded to the above, and we may also note what will not be reviewed in this paper. Literature published in languages other than English is not reviewed; and the technical demands of the forced oscillation technique (FOT) in animal studies are beyond the scope of this presentation. The mathematical analyses utilized in FOT are not reviewed. The theoretical models used to represent the respiratory system are not universally agreed upon; and the details of biomechanical modeling are beyond the scope of this review. They are however, well described by Peslin and Fredberg.[67] Finally, the clinical focus of this review does not gainsay the value of specialized research investigations beyond the scope of current clinical FOT application. FOT has been tailored to operate in the presence of mechanical ventilatory assistance, in endotracheally intubated patients; and both the Barcelona and Paris groups have demonstrated the clinical usefulness of FOT in assessment and treatment of sleep apnoea.[1,2,3,21–25,54,55,81] Special respiratory manoeuvres, special body enclosures and advanced techniques to apply pressure oscillations now permit both lower and higher frequencies of forced oscillation than commonly used clinically.[7,15,28,29,33,63,64,68,74] Mead and coworkers,[30–32,50] and Pimmel and coworkers,[34,52,71,78,79] have provided valuable physiological insights and avenues for future exploration.

DEFINITIONS

FOT measures *impedance* of the respiratory system to 'forced' pressure oscillations produced by a loudspeaker. Respiratory impedance is a complex quantity that includes both *resistance* and *reactance*. Resistance is the more familiar parameter, comprising the pressure-flow relationship of that portion of the pressure oscillation which is 'in phase' with airflow. It is designated *Rrs*.

Reactance is a complex quantity related to those portions of pressure oscillations not in phase with

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airflow, designated *Xrs*. Although Xrs is represented quantitatively as a single number, it is actually the sum of two components that represent opposing ('reacting') forces: those due to elastic elements of the respiratory system, and those due to inertial forces arising from the acceleration of tissues and gas in the respiratory system. Elastic elements of the respiratory system are distended by flow into them and develop a 'back pressure' only *after* some flow has occurred. Accordingly, elastic oscillatory pressure changes are *delayed* relative to flow. In contrast, to overcome the inertia of tissue or gas, pressure must build up *before* flow can change. Accordingly, inertial pressure changes must *precede (lead)* flow changes.

It is conventional to plot reactance as a graph of *phase angle* at different frequencies of oscillation. Because oscillatory pressures are the driving force for oscillatory flows, phase angle is defined as the degree to which oscillatory pressure *leads* flow. When pressure change lags after flow change, the phase angle between oscillatory pressure and flow is *negative*, whereas when pressure change leads flow change, phase angle is positive.

At low oscillation frequencies, elastic elements are the predominant 'reactant' to the pressure oscillation, and total oscillatory pressure lags after oscillatory flow. Thus, phase angle between oscillatory pressure and flow is negative; and Xrs has a negative sign. At higher frequencies, inertial forces become the major reactant, and pressure leads flow, so that Xrs is positive at higher frequencies. The point at which elastic and inertial reactance magnitudes are equal is associated with zero Xrs. At this point, the total oscillatory pressure is dissipated in overcoming flow resistance. This point is known as *resonant frequency* (Fres). Fres is a useful reference, being that frequency at which flow-resistance (Rrs) can be measured directly from the overall oscillatory pressure and flow. (See Fig. 1).

Currently available FOT methods fall into two general categories: those that use a single frequency, and those that use multiple frequencies. *Monofrequency* FOT methods often measure only Rrs, and apply oscillations at a frequency close to Fres. These methods have been used to assess upper airway resistance in sleep-disordered breathing and to assess instantaneous respiratory impedance at different times within the respiratory cycle.[25,68] *Multifrequency* FOT methods apply frequencies both below and above Fres and provide calculated measures of Rrs and Xrs at different frequencies. The multifrequency approach is now used clinically to assess for the presence and severity of airflow obstruction.

Historical development of FOT methods

The history of FOT begins with the classic study of DuBois et al,[16] in 1956, demonstrating that normal subjects who relaxed at the end of expiration and suspended their own breathing efforts manifested a Fres of about 6 Hz. Mead[50] extended this approach, demonstrating that 'forced' oscillations (FO) could be superimposed on the normal breathing pattern. Fisher et al[27] studied a larger group of normal subjects and patients with obstructive lung disease, superimposing FO, at a frequency equal to Fres, upon the normal breathing pattern. In normal subjects, mean Rrs was 2.3 cm H_2O/lps and Fres was 5–8 Hz. Mean Rrs in patients with obstructive lung disease was 8.1 cm H_2O/lps.

In 1968 Grimby et al[32] applied FO at frequencies between 3–9 Hz in patients with chronic airflow obstruction (CAO). They were the first to demonstrate a phenomenon that was to become classic for the identification of increased airflow resistance, namely, *frequency-dependence of resistance* (f-d Rrs) during FO. It had long been known that patients with airflow obstruction showed decreased lung compliance when breathing at increased respiratory frequencies.[37,58] Otis et al[58] predicted similar decreases in airflow resistance at higher respiratory frequencies in CAO; and Grimby et al[32] demonstrated such f-d Rrs at oscillation frequencies an order of magnitude greater than commonly encountered breathing frequencies. This finding introduced a somewhat counter-intuitive notion: resistance to airflow in the lung may be substantially elevated in severe CAO, but resistance in patients with CAO was not 'constant;' it decreased as frequency increased. The higher the frequency, the more closely patients with CAO might approach normal values of airflow resistance. It became common thereafter to specify Rrs at a low frequency (4–6 Hz) to avoid masking differences between CAO and normal subjects. Figure 1 shows a typical graphic representation of FOT data in normal subjects and patients with CAO.

These initial studies all used manual systems to measure Rrs, using one or more different frequencies of sine wave pressure oscillations. In 1975, Michaelson et al[51] introduced *spectral analysis* of computer-driven random noise pressure oscillations of a loudspeaker. More than simply using computer-assisted analyses, this comprehensive paper introduced *coherence* as an 'index of causality between the input and output of a linear system,' whereby if the system is not linear, or is contaminated by extraneous noise, the coherence provides a 'quality-assurance' index, analogous to a correlation coefficient. By averaging several power spectra, a 95% confidence interval for the average estimates of impedance could be computed, as a function of the number of spectral estimates averaged, and the coherence.

Michaelson et al[51] also made a quantitative estimate of the effect of alternate pathways for dissipation of forced pressure oscillations. Thus, if part of the flow

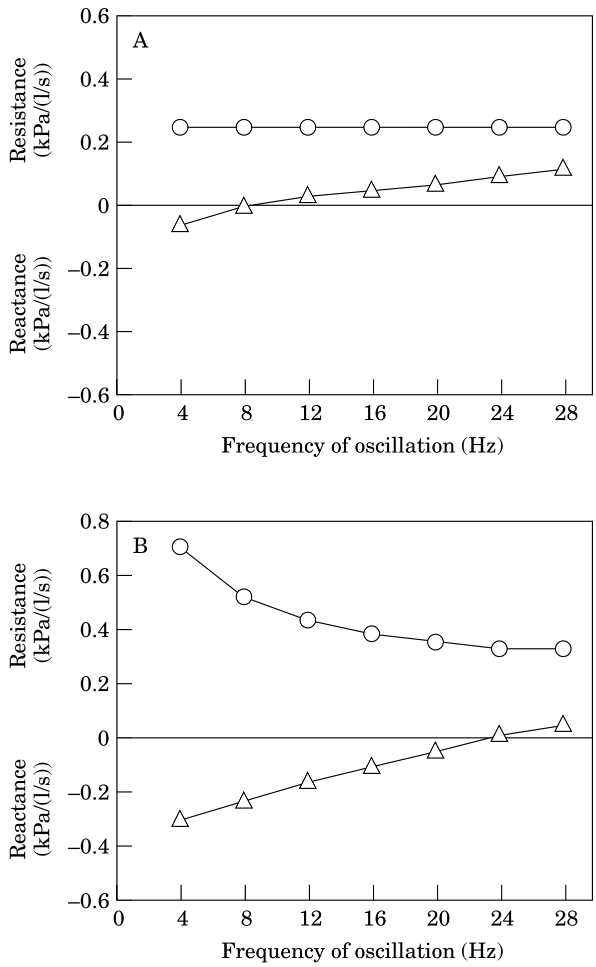

Fig. 1 Schematic representation of Resistance (Rrs) and Reactance (Xrs) at different frequencies of forced oscillation. Y-axis: R, X in kPa/lps. X-axis: Frequency of oscillation, in Hz. A: Normal adult. Resistance is constant at all frequencies analysed. Reactance is very slightly negative at the lowest frequency (4 Hz) and rises to cross zero (resonant frequency, Fres) at 8 Hz; and is positive at all higher frequencies. B: Airflow obstruction. Resistance is elevated, most at lower frequencies; and decreases as frequency increases. Reactance is markedly negative at low frequencies, and does not reach zero (Fres) until 24 Hz.

delivered to the mouth by FO pushes the cheeks (extrathoracic airways) outward, then to the extent that extrathoracic airways change size with FO, part of the flow measured at the mouth does not enter intrathoracic pulmonary structures. To minimize the movements of the mouth, they asked subjects to compress their cheeks with their hands. They also measured impedance of the mouth, (including oral cavity, pharynx, larynx and mouthpiece assembly) and corrected measured impedance for the mouth impedance. Smokers differed only slightly from normal subjects, but substantial differences in both resistance and reactance (impedance magnitude and phase angle) were found in patients with CAO. Importantly, patients with CAO showed prominent f-d Rrs, even after correction for mouth impedance.

Michaelson set out key parameters and limiting conditions; and the majority of subsequent studies using random noise followed this approach. Spectral analysis improved ease of FOT application, and expanded the information derived from the method. Computer-driven pressure oscillations included a wide range of frequencies applied in a single burst, commonly between 2 and 32 Hz.

Shortly after this first report of spectral analysis, Landser et al[45] meticulously documented spectral analyses in both healthy nonsmokers and patients with CAO, using impulses repeated every 0.5 sec to drive a loudspeaker. They validated impulse FOT data calculations by comparison with sinusoidal oscillations at the same frequency (6 Hz), using both a mechanical system and human subjects. They demonstrated f-d Rrs in patients with CAO that decreased substantially after bronchodilator inhalation.

Kjeldgaard et al reported f-d Rrs in asymptomatic smokers.[38] This identification of 'early airway disease' associated with f-d Rrs in asymptomatic smokers, was reinforced by larger numbers and by spectral analyses when Hayes et al[34] subsequently confirmed the differences between normal nonsmokers and asymptomatic smokers for f-d Rrs, and showed an increased Fres in the smokers. Shortly thereafter, the Leuven group published an important study of more than 400 healthy male subjects.[44] They chose pseudorandom noise pressure oscillations, rather than their previous impulse pressure oscillations, having reported earlier that this improved signal-to-noise properties.[53] Average Rrs was similar to that reported by DuBois et al;[16] but importantly, the smokers showed a significant f-d Rrs, whereas nonsmokers did not. In this group of more than 400 subjects, Fres was 7–10 Hz.

By the mid 1980's then, expected values for normal subjects for FOT Rrs and Fres were established. Impulse oscillation and random noise oscillation had been shown to provide comparable results. F-d Rrs was established as characteristic of patients with moderately severe or severe CAO and also appeared in some subjects with early airway disease, including asymptomatic smokers.[4,6,8,13,38] Another large population sample was reported by the Leuven group comparing healthy male subjects with more than 125 male patients with respiratory complaints.[10]

This second comprehensive Leuven study set a landmark for descriptions of abnormalities in patients with airflow obstruction, with characteristic changes in Xrs as well as in Rrs. Patients with moderate or moderately severe airflow obstruction showed a substantial rightward shift of the reactance-frequency (Xrs-f) curve with a significant difference in its shape. Interestingly, patients with severe CAO differed from moderately severe CAO not in their Rrs values, but rather in Xrs values: the entire Xrs-f curve in severe CAO was shifted more to the right. At the other end of the disease spectrum, symptomatic patients, with normal or nearly normal spirometric indices, differed from normal subjects by a shift of the Xrs-f curve to the right and small but significant f-d Rrs.

In children, Stanescu et al[73] and Clement et al[9] demonstrated that f-d Rrs occurred in normal healthy children up to about the age of 13 years. A number of studies reported reference FOT values in healthy children, and the utility of FOT in bronchiolitis, 'wheezy,' and asthmatic children.[5,14,17–20,39–43,56,57] Lebecque et al[46] showed that both low frequency Rrs (at 6 Hz) and f-d Rrs correlated very closely with change in FEV1 during histamine challenge in children; and reviewed the pediatric FOT literature prior to 1987. In a series of studies of young children, Bisgaard, Klug, and Nielsen assessed bronchial hyperresponsiveness and response to anti-asthma treatment in small children[5,39,40,42] using impulse oscillometry with Rrs and Xrs at 5 Hz (R5 and X5) as primary study variables. Baseline X5 and R5 in young asthmatic children were significantly improved by inhaled steroids; and a significant protective value of inhaled steroid treatment against cold air challenge was demonstrated, as measured by X5 and R5 in these children.[56,57] Impulse oscillation FOT reference values of X5 and R5 in children were roughly similar to values previously reported using random noise oscillation.[9,20,41] Modest differences notwithstanding, it goes without saying that individuals retested from time to time should be compared on the same system.

In the one and a half decades after spectral analysis was first reported, dozens of reports documented resistance and reactance in normal subjects, healthy smokers, adult patients with lung disease, normal children, and children with airflow obstruction. However, controversy over specific mechanical models of the respiratory system may have diluted the clinical impact of these important studies. One issue of controversy deserves special mention. This is the issue of whether f-d Rrs was simply an 'artifact' introduced by the influence of partial dissipation of pressure oscillations in the extrathoracic airways when intrathoracic resistance was increased. Peslin et al[65,66] used a plethysmograph surrounding the head to estimate the contributions of extrathoracic airway (including oral cavity) movements. They concluded that true intrathoracic Rrs was underestimated by conventional FOT application, and that little f-d Rrs occurred after proper correction in patients with CAO. Questions concerning variability of glottic aperture during normal breathing[31,68] may also have contributed to uncertainties over the clinical role of FOT. However, as pointed out by Coe et al,[11] despite the possibility that the upper airway effect might exaggerate the degree of true f-d Rrs of *intrathoracic* resistance, it served to increase the discriminatory value of f-d Rrs as a simple, empirical test of early airway disease.

Over the past decade a consensus developed that FOT had clear clinical utility, and related predictably to physiological changes in the respiratory system, produced by a variety of protocols. Yap et al[80] and Lorino et al[48] showed that low-frequency Rrs (and f-d Rrs) increased in the supine posture, or with negative pressure, due in large part to the fall in resting lung volume. Brochard et al[6] and Coe et al[11] showed that low frequency Rrs and f-d Rrs increased in smokers with greater cigarette exposure. Chinet et al[8], Phagoo et al[69] and Van Noord et al[75,76] showed that asthmatics and normals manifested variability coefficients of FOT similar to those of plethysmographic parameters, about 7–10%. FOT changes in response to carbachol, methacholine, and histamine (respectively) included increased low frequency Rrs, f-d Rrs, and rightward shift of the Xrs-f curve.[8,69,75,76] FOT changes were comparable to plethysmographic changes in terms of provocative dose or the slope of the dose-response. Decramer et al[13] reported similar FOT changes in smokers and asthmatics exposed to hyperventilation with subfreezing air.

Despite this consensus, isolated studies raised concerns about the sensitivity, specificity, and applicability of FOT to large-scale epidemiologic population studies.[12,35,36,60,77] These reports notwithstanding, it is still clear that FOT offers useful information in occupational medical hazards.[6,59,70] Even within a given investigative group, sensitivity and specificity may vary, depending on the investigator's familiarity with specific measurement methods, or the specific FOT indices and 'gold standards' used.[12,14,35,36,43,61,75,77,82]

The advance from reporting simple descriptions of FOT indices to the use of specific FOT indices as a measure of dose-response to airway challenge or to cigarette smoke or industrial chemical exposure, marks the beginning of the current era of clinical use of FOT. As pointed out by Pride[72] the interpretation of f-d Rrs may not permit clear distinction between central and peripheral airway responses as originally hoped back in the 1970's; but the balance of the (clinical) advantage between FOT and other methods of measuring lung mechanical function has moved towards FOT.

CLINICAL FOT PARAMETERS:

The choice of 'clinically relevant' FOT indices has varied among different centers, depending on authors' views of respiratory system 'models,' differences in adult and child FOT indices, and the parameters made available in commercial instrumentation. In the following, we describe clinical utility in terms of physiological, rather than mathematical or modeling issues.

The enhanced sensitivity of FOT over spirometry for detecting airflow obstruction has been clearest when using indices other than simple estimates of resistance or reactance at one frequency. Thus, the empirical phenomenon of f-d Rrs has been closely associated with increased intrathoracic airflow resistance, quite apart from the theoretical model that predicted frequency dependence of resistance.[58] In contrast to resistance at one oscillation frequency, f-d Rrs is an example of a physiological index integrated over a range of different frequencies.

The value of using an integrative response has many physiological precedents. Perhaps the use of glycosylated hemoglobin in diabetic patients is the most well known. HbA1c provides a measure of the patient's time-integrated blood sugar levels, which has proven more useful than isolated blood sugar values in clinical management of diabetic patients.

In the respiratory system, FOT provides indices of mechanical lung function over a wide range of frequencies. Rrs at one frequency may not detect subtle abnormalities, for example in cigarette smokers with normal spirometry. Several 'integrative' approaches may be pursued: it has been shown that integrating individual subjects' lung volume by normalizing Rrs for absolute lung volume enhanced Rrs sensitivity.[8] However, absolute lung volume is not usually known, and in any event requires much more labor-intensive methods than FOT. In contrast, the value of Rrs at low (4–6 Hz) relative to higher (15–30 Hz) frequencies has been useful to discriminate between smokers and nonsmokers, or degree of cigarette smoke or irritant chemical exposure.[6,8,10,11,34]

In contrast to Rrs, reactance has hitherto been quantified in most previous studies by only one or two values, usually Xrs at one low frequency (4, 5, or 6 Hz) and Fres. Like Rrs, Xrs shows the most dramatic changes with disease and after treatment at the lowest frequencies. However, the problem with individual low frequency values for both Rrs and Xrs is that they are subject to the greatest intra- and inter-individual variability, due to the proximity of natural breathing harmonics to 4–6 Hz. Thus, while low frequency Rrs and Xrs have the greatest potential 'clinical signal' they also have the greatest 'noise.' The Leuven group have added parameters that incorporate more of the continuous distribution of Xrs data, including derivatives of the Xrs-frequency distribution, namely the slope and shape (curvilinearity) of the Xrs-frequency curve. These parameters have shown significant discriminatory ability beyond the value of Xrs at one low frequency.[10,44] While such derivatives have been useful in analyses of large population studies, it is desirable to provide an 'on-line' index of Xrs that is clinically useful for an individual patient.

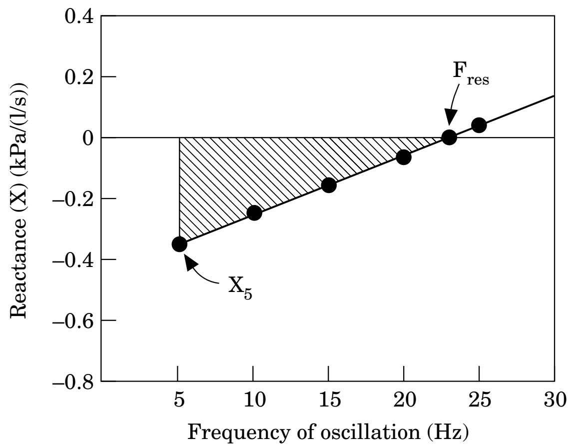

Fig. 2 Schematic representation of low frequency reactance area (AX). All negative values of reactance are summed by the integral of X, from 5 Hz to Fres. AX shown by the shaded area. Changes in this area are roughly proportional to the product [(Fres-5) * X5]. See text for discussion.

To improve Xrs signal-to-noise, the author has developed an integrated response index for reactance. If one integrates all the Xrs values between the lowest frequency studied and Fres, the cumulative data are equal to the low frequency reactance area under the abscissa and above the Xrs-frequency curve. This index is shown schematically in Fig. 2. It is delimited to take advantage of the two parameters hitherto most commonly used to describe Xrs, namely, Xrs at the lowest oscillation frequency, and Fres. However, it also includes Xrs at frequencies slightly higher than the lowest values, where clinical signal is still advantageous and noise is decreased, up to Fres. Frequencies below Fres are most sensitive to 'capacitance.' Capacitance relates to lung elastic properties; and the Leuven group[10] has shown that the characteristic change in the Xrs-frequency curve in airflow obstruction, relative to normal subjects is the flattening of its shape (more linear). This is consistent with the previously observed frequency-dependent decrease in lung compliance in airflow obstruction.[58] Thus the low frequency reactance area integral takes advantage of the Xrs-frequency curve shape change to amplify the clinically relevant signal, while relative noise is decreased, providing improved signal to noise.

Representative data from the author's clinical studies in patients with COPD obtained with a commercially available FOT instrument, (IOS [Jaeger]), are shown in Fig 3. Fig. 3 shows FOT data before and after nebulized beta agonist bronchodilator (pre- and post-BD) in a middle aged male with severe COPD. Panel A shows the patient prior to initiation of inhaled steroid therapy, and Panel B, 10 weeks later after clinical improvement with inhaled steroids. In Panel A, FOT data show gross abnormalities. The entire reactance curve is displaced substantially

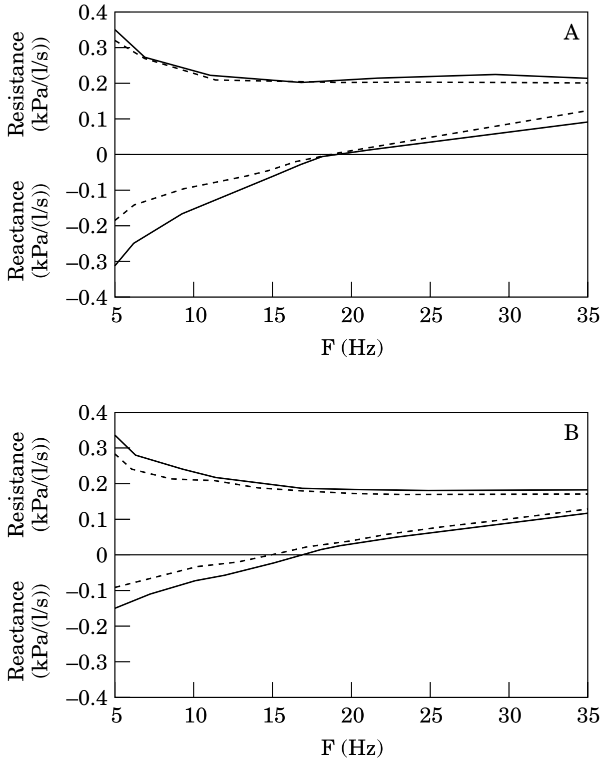

Fig. 3 Representative data in chronic airflow obstruction. Middle aged male patient with severe chronic bronchitis and emphysema. Axes as in Fig. 1. A: Baseline, prior to inhaled corticosteroid (ICS) therapy. Continuous line, pre-bronchodilator (BD); dashed line post-BD. Note that reactance is substantially displaced to the right of normal (cf Fig 1a) at all frequencies. Post-BD, all reactance values below Fres are less abnormal, and AX is reduced by 40%, compared to pre-BD. Resistance is elevated, most at low frequency (5–10 Hz). Little change from pre- to post-BD. B: After 6 weeks of ICS therapy. Reactance is improved both pre- and post-BD. The improvement in pre-BD with ICS therapy is of the same order of magnitude as that produced by BD, prior to ICS therapy. From pre- to post-BD, there is a 45% improvement in AX, and 15% decrease in R5. Pre-BD FEVl = 1.1 L both prior to and with ICS therapy, with an improvement post-BD of about 100 ml on both occasions.

rightward from normal, with a large low frequency reactance area (AX). Resistance is elevated, more at low frequencies (5–10 Hz) than at frequencies above 10 Hz. After BD, AX decreases by 40%; but R5 shows little change. FOT data in panel B are improved both pre- and post-BD compared to Panel A, consistent with the patient's clinical improvement. In panel B, AX shows a 40% improvement after BD, while R5 shows a 15% improvement post-BD. Pre-BD AX is substantially improved by inhaled steroid, with relative changes comparable to those caused by nebulized BD. Thus, both acute (pre- to post-BD) and chronic (without or with inhaled steroid) effects of treatment show clear improvements in reactance area.

Looking now at previous FOT studies with emphasis on Xrs, it may be noted that many of the previously cited studies showed larger relative changes in the overall Xrs-frequency curves than in Rrs. While Clement et al[10] showed identical Rrs between 8–12 Hz for normal subjects and patients with mild respiratory complaints, the Xrs-frequency curve was distinctly shifted to the right. If only the value of Xrs at the lowest frequency, or Fres is examined, differences between patients and normal subjects were modest indeed.[10,77] However, the low frequency AX shows a clear difference between the two groups. The same large difference in low frequency AX, between the lowest frequency studied and Fres, is obvious comparing patients with severe COPD and those with moderately severe airflow obstruction.[10]

CURRENT CLINICAL FOT IMPLEMENTATION

FOT instrumentation varies significantly among the many laboratories reporting clinical studies. Most groups cited above developed their own instrumentation prior to the mid 1990s. Differences in FOT instruments notwithstanding, it has become clear that FOT measures of lung function are not only more sensitive, but more specifically responsive to small airway function than maximal-effort forced spirometric measurements. Two commercially available instruments are now in fairly wide use. These instruments differ in the manner of driving the loudspeaker to produce the forced pressure oscillations. The Sensormedics ROS (respiratory oscillation system), drives the loudspeaker to produce pseudorandom noise of sinusoidal pressure oscillations in bursts of 16 sec duration, and was developed following the experience of the Paris group. The Jaeger IOS (impulse oscillation system), has taken over where Landser et al[45] left off, as it were. IOS drives the loudspeaker to produce brief (120 msec duration) individual pressure impulses, alternating between pushing (positive pressure) and pulling back (negative pressure) five times each second.

ROS (Sensormedics) has only recently been developed for clinical use although the instrument itself has been well proven by the extensive studies of the Paris group.[3,6,8,14,48,49,81,82] ROS applies an algorithm developed by Lorino et al[49] to provide data quality assurance, based on a coherence function. ROS analyses treat the 16 sec data record as a unit, and calculate resistance and reactance between 4 and 30 Hz at multiples of 1 Hz. If coherence at a particular frequency is less than the threshold demanded for quality assurance, these data points are not included in the analysis. A maximum of three repeated 16-sec measurements may be averaged. Raw (primary) data can be assessed in four 4-sec subunits. This is a useful option for the user, as it allows rejection of a subunit contaminated by artifact. One disadvantage of the continuous ROS oscillation over multiple breaths, is that it is not currently feasible to separate inspiratory from expiratory data.

Clinical parameters specified by ROS include resistance (R) at 6 and 24 Hz, slope (S) of R between 4–16 Hz, Fres, and R extrapolated from 16–4 Hz backwards to zero Hz (R0). It should be emphasized that such backward extrapolation is not meant to define an actual R at 'zero' frequency. Instead, it is simply a convenient way to estimate a value for total respiratory resistance derived from the observed frequency-dependence. Since resistance falls with increasing frequency in patients with CAO, one would expect a different value at 4, 5, 6 or 8 Hz (frequencies commonly reported in FOT studies). It is convenient therefore to extrapolate backwards to a 'standard' frequency.

IOS (Jaeger) is substantially 'older' commercially. While ROS offers a convenient listing of the slope of f-d Rrs, IOS provides a frequency-integrated measure of reactance at low frequencies, up to Fres (low frequency AX, as described earlier). IOS also provides numeric values of Fres, and Rrs and Xrs at multiples of 5 Hz. Most importantly, IOS provides numeric values of coherence between 5–35 Hz, and separate inspiratory and expiratory numeric values of coherence, Rrs, Xrs, and AX at multiples of 5 Hz. Recordings can be of any specified duration up to 120 sec, and any number of recordings can be made at one sitting.

In a recent pilot comparison study, the author has assessed adult patients with chronic airflow obstruction pre- and post-nebulized BD using both IOS and ROS. Pre- to post-BD differences in Rrs and Xrs were comparable, as measured by both instruments. ROS R0 and R6 changed comparably to IOS R5. ROS Slope (R4–16) changed comparably to the graphic changes in IOS R between 5–15 Hz. Post-BD shift to the left of the ROS Xrs-frequency data was similar to that of IOS Xrs-frequency.

Interestingly, Jaeger and Sensormedics have recently become part of the same corporation. One advantage of this commercial cooperation is that standardized clinical FOT parameters can be implemented in both instruments. Another recent development of the joint cooperation between IOS and ROS is a new mouthpiece that includes a built-in tongue depressor, available for both instruments. Initial studies with this new mouthpiece show decreased variability in repeated intra-individual FOT measurements.

CLINICAL STANDARDS FOR FOT

Since patients are asked to breathe normally during FOT measurements, they have freedom to choose their respiratory rate, respiratory effort, tidal volume, and resting lung volume. Some subjects may not relax when breathing on respiratory equipment, and may swallow from time to time during the test procedure. Dentures may cause discomfort while breathing through a mouthpiece. The nose clip may cause additional discomfort. The tongue may get in the way of the airstream. Coughing may cause transient bronchospasm, as may breathing at the extremes of the vital capacity. Patients with CAO may actively force their expiratory effort, causing wheezing, and dynamic compression of intrathoracic airways during their resting breathing (with marked increase in resistance during expiration). Accordingly the technique used by the operator is critical to reassure patients and ensure as much freedom from artifacts as possible. Thus far, operator technique has been left up to individual investigators; but the European Respiratory Society is currently developing a set of clinical performance standards for FOT.

Most investigators optimize data quality in FOT by excluding measurements with low coherence to avoid problems caused by the above noted artifacts. Following introduction by Michaelson et al[51] there has been relatively good agreement among investigators that coherence is a useful guide to quality assurance. Since the desired confidence interval for spectral estimates is determined both by the number of estimates averaged and the coherence,[51] Miller and Pimmel modelled the expected variation of repeated measurements as a function of coherence and number of repetitions.[52] Chinet et al[8] made use of this approach to guide selection of a threshold value for coherence in a particular set of measurements as a function of number of repeated measures. This approach has also been reported by Farre et al;[26] and may well serve as a basis for future standardization of clinical performance of FOT systems.

CONCLUSIONS

Monofrequency FOT is easier for clinicians to understand, when there is one parameter, resistance, at only one frequency. However, use of fixed frequency FOT is optimally suited to detect large changes in respiratory resistance, such as during sleep disordered breathing, or in patients on mechanical ventilation in intensive therapy units.

Multifrequency FOT has come of age for assessment of clinical status in patients with an established diagnosis of CAO, and most would agree, to establish this diagnosis at a relatively early stage. Changes over time are easily demonstrable when using the patient as his own control. Sufficient normative data have been published so that the clinician or clinical researcher can even detect changes in apparently normal subjects consistent with early airway disease prior to the onset of clear spirometric changes. Large-scale population studies have not yet reported clear associations among various FOT indices and other aspects of pulmonary health, including exposure to environmental pollution, respiratory symptoms, and conventional spirometry. Initial epidemiological investigations must now be considered only preliminary, until international agreement on clinically relevant FOT indices is reached. At the present time, use of commercially available instrumentation may demonstrate slightly different normal limits than those defined earlier; but repeated measurements in the same patient with existing commercially available instruments appear reliable and sensitive to acute changes in clinical status. Within-patient variability is comparable to FEV_1, although generally slightly larger. Sensitivity to bronchial challenge is greater for FOT than FEV_1, in spite of slightly greater baseline variability of FOT parameters. Sensitivity of FOT indices to anti-inflammatory agents is greater than FEV_1 in patients with established CAO. Ease of administration is much improved over FEV_1, because maximal coordinated efforts are not needed. A corollary is that FOT measurements can be repeated frequently without distress to patients, to measure temporal changes in clinical status over the course of many hours. This is especially useful in assessing efficacy of long-acting pharmacological agents. Finally, FOT is useful in children below the age when they are capable of providing reliable spirometric data. Again, normative standards have been well described, as a function of age and size; and responses to bronchial challenge are well documented. Pharmaceutical clinical trials incorporating FOT are currently underway in both children and adults.

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