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ERS TASK FORCE

The forced oscillation technique in clinical practice: methodology, recommendations and future developments

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ABSTRACT: The forced oscillation technique (FOT) is a noninvasive method with which to measure respiratory mechanics. FOT employs small-amplitude pressure oscillations superimposed on the normal breathing and therefore has the advantage over conventional lung function techniques that it does not require the performance of respiratory manoeuvres.

The present European Respiratory Society Task Force Report describes the basic principle of the technique and gives guidelines for the application and interpretation of FOT as a routine lung function test in the clinical setting, for both adult and paediatric populations.

FOT data, especially those measured at the lower frequencies, are sensitive to airway obstruction, but do not discriminate between obstructive and restrictive lung disorders. There is no consensus regarding the sensitivity of FOT for bronchodilation testing in adults. Values of respiratory resistance have proved sensitive to bronchodilation in children, although the reported cutoff levels remain to be confirmed in future studies.

Forced oscillation technique is a reliable method in the assessment of bronchial hyperresponsiveness in adults and children. Moreover, in contrast with spirometry where a deep inspiration is needed, forced oscillation technique does not modify the airway smooth muscle tone. Forced oscillation technique has been shown to be as sensitive as spirometry in detecting impairments of lung function due to smoking or exposure to occupational hazards. Together with the minimal requirement for the subject's cooperation, this makes forced oscillation technique an ideal lung function test for epidemiological and field studies. Novel applications of forced oscillation technique in the clinical setting include the monitoring of respiratory mechanics during mechanical ventilation and sleep.
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CONTENTS

As a tool for the investigation of respiratory mechanics in clinical practice, the forced oscillation technique (FOT) is well supported theoretically and has the advantage of being a noninvasive, versatile method and demanding minimal cooperation of the patient. The most attractive feature of FOT is that the forced oscillations are superimposed on the normal breathing, avoiding the need for any special breathing manoeuvre or any noticeable interference with respiration.

During the past decade, advances in basic research and FOT applications, as well as new developments in technology, have evoked new interest from both the clinical and industrial fields. To address demands for further standardisation of FOT, a European Respiratory Society Task Force was established to update the standardisation work carried out during the Commission of the European Communities Biomedical Engineering Advisory Committee (COMAC-BME) programme of respiratory impedance (Zrs) measurement development [1], and to develop clinical guidelines for Zrs measurement. The present report summarises the most important underlying concepts of the FOT, offers guidelines for its implementation and use in the clinical environment, and gives a brief overview on the latest developments of potential clinical impact.

Methodology

Since the first FOT measurements by DuBois *et al.* [2], numerous variants of the FOT have been developed in terms of measurement configuration, oscillation frequencies and evaluation principles. This short review is focussed on the routine clinical applications, addressing the most basic concepts only, and the reader is referred for more detailed information to monograph articles [3–7].

Potential and limitations

The essence of the FOT can be elucidated by contrasting its principle with that of the respiratory mechanical measurements that depend on spontaneous breathing activity or respiratory manoeuvres. Uniquely, for the FOT, external driving signals (*i.e.* forced oscillations) are used to determine the mechanical response of the respiratory system and the investigator uses specifically developed forcing waveforms to explore the respiratory mechanical properties, relying on the well-developed arsenal of linear system analysis. FOT thus possesses solid theoretical foundations and a high degree of versatility, which are far beyond the capability of conventional respiratory mechanical tests. However, the requirement of linearity necessitates the use of small-amplitude oscillations, which may leave undisclosed some energetically and functionally important nonlinear properties that manifest during tidal breathing, and assumes methodological rigor in both data collection and analysis.

Respiratory impedance

The key concept of the forced oscillatory respiratory mechanics is the "impedance" (Z), the spectral (frequency domain) relationship between pressure (P) and airflow (V') (see Appendix). In simple terms, Z can be conceived as a generalisation of resistance, since it embodies both the in-phase and out-of-phase relationships between P and V'. The in-phase component is called the real part of Z (or resistance (R)), whereas the out-of-phase relationship is expressed by the imaginary part (or reactance (X)), and both appear as functions of the frequency of oscillation (f). In other words, R describes the dissipative mechanical properties of the respiratory system, whereas X is related to the energy storage capacity and thus determined jointly by the elastic properties (the relationship between P and volume) dominant at low oscillation frequencies and the inertive properties (the relationship between P and volume acceleration), which become progressively more important with increasing f.

Measurement arrangements

Depending on the sites of the P and V' measurements and of the application of the forced oscillations, different kinds of impedance of the respiratory system can be defined. Most commonly, the forced oscillations are applied at the airway opening, and the central airflow (V'ao) is measured with a pneumotachograph attached to the mouthpiece, face mask or endotracheal tube (ETT). Pressure is also sensed at the airway opening (Pao) with reference to body surface (in this case, atmospheric) pressure (Pbs). The input impedance of the respiratory system (Zrs,in) is then the spectral (frequency domain) relationship between transrespiratory pressure (Prs=Pao-Patm) and V'ao: Zrs,in(f)=Prs(f)/V'ao(f). When Zrs is partitioned into pulmonary (ZL) and chest wall impedance (Zw) on the basis of the measurement of intraoesophageal pressure (Pes), ZL and Zw are obtained from ZL=(Pao-Pes)/V'ao and Zw=(Pes-Pbs)/V'ao, respectively. A special version of the input FOT is the head generator technique, where Pao is applied around the head, in order to minimise upper airway wall shunting [8]. An alternative instrument that can be used to estimate Zrs,in and that does not require the recording of flow (V'), is a wave tube connecting the source of forced oscillations (usually a loudspeaker) and the subject; Zrs,in is measured as the load impedance on the wave tube, on the basis of the geometric and physical properties of the tube and the inside air, and the pressure recorded at the inlet and outlet of the tube [9]. Transfer impedance is obtained when the oscillations are imposed and P and V' are measured at different sites of the respiratory system; accordingly, various measurements of transfer impedance can be instrumented. However, if the impedance of the total respiratory system (Zrs,tr) is considered, either the oscillatory excitation at the airway opening is combined with the plethysmographic measurement of output, "body surface" flow, or the oscillations are imposed in a "head-out" plethysmograph on the body surface, with the measurement of V'ao. As Zrs,in and these two variants of Zrs,tr are affected differently by the parallel elements of the respiratory system, such as alveolar gas compressibility and upper airway wall movements, they can be selected or combined to obtain more reliable estimates of the airway and tissue impedance. The present review is restricted to the most easily implementable FOT, namely Zrs,in.

Oscillation frequencies

For routine clinical applications of FOT it is usual to apply a medium frequency range, *i.e.* the imposed oscillations start from 2–4 Hz, roughly 1 decade above the spontaneous breathing rate, and extend up to a few times 10 Hz. In this frequency range, the healthy respiratory system exhibits a largely frequency-independent respiratory resistance (Rrs) whose major component is airway resistance (Raw) (fig. 1). Respiratory reactance (Xrs) undergoes the transition from negative values (when the elastic reactance dominates) to positive values increasing with f (the dominance of inertial reactance). At the characteristic resonant frequency ($f$res), where Xrs crosses zero, the elastic and inertial forces are equal in magnitude and opposite. The low-frequency oscillations include the frequencies of spontaneous breathing and, accordingly, can be applied during apnoeic conditions only, whereas the high-frequency range contains oscillations up to several 100 Hz. Use of low-frequency and high-frequency forced oscillations reveals different mechanical properties of the respiratory system, and these techniques are promising as lung function test methods; for this reason they are considered in the "New developments" section. The present section of this report focuses on the most commonly used medium-frequency range FOT.

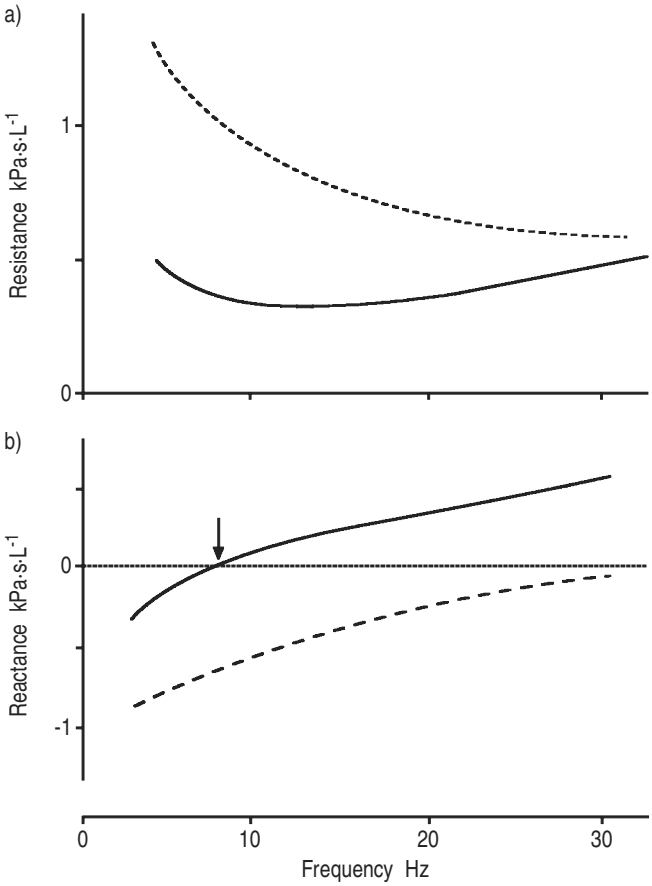

Fig. 1. – Schematic illustration of the frequency dependence of respiratory impedance of adults in the medium frequency range, in health and disease. Compared to the normal impedance data (–), in airway obstruction, respiratory resistance (- - -) is higher (a) and negatively frequency-dependent, whereas respiratory reactance is lower (b). Arrow indicates resonant frequency.

Both single-frequency and composite signals have been used in clinical practice. When the FOT is applied to explore the patterns or mechanisms of frequency dependence of Z_{rs} in health and disease, the simultaneous application of several frequency components, *i.e.* the use of composite signals, such as pseudorandom noise or recurrent impulses, is preferred. The single-frequency FOT may be used in the tracking of relatively rapid changes in Z_{rs}, *e.g.* those occurring within the respiratory cycle, or as an accessory device for monitoring airway patency, and it may also be useful in the evaluation of changes in the bronchomotor tone.

Recommendations for measurements

Set-up

The subject is connected *via* a mouthpiece to the set-up that most commonly utilises a loudspeaker to deliver the forced oscillatory signal (fig. 2). The P and V' signals are measured next to the mouthpiece. To enable spontaneous breathing of the subject, a shunt pathway open to the atmosphere is necessary; this is usually a wide-bore side tube (with a high impedance to present a small leak for the high oscillatory frequencies and a low resistance against spontaneous breathing) placed in parallel to the loudspeaker. A mechanical resistor may also be used for this purpose. A bias flow to flush

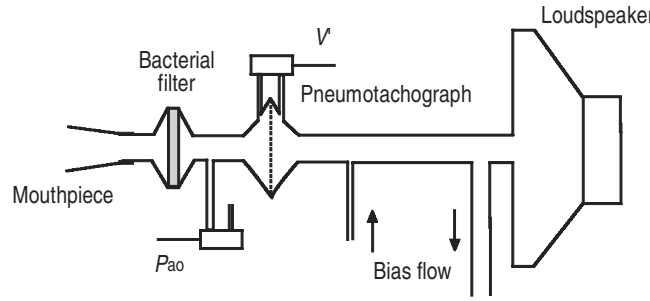

Fig. 2. – Schematic arrangement of the forced oscillatory respiratory impedance ($Z_{rs,in}$) measurement. P_{ap}: airway opening pressure; V': airflow.

the dead space is optional and can preferably be introduced between the loudspeaker and the pneumotachograph. When a bacterial filter is placed between the set-up and the patient for hygienic purposes, the measured Z_{rs} should be corrected for the impedance of this filter. The dead space of the filter should be minimal to avoid shunting effects at high Z_{rs}.

Apparatus

The FOT system should impose a load against spontaneous breathing of <0.1 kPa·s·L^{-1} below 5 Hz. When using composite signals, the loudspeaker should be able to develop a peak-to-peak pressure variation of 0.2 kPa at the airway opening. The largest P developed in the system should not exceed 0.5 kPa.

The differential pressure transducer used for flow measurement together with its connections to the pneumotachograph should be symmetrical and of low compliance, providing a common mode rejection ratio of at least 60 dB up to the highest frequency investigated [10]. The pressure transducers should have a low sensitivity to accelerations, or at least be protected against vibrations. The flowmeter and the pressure transducer should be linear (within 2%) up to at least 1 L·s^{-1} and up to 0.5 kPa, respectively.

Calibration

The calibration should take into account the relative static gain and the relative frequency characteristics of P and V' measuring devices. To check the overall accuracy of the measurement set-up, the use of a reference impedance, whose theoretical impedance is known from physical principles, is recommended. The magnitude of the impedance of this device should be comparable at all measured frequencies to that of the highest Z_{rs} encountered or expected in the measured subject population, *i.e.* reference impedance with a magnitude of $\sim$1.5 kPa·s·L^{-1} and $\sim$4 kPa·s·L^{-1} are suggested for calibration in adult and infant studies, respectively. After proper calibration, a maximum error of 10% or 0.01 kPa·s·L^{-1}, whichever is greater, is allowed over the frequency range of interest. Proper calibration and evaluation of the accuracy of FOT set-ups is particularly important since it has been shown that systematic differences in Z_{rs} were obtained with different devices [11].

Input signals

It is important to ensure that the test signal is applied for long enough to include several breathing cycles. The amplitude of the signal should be large enough to guarantee a satisfactory signal-to-noise ratio, but not too large so as to avoid discomfort for the subject, nonlinear behaviour of the respiratory system and synchronisation between breathing and

input signals. A peak-to-peak size of the composite signal of 0.1–0.3 kPa seems optimal [12].

In studies exploring the frequency dependence of Z_{rs}, the use of multifrequency (composite) signals, preferably including the 4–30 Hz range, is recommended. Usually, the amplitude spectrum of the composite signal is coloured so as to enhance the power at lower test frequencies. This improves the signal-to-noise ratio at the lower frequencies that are more contaminated by components of the spontaneous breathing signal. Special procedures have been developed to optimise the composite forcing waveform [13]. Alternatively, when the Z_{rs} data at a single frequency are of interest, a sinusoidal signal at the lowest possible frequency should be used. The lowest frequency at which Z_{rs} can be measured reliably is governed by the relative power of the harmonics of the breathing signal and applied forced oscillation at that frequency.

Signal processing

Averaging pseudorandom signal epochs by time [14] or the use of the so-called "unbiased estimators" [15, 16] reduces the errors introduced at the low frequencies (in adults below ~6 Hz) by the higher harmonics of the breathing signal.

The FOT device should be specified according to the data processing technique used in the calculation of Z_{rs} (number and length of time blocks, overlapping, windowing, lowpass and/or highpass filtering, way of calculating coherence function, *etc.*) [17].

Report of results

The mean and SD of all Z_{rs} data obtained from successive measurements should be reported. The coefficient of variation (CV) at every measured frequency is the main index of the reliability and repeatability of Z_{rs} data. Reliability indices of the individual measurements, such as the coherence function, are optional to report.

In addition to the R_{rs} and X_{rs} data measured at a given frequency (R_{rsf}, X_{rsf}), impedance parameters may be estimated using various model analyses. However, model parameters and curve (polynomial) fittings without raw data are unacceptable.

Measurement conditions

Subject's position. Measurements are performed in the sitting position with the head in a neutral or slightly extended position. Flexion of the head should be avoided. During the measurement, the subject (or technician) firmly supports his/her cheeks and the floor of the mouth using both hands and a noseclip is worn. The subject is instructed to breathe quietly at FRC level. When measuring young children, allowing the parents to accompany them in the lung function laboratory improves cooperation. The child should be given some time to adjust to the laboratory environment and trained to breathe quietly through the mouthpiece and to wear the noseclip for a short period of time. The parents can also be given those pieces of equipment to train their child at home should difficulties be encountered.

Volume history. Immediately before the measurement is made, the volume history of the subject should be monitored for at least 30 s. At least 3 min of quiet breathing should be allowed for recovery if forced respiratory manoeuvres have been made before Z_{rs} is measured.

Measurement acceptance criteria. Swallowing, glottis closure, leak around the mouthpiece, improper seal with the noseclip, irregular breathing or acute hyperventilation during the measurement are reasons to discard the measurement. Most of these events can be detected on the flow signal which should therefore be displayed on the screen during the measurement. If a measurement is considered artefactual, both R_{rs} and X_{rs} should be rejected.

Number of measurements. A total of three to five technically acceptable measurements should be performed. The subject should come off the mouthpiece in between successive measurements in order to establish the short-term variability of Z_{rs} in a uniform manner. A further indication of baseline variability may be obtained by repeating the baseline measurements 10–20 min later; this is important in the interpretation of bronchomotor tests, particularly when Z_{rs} is the sole index used in evaluating bronchial reactivity. Evaluation of a change in R_{rs} in response to challenge is dependent on the baseline CV value. When baseline reproducibility is poor, further histamine (His) or methacholine (Mch) study is inappropriate both because of difficulty with test interpretation and the risk of underlying poor asthma control.

The upper airway artefact

With the standard $Z_{rs,in}$ set-up, a component of the measured input flow is lost in the oscillatory motion of the compliant upper airway walls and never enters the lower respiratory system. By the support of the cheeks and mouth floor, it is not possible to eliminate this shunt effect completely [18–20], which increases as Z_{rs} rises. Overall, as upper airway impedance (Z_{uaw}) falls steeply with increasing frequency, upper airway shunting is minimal at low frequencies and becomes increasingly important as oscillation frequency rises. This leads to an artifactual frequency-dependence of R_{rs} and a shift of X_{rs} to higher frequencies (with an increased f_{res}) in children and adults [19, 20]. The upper airway artefact is particularly important in children for whom Z_{uaw} approximates adult values [21], since Z_{rs} is larger in children and rises progressively with decreasing age.

Several different approaches have been proposed to minimise the effects of the upper airway shunt. One method used to correct for the upper airway shunt by separately determining Z_{uaw} during a Valsalva manoeuvre [18] has been shown to undercorrect Z_{rs} [19, 22], and is also impractical during routine Z_{rs} measurements. Another approach is to apply the oscillating pressure signals around the head and at the mouth (the head generator technique [8]) and this considerably reduces the motion of the cheeks, minimising though slightly overcorrecting for the Z_{uaw} shunt artefact. Compared to the standard method, use of the head generator technique results in R_{rs} values that are larger but less frequency dependent, a steeper increase in X_{rs} with frequency (and therefore lower f_{res}) and larger R_{rs} changes during Mch challenge that are independent of baseline Z_{rs} [19, 23, 24]. By using the change in admittance (the inverse of impedance) instead of R_{rs} to express the response to bronchoprovocation, the result is practically free from the upper airway artefact [25], this way potentially increasing the sensitivity of the conventional set-up.

Studies differ in their assessment of the convenience of the head generator technique. One study suggested that tolerance was poor by some subjects and that data rejection increased at low frequencies (<10 Hz) [24]. However, in another study satisfactory data could be obtained in all the 380 normal adult subjects but one [26]. In adults, the sensitivity in detecting airway obstruction appeared to be similar with both techniques [24]. In children, the diagnostic value of R_{rs10} in identifying responses to bronchodilators improved slightly with the head generator compared to the standard method,

whereas the parameters derived from X_{rs} obtained with the standard method had a better diagnostic value than the head generator technique [27].

In conclusion, with the standard FOT technique, Z_{rs}, especially at higher frequency, is affected by the motion of the upper airway walls. This upper airway shunt results in an artificial frequency dependency of R_{rs} and X_{rs} is decreased with increased f_{res} in the presence of a high Z_{rs}. Although elimination of the upper airway shunt during standard $Z_{rs,in}$ measurement is impossible, firm and uniform support of the upper airway walls should be applied. More accurate Z_{rs} data can be obtained using the head generator technique, which minimises the upper airway shunt. However, further studies are needed to identify the improvements offered by this method in terms of its sensitivity and specificity in clinical practice.

Clinical applications

Reference values

Adults. A relatively limited number of reference studies of $Z_{rs,in}$ as a function of frequency exist in adult subjects. Healthy subjects exhibit a virtually frequency-independent R_{rs}, with a frequency-dependent X_{rs} usually behaving according to an inertance-compliance system exhibiting an f_{res} <10 Hz.

An overview of the average R_{rs} values of healthy adult subjects reported from different laboratories is given in table 1. In half of the studies, relatively young subjects (an average age of <35 yrs) were investigated; the selection criterion of the subjects was not always reported, or the sample population was limited to a specific subgroup of subjects. Nevertheless, the average R_{rs} of healthy adults varied little among the different studies, and slightly higher R_{rs} values were found for females (0.31 kPa·s·L^{-1}) compared with males (0.25 kPa·s·L^{-1}). Prediction equations for the average R_{rs} and X_{rs}, and the slope of the R_{rs} *versus f* relationship are given in table 2 [32]. ZERAH *et al.* [33] analysed R_{rs} data obtained in 40 healthy volunteers by performing linear regression on the data from 4–16 Hz, and back-extrapolating the regression line to 0 Hz to obtain the parameter R_{rs0}, and its inverse, respiratory conductance at 0 Hz (G_{rs0}). G_{rs0} was dependent on height and age but not on sex or body weight.

Children. Normal values have been collected by several research groups [30, 34–45]. An overview of the regression equations of R_{rs} as a function of body height is given in table 3, and the corresponding data are shown in figure 3. R_{rs} usually falls inversely with height, and, except for one study [34], no sex-related differences in R_{rs} have been described. In most of these studies, a similar R_{rs} *versus* height dependence has been obtained.

The negative frequency-dependence of R_{rs} becomes more pronounced with decreasing age [34–36, 40, 41]. In small children, f_{res} is high (sometimes >20 Hz) and then decreases as X_{rs} becomes less negative with growth. The characteristics of the X_{rs} *versus f* relationship are significantly modified when a head generator is used to minimise the upper airway wall motion, shifting the curve to the left and reducing f_{res} [20, 46, 47].

Clearly, further large scale studies in adults across a wide age range are needed to validate existing reference values. In children, available regression equations of R_{rs} as a function of body height show a fairly close agreement.

Table 2. – Prediction equations for the average resistance ($R_{rs}(0)$), average reactance ($X_{rs}(0)$) and slope of resistance to frequency ($R_{rs}(1)$), and the residual SD (RSD)

Male
$R_{rs}(0)$=–0.2454.H+0.001564.W–0.00055.A+0.5919 (RSD=0.0493)
$R_{rs}(1)$=0.00842.H–0.000047.W–0.000018.A–0.0095 (RSD=0.00197)
$X_{rs}(0)$=0.1479.H–0.000402.W–0.00022.A–0.1721 (RSD=0.0306)
Female
$R_{rs}(0)$=–0.4300.H+0.00165.W–0.00070.A+0.9312 (RSD=0.0619)
$R_{rs}(1)$=0.01176.H–0.000106.W–0.000045.A–0.00817 (RSD=0.00256)
$X_{rs}(0)$=0.2487.H–0.001700.W–0.00053.A–0.2158 (RSD=0.0406)

$R_{rs}(0)$ and $X_{rs}(0)$ in kPa·s·L^{-1}, $R_{rs}(1)$ in kPa·s^2·L^{-1}. H: height (m); W: weight (kg); A: age (yrs). Reproduced with permission from [32].

Reproducibility

The short term intra-individual CV of FOT indices in healthy adults range 5–15% (table 4), which is comparable to the variability of resistance values obtained with other methods (body plethysmography (s*G*aw), interrupter technique, *etc*). For adult patients with airway obstruction the CV values were hardly different from that of healthy subjects.

Similar estimates of short term CV, ranging <5–14% have been obtained in children [34, 38, 39, 51, 53–57]. A significant circadian rhythm has been identified in about one-third of an asthmatic children population, although the amplitude of the diurnal variations of R_{rs} did not exceed 20% [58].

The day-to-day variability has been reported to be slightly larger than the within-day variations in adults, with a CV of 10.0 *versus* 8.3% [49] and 10.8 *versus* 8.6% [51]. In children,

Table 1. – Overview of the average respiratory resistance (R_{rs}) value obtained in healthy adults.

Reference	Selection criteria	Frequency band Hz	Male			Female		
			R_{rs} kPa·s·L^{-1}	n	Age yrs	R_{rs} kPa·s·L^{-1}	n	Age yrs
[28]	Male Air Force members/applicants	4–24	0.25 (0.06)	224	26 (10)			
[29]	?	8–24	~0.26	442	29			
[30]	Patients undergoing rehabilitation and healthy hospital workers	10	0.29 (0.08) M+F	102	50			
[31]	?	6–24	0.26 (0.06)	126	33 (12)	0.30 (0.06)	100	29 (12)
[24]	"Healthy" subjects referred for lung function testing	10–32	0.26 (0.07)	32	48 (15)	0.34 (0.07)	28	55 (13)
[32]	"Healthy" subjects referred for lung function testing	6–24	0.25 (0.05)	137	53 (14)	0.31 (0.07)	140	58 (14)

Data are presented as mean (SD). M: male; F: female; n: number of subjects studied.

Table 3. – Overview of the regression equations of respiratory resistance (Rrs) as a function of height in healthy children

Reference	Frequency band Hz	Subjects n	Age yrs	Rrs kPa·s·L^{-1}	RSD
[42]	15–35	16	3–5	$R_{rs(15-35)}$=-0.00529×H+1.102	
[41]	4, 9	130	3–14	R_{rs4}=2.47–0.013×H	
[36]	3–10	121	4–16	R_{rs4}=1.87×10^4×H$^{-2.12}$	
[38]	2–26	138	2–16	R_{rs6}=9.2×10^{-5}×H^2–0.0341×H+3.52	0.15
[40]	2, 4, 12	218	2–18	log(R_{rs4})=4.413–2.18×log (H)	10.2%
[34]	2–26	255	2–12	R_{rs6}=0.00017×H^2–0.05407×H+4.77323	0.175
[39]	10	377	3–18	R_{rs10}=1.392–0.00635×H	0.066
[44]	5	247	3–6.5	R_{rs5}=-0.009528×H+2.0643065	
[45]	8, 12, 16	199	3–17	ln (R_{rs8})=10.990–2.370×ln (H)	

H: height (cm); RSD: residual SD.

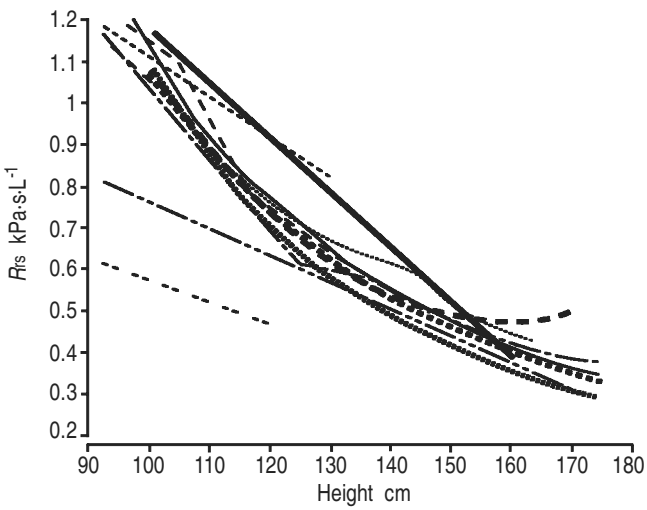

Fig. 3. – Regression curves or mean values of respiratory resistance (Rrs) *versus* height in different studies. — : [40]; – – – : [37]; - - - : [36]; ·····: [35]; ▬ : [41]; ▬ ▬ : [44]; – - – : [38]; – - - – : [39]; -- -- -- : [42]; ▪▪▪ : [34]; ▪▪▪▪▪▪▪▪▪▪: [45].

the day-to-day CV and the weekly variability were found to be 16% [54] and 17% [34].

Diagnostic capacity

Whereas the difference in Zrs parameters between subjects with normal and abnormal spirometry has been repeatedly pointed out, there is currently no recognised FOT index of airway obstruction. Interpretation of Rrs deviations from normal inpatients and pathological conditions should take into account the wide scatter of Rrs values among normal individuals. To this end, the difference between observed and predicted Rrs may be divided by the SD of the corresponding reference population. This ratio will be referred to as the SD index.

Table 4. – Short term (within day) intra-individual variability of forced oscillation technique (FOT) indices in adult, healthy subjects and patients

Reference	FOT index	Subjects studied	CV %
[48]	Rrs10	Healthy subjects	11.3
		Asthmatics	10.3
[49]	Rrs8	Healthy subjects	8.3
		Asthmatics	10.0
[50]	|Zrs10|	Asthmatics	4.9
[12]	Rrs4–32	Healthy subjects	4.7
[30]	Rrs10	Healthy subjects	9.8
[51]	Rrs10	Healthy subjects	8.6
		COPD patients	8.8
[52]	Rrs6	Patients with airway obstruction	15.2
[52]	Rrs6-26	Patients with airway obstruction	12.1

Rrs6, Rrs8, Rrs10: Rrs measured at 6, 8 or 10 Hz; |Zrs10|: modulus at 10 Hz; CV: coefficient of variation.

Adults. The pattern of change in Zrs in various pulmonary function abnormalities consists of an increase in Rrs, especially in the lower frequency range, and a decrease in Xrs, associated with an increase in $f$res. CLÉMENT *et al.* [29] demonstrated that conventional FOT was a sensitive tool to separate healthy subjects from patients with respiratory complaints (both with and without a reduced forced expiratory volume in one second (FEV1)). In a later study, the same investigators showed that the sensitivity to detect symptomatic people was similar for FOT and spirometry [32].

In adult patients with intrapulmonary airway obstruction, Rrs is increased at the lower frequencies and falls with increasing f. The negative frequency-dependence of Rrs is explained on the basis of mechanical inhomogeneities of the lungs [2]. VAN NOORD *et al.* [59] studied the discriminative power of conventional lung function parameters and FOT in three groups of patients suffering from asthma, chronic bronchitis or emphysema with a similar reduction in FEV1. A discriminant analysis showed that the FOT parameters were among the best lung function indices in discriminating between the three groups; Rrs was highest in asthmatics and the frequency dependence of Rrs and decrease in Xrs were lowest in emphysema. In early emphysema, patients may present with normal values of Rrs and Xrs [60]. WESSELING and WOUTERS [61] found abnormal Zrs data in 70% of the subjects with chronic bronchitis in the presence of normal spirometry.

The negative frequency dependence of Rrs, which is characteristic of patients with bronchial obstruction, has also been observed in adult patients with upper airway obstruction but without any sign of intrapulmonary disease [62]. This finding can readily be explained by the shunt effect of the upper airway walls on the elevated distal impedance. Although the FOT may fail in distinguishing between intra and extrapulmonary obstruction, it may be very useful for the noninvasive diagnosis and follow-up of patients at risk for tracheostenosis [63]. In this recent study, FOT indices proved to be much more closely related to the tracheal dimensions than spirometric indices, thus suggesting that FOT is more sensitive in disclosing the upper airway stenosis.

Surprisingly, no distinctive patterns in Zrs have been observed in restrictive lung disorders: the changes in Zrs are similar to those of moderate obstructive lung disease. Greater negative frequency dependence and higher values of Rrs and decreases in Xrs were measured in patients with restrictive disorders,

such as fibrosing alveolitis [64] and kyphoscoliosis or ankylosing spondylitis [62]. Again, this observation can be explained on the basis of the upper airway shunt impedance, which may mask the differences between the alterations in pulmonary mechanics resulting from various respiratory disorders. Further studies employing the head generator technique are necessary to confirm this assumption. Obese subjects exhibit an increased R_{rs} resulting from a reduction in lung volume [65].

In conclusion, in patients with various diseases associated with pulmonary function abnormalities, an increase in R_{rs}, especially in the lower frequency range, and a decrease in X_{rs} with a concomitant increase in f_{res}, are observed. However, the standard FOT does not offer the distinction between the underlying restrictive and obstructive changes, or intra and extrapulmonary disorders.

Children. Stable asthma. Most FOT studies in well characterised paediatric asthma deal with children in a stable condition who undergo provocation tests (see below), and relatively few data are available regarding the assessment of baseline airway obstruction. In an early study by COGSWELL [37] 23 of 42 asthmatic children showed an R_{rs5} SD index >2. LEBECQUE and STANESCU [66] found that R_{rs10} provided information concordant with FEV1 in most asthmatic children. HOLMGREN *et al.* [67] observed a larger baseline R_{rs4} SD index in asthmatic children compared with healthy controls, in keeping with the FEV1 SD index. In a large population of children with various respiratory conditions, including chronic cough and asthma, R_{rs} was characterised by the extrapolated R_{rs0} value [57]. The SD index of R_{rs0} was significantly larger in children with abnormal FEV1 than in those with normal FEV1 and, within the latter population, significantly different between the children with normal and those with abnormal midexpiratory flow.

R_{rs} measured by the FOT in the lower range of the frequency spectrum is significantly different between healthy and asthmatic children, and it distinguishes between the asthmatics with and without abnormal spirometry. Further research is needed to establish a practical FOT index to define airway obstruction on a routine basis.

Acute asthma. A recent study evaluated the feasibility of FOT in an emergency department, assessing 150 children (age 2–17 yrs) [68]. One-quarter of the subjects (median age 3 yrs) were unable to breathe steadily *via* the measuring device. The success rate for achieving reproducible measurements increased from 0% (at age 2 yrs) to 83% (at age 5 yrs), respectively. Across all ages, the ability to cooperate with spirometry and its reproducibility was similarly poor. R_{rs8} % pred was found to correlate with clinical asthma severity [68]. A further emergency room study in preschoolchildren revealed how R_{rs8} related only marginally to asthma severity ratings, but showed that significant correlations between these two rating methods were present when assessing responses to treatment [69].

In acute asthma, FOT measurements may prove useful for objectively assessing bronchodilator responses and to a lesser extent in scoring asthma severity. Limitations of FOT in preschoolchildren include lack of cooperation, poor tolerance of the dead space of the test instrument, poor signal-to-noise ratios due the more rapid respiratory rate, and impaired discriminative power, due to the increased influence of the upper airway wall compliance. Methodological improvements in FOT may ameliorate some of these factors.

Cystic fibrosis. In children with cystic fibrosis (CF), Z_{rs} exhibits a generally poor relationship to the conventional spirometric indices [37, 66, 70, 71]. Specifically, FEV1 correlated poorly to R_{rs10} [66] and R_{rs6} [71], in sharp contrast to the good agreement observed in asthmatics [66]. As the relationship between spirometry and plethysmographic R_{aw} was similarly poor, this problem is unlikely to be unique to FOT. In CF patients who demonstrated paradoxical response to a bronchodilator, the decrease in FEV1 induced by salbutamol was not paralleled by an increase in R_{rs6} [71]. From this, salbutamol was postulated to relieve bronchoconstriction and increase airway wall compliance. Consequently, R_{rs} was decreased during tidal breathing but flow limitation during forced expiration was facilitated [71].

The discrepant information between FOT and spirometry in CF patients may reflect alterations in the elastic properties of the bronchial wall. Whatever the mechanisms, the routine assessment of lung function in these children should be interpreted with much caution, when either spirometry or FOT is available alone. Further comparative assessments are indicated to clarify the mechanisms of impairment in respiratory function in CF.

Chronic lung disease of prematurity. In a small population of children with a history of premature birth and chronic lung disease studied at a mean age of 6 yrs, the values of R_{rs6} were weakly related to the clinical history, whereas the frequency dependence of R_{rs} was a more sensitive index in discriminating between children with and without chronic lung disease [72]. At a mean age of 8 yrs, significant alterations in R_{rs5} and X_{rs5} were observed in subjects with chronic lung disease as compared with the healthy controls. Furthermore, X_{rs5} and f_{res} both differentiated between the presence and absence of chronic disease in premature infants [73]. In the same study, X_{rs5} and R_{rs5} also showed significant correlations with FEV1. A good agreement between R_{rs5} and plethysmographic R_{aw} was reported up to 1 $kPa \cdot s \cdot L^{-1}$, while the relationship plateaued at higher values of R_{aw} [73], possibly because of the increased impact of the upper airway artefact [23].

In conclusion, abnormal R_{rs} and X_{rs} may be found at school age in children with a history of premature birth and chronic lung disease. However, more studies are needed to characterise the changes in Z_{rs} during growth in these children.

Follow-up and field studies

In evaluating the development of pulmonary disease, the long-term monitoring of therapeutic efficiency and the staging of respiratory function decline during aging, FOT provides a convenient follow-up technique [74]. However, for longitudinal follow-up of chronic obstructive pulmonary disease (COPD) patients, changes in R_{rs} up to 26% may result from spontaneous variation in resistance [51].

Smoking. In an early study, use of FOT alone failed to clearly separate smokers from nonsmokers [28]. COE *et al.* [75] analysed R_{rs} and its frequency dependence in healthy never-smokers and in smokers. There was a strong trend for R_{rs} (especially at lower frequencies) and the frequency dependence of R_{rs} to elevate with increasing age in the smokers. Increases in R_{rs} and the frequency dependence of R_{rs} were usually present when spirometry indicated bronchial obstruction. The frequency dependence of R_{rs} proved even somewhat more sensitive than spirometry in the detection of mild airway disease.

The frequency dependence of R_{rs} and its change between air and helium (He)/oxygen (O_2) breathing were shown to be more sensitive than the results of spirometry in the detection of early airway abnormalities associated with smoking history and occupational exposure [76]. A study on the additional

effects of smoking habits on the activity of miners showed that, although FOT provided sensitive indices of the effect of occupational exposure on central airways, it did not detect the additional effect of smoking [77].

Epidemiological surveys and field studies. The information offered by FOT on respiratory impairment is in every way as significant as spirometry and FOT does not require active cooperation. Feasibility in various epidemiological surveys and field studies has been excellent [78]. Both the standard and head generator methods exhibit comparable potential to classify a variety of respiratory status measures amongst agricultural workers (smoking status, cough, expectoration and airway obstruction assessed by maximum expiratory flow/volume curve) [79].

FOT has proved as sensitive as spirometry in the detection of impairment in ventilatory function in workers exposed to occupational dangers [80, 81].

The performance of FOT in the assessment of bronchial hyperresponsiveness (BHR), as compared with spirometry was studied in 119 active workers with normal baseline pulmonary function [81]. When a 65% increase in R_{rs0} was used to classify the subjects according to the presence or absence of a 20% fall in FEV1, FOT reached a sensitivity of 75% and a specificity of 76%. Using a simplified FOT index, the two-point dose response slope of the change in R_{rs10}, BOHADANA *et al.* [82] established a sensitivity of 91% and a specificity of 96% in the accurate detection of "spirometric" BHR in various patients referred for BHR testing. This suggests that this simple index can be used for BHR testing in occupational epidemiology.

In sickle cell disease, an increase in R_{rs} is correlated with the number of acute chest syndrome episodes, which demonstrates that obstructive lung dysfunction is fairly common in this type of disease [83].

In a survey of respiratory health involving >1,500 children aged 6–12 yrs, measurements of Z_{rs} failed to differentiate symptom-free children from those with a history of chronic cough or asthma-like symptoms in the previous year [35]. This was thought to reflect either the poor diagnostic value of the technique or the lack of functional abnormality associated with such a history of respiratory symptoms.

In conclusion FOT has proven to be at least as sensitive as spirometry to detect impairment of lung function due to exposure to cigarette smoke or occupational hazards. The sensitivity to detect mild airway disease and the minimal requirements for subject's cooperation make FOT a very suitable lung function test for epidemiological and field studies.

Identification of airway reactivity

The interpretation of changes in a lung function parameter measured in response to bronchomotor agents must rely on an estimate of the variability of that parameter. For instance, a response larger than twice the average baseline CV is usually considered positive. The magnitude of the change induced by bronchodilating or bronchoconstricting agents can also be expressed as the difference between postbronchodilator (or challenge) R_{rs} and R_{rs} at baseline divided by the (average intrasubject) SD of the baseline measurements. This ratio will be referred to as the SD score.

Reversibility

Adults. The first reports on the changes in Z_{rs} in response to bronchodilation in COPD patients were based on measurements made in a very limited number of patients [18, 84]. Overall, R_{rs} decreases after bronchodilation, especially at low frequencies. This reduces the negative frequency dependence of R_{rs}, and, by increasing X_{rs}, f_{res} returns towards lower and more normal values. Studying Z_{rs} changes in COPD patients, WOUTERS *et al.* [85] noted that only X_{rs} data showed significant changes, whereas low-frequency data suffered from poor coherence. In a large group of patients with airway obstruction (presumably mainly COPD patients), VAN NOORD *et al.* [52] observed significant postdilator falls in R_{rs}, with a significant correlation between FEV1 and R_{rs6}. In this study, a threshold value for significant bronchodilation was defined from the within-subject variability of the different lung function indices, a decrease of >45% in R_{rs6} from baseline value. Here, FOT indices were markedly less sensitive than body plethysmographic or spirometric indices for detecting significant bronchodilation. By contrast, ZERAH *et al.* [33], who studied the reversibility of airway obstruction in two small yet well-defined groups of patients with asthma and COPD, came to precisely the opposite conclusion. Employing a threshold value of 10% predicted for both indices, the changes in FEV1 and G_{rs0} after bronchodilator inhalation were compared. FEV1 and G_{rs0} both exhibited comparable changes with a similar sensitivity and specificity to differentiate asthmatics from COPD patients. These authors concluded that FOT can be used as an alternative, equivalent technique to forced expiration to assess the degree of bronchodilation.

It is obvious that the correlation between the changes in FEV1 and those in Z_{rs} indices strengthens with increasing response to bronchodilation. Therefore, the correlation between spirometry and Z_{rs} is dependent on the population studied (asthmatics *versus* COPD patients).

To summarise, there is no consensus regarding the sensitivity of Z_{rs} measurement compared with that of spirometry and the correlation between their indices in bronchodilation testing. Further research in larger, well-defined groups is needed to establish whether FOT and spirometry are equivalent or complementary lung function techniques in the assessment of reversibility of airway obstruction.

Children. Indirect evidence of airway obstruction associated with asthma may be provided by a positive response to a bronchodilator. In a large population of children with chronic respiratory symptoms, the best cut-off value to establish significant reversibility in response to salbutamol with reference to an increase in FEV1 $\geq$ 10% pred was a decrease in R_{rs0} of $\geq$ -1 SD score, or equivalently a 27.8% decrease in R_{rs0} [57]. This cut-off value was associated with a sensitivity and specificity of 69% and 78%, respectively. In addition, in children unable to perform forced expiration manoeuvres, the cut-off value identified a subgroup of patients whose high baseline R_{rs0} normalised after bronchodilator inhalation [57]. In a study of asthmatic children, inhalation of salbutamol induced a decrease in R_{rs10} from 155–99% pred, which corresponded to an increase in FEV1 from 65–85% pred [66]. In children treated for acute asthma in a paediatric emergency department, the decrease in R_{rs8} after salbutamol was found to correlate with the reduction of signs of respiratory distress and the improvement in FEV1. In those children unable to perform spirometric manoeuvres, the reduction in R_{rs8} after salbutamol was also associated with a clinical response, and the optimal change in R_{rs8} to assess reversibility was 19% [86]. Below aged 7 yrs, considerable overlap exists in bronchodilator response between healthy and asthmatic children. An average decrease of 12% in R_{rs5} was observed in the healthy children; to exceed the 95% confidence interval for bronchodilator response in healthy children, a cut-off value of a 41% decrease in R_{rs5} should be used to support the diagnosis of asthma in reversibility testing [44]. In young children, FOT has been

shown to provide a useful and objective method to assess airway responses to bronchodilator drugs, such as metaproterenol, ipratropium bromide or salbutamol *versus* placebo [87–90], and to characterise dose/response curves [88, 91]. For example, the bronchodilating effect of nebulised oxitropium bromide (750 and 1500 μg) in preschool asthmatic children was shown to last for up to 4 h postinhalation, whereas no additive bronchodilation by fenoterol could be shown [92] .

When defining reversibility of airway obstruction, the FOT criterion should take into account the "normal" physiological response to inhaled β_2 agonist. This has been reported to be a 12% decrease from the baseline value for Rrs in young children. Using comparison with spirometry, the optimum definition of significant bronchodilation has been defined as a decrease in Rrs of $\geqslant 1$ SD score. However, more research is needed in well-defined and different age groups of children to confirm that this cut-off level is appropriate.

Bronchial hyperresponsiveness

The degree of airway responsiveness is commonly assessed with a bronchial challenge test where His, or Mch, is administered in increasing doses until either a bronchoconstriction is observed or a preset maximum concentration has been reached. Clinical methodology for BHR testing has been standardised and the result of the test is expressed as the provocative dose (PD) or concentration (PC), which induces a predetermined deterioration of lung function, usually defined as a decrease in FEV1 of 20% of the baseline value, noted as the PD20FEV1 or PC20FEV1 [93, 94]. In terms of FOT parameters, the dose of the bronchoconstrictor agent that produces a 50% increase in Rrs, or equivalently a 33% decrease in Grs, will be noted as PD50Rrs or PD33Grs.

Adults. A significant correlation between the changes in Rrs and FEV1 following bronchoconstriction has been reported by several investigators [50, 81, 95–97]. SNASHALL *et al.* [50] compared FEV1 to the modulus of Zrs at 10 Hz ($|Z$rs10$|$) in the assessment of BHR in 24 asthmatic patients; the increase in $|Z$rs10$|$ after challenge was on average 2.7 times as much as the decrease in FEV1. Based on the average within-subject CV, they argued that PC30$|Z$rs10$|$ was equivalent to PC20FEV1. In all but one patient, PC20FEV1 was larger than PC30$|Z$rs10$|$, and in six patients PC20FEV1 was more than two doubling doses of PC30$|Z$rs10$|$. In another study, PC20FEV1 was compared with PC40Rrs8 when analysing the response to His and Mch challenge in 23 stable asthmatics [97]. For both agents, PC40Rrs8 was about three times lower than PC20FEV1. Using the same argument on the average within-subject CV, BOHADANA *et al.* [82] compared PD47Rrs10 (and PD47Rrsmean) to PD20FEV1 in assessing BHR to carbachol challenge. However, by using this cut-off value, far more patients were classified as positive responders than based on FEV1 (for Rrsmean and Rrs10, 58 and 52 positive responders of the 71 tested patients, respectively, compared to the 23 positive responders for FEV1). In volunteers subjected to His challenge, NEILD *et al.* [48] showed that PD35Rrs10 was comparable to PD10FEV1, and, consequently, lower than PD20FEV1. The repeatability of PD35Rrs10 was slightly lower than that of PD10FEV1. VAN NOORD *et al.* [98] compared PD15FEV1, PD47Grs6 and PD40sGaw in analysing the response to His challenge in 53 subjects with a history of episodic wheezing. The parameters with the best sensitivity to detect the effect of His were, in decreasing order, sGaw, Grs6 and FEV1; their results also suggested that the sensitivity of Grs6 was larger than that of FEV1 in subjects with a more pronounced bronchial hyperreactivity. FOT was also compared with spirometry in the assessment of BHR in an active working population [81]; the best cut-off point was an increase of 65% in Rrs0, which reached a sensitivity of 75% and a specificity of 76% with PD20FEV1 as the gold standard for classification of the subjects. SCHMEKEL and SMITH [99] used inhalation of cold air as a bronchial challenge test in both asthmatics and healthy controls. Their results indicated that FOT was more able to discriminate between the two groups than spirometry, when using the clinical diagnosis as the gold standard. $f$res had the highest specificity (100%) and sensitivity (89%), and even Rrs5 had a higher diagnostic capacity than FEV1 (specificity and sensitivity of 89% and 88%, and 88% and 73% for Rrs5 and FEV1, respectively). CHINET *et al.* [100] compared FOT (Grs0) with sGaw in providing information on bronchial sensitivity. They found a close relationship between Grs0 and sGaw in terms of threshold dose and the slope of the dose/response curves in normal and hyperresponsive subjects, with equivalence between PD50sGaw and PD42Grs0.

The deep inspiration that precedes forced expiration may modify airway smooth muscle tone, and, therefore, may influence the result of the BHR test. FOT has the considerable advantage that it measures airway properties during quiet breathing. This may be the reason why FOT has proved more sensitive than FEV1 to detect changes in BHR in asthmatics after corticosteroid treatment [101].

FOT has been used to study the site of airway obstruction during induced bronchoconstriction in normal subjects [102, 103] and in asthmatics [104], to evaluate the response to inhaled allergen in asthmatics [96], to examine the effect of posture [105] and hypoxia on BHR [106] and to investigate the ventilatory pattern after induced bronchoconstriction in asthmatics and normal subjects [107].

In conclusion, the values of Rrs (or Grs) at low frequency have been shown to be reliable and sensitive indices to assess the bronchial response in clinical BHR testing. There is evidence that FOT and plethysmography provide comparable information on bronchial sensitivity and responsiveness and may be superior to spirometry. It is not yet clear which cut-off value for Rrs corresponds best to the 20% decrease in FEV1. Threshold values up to the 47% increase in Rrs have been associated with lower PD, or a higher number of positive responders than in the case of PD20FEV1; other studies estimate this threshold value between 65–90% increase in Rrs.

Children. The Mch or His dose/response curves have usually been characterised by the values of PD40Rrs or PD50Rrs. Most of the meaningful FOT data have been obtained at low frequency. A better sensitivity to detect a bronchial reaction to allergen challenge was reported for Rrs4 (determined using sinusoidal excitation) than for FEV1 in asthmatic schoolchildren aged 6–14 yrs [53]. Significant linear relationships between changes in FEV1 and Rrs indices were observed by DUIVERMAN *et al.* [108] and LEBECQUE *et al.* [109] during Mch and His provocation, respectively. In 20 asthmatic children aged 9–16 yrs, the PD40Rrs6 was found to correlate well with PD20FEV1 [108]. A close relationship was found between the effect of His and of Mch in asthmatic children, aged 3–7 yrs, as determined with FOT [110]. The sensitivity of Zrs values to carbachol challenge in children aged 5–16 yrs was found equivalent to that of specific airway resistance (sRaw) [55]. In a population of asthmatics aged 8–15 yrs, the response to His was similarly estimated by transcutaneously determined PO_2 ($PtcO_2$) and Rrs4, and PD50Rrs4 was inversely correlated to the clinical severity of asthma [67]. By contrast, in a detailed study in children aged 5 yrs, comparing the Mch-induced changes in Zrs,in and $PtcO_2$, a low diagnostic power for Rrs6 and Rrs8 was observed [111]. FOT has been evaluated in young asthmatics for the detection of the response to Mch in comparison with

$PtcO_2$, sRaw and the Rrs measured by the interrupter technique (Rrs,int). The sensitivity was lower for Xrs5 than for sRaw, but larger than for $PtcO_2$, Rrs$_5$ or Rrs,int in the children aged 2–4 yrs [112]. In the asthmatics aged 4–6 yrs, a better sensitivity in detecting the Mch response was observed for Rrs5 and Xrs5 than for sRaw, $PtcO_2$, Rrs,int and FEV1, whereas the higher-frequency values of Rrs and Xrs were apparently not associated with a good diagnostic score [113].

In the pattern of impedance change after provocation, the increase in Rrs was accompanied by a decrease in Xrs in most of the studies. Since the apparent elastic properties of the respiratory system as reflected by Xrs at lower frequencies [112, 114], appear as a sensitive measure in the provocation tests, the variations of the Xrs values should be documented.

FOT measurements have shown to reliably reflect the changes in lung function during bronchial challenge in children, with sensitivity comparable to that of bodyplethysmography and spirometry. PD50Rrs is closely related to PD20FEV1. There are indications that Xrs may be more sensitive than Rrs to detect the response to bronchial challenge, especially in the very young child, but more research is needed to establish the place of Xrs in the evaluation of BHR. Additionally, it is recommended that measurement of Zrs is associated with the careful clinical evaluation, which includes monitoring of transcutaneous sO_2 during bronchial challenge. These aspects are important because of the lack of criteria to define airway obstruction in the baseline condition, especially in the young child.

Forced oscillation technique in infancy

Like other pulmonary function tests in this age group, poor cooperation means that Zrs must be measured during sedation and that testing can be lengthy and technically extremely demanding. For this reason, collection of normal Zrs data in infants has been hampered, as have routine applications of FOT in this subject group.

Standardisation of the measurement conditions for lung function testing is a crucial issue for the infant's safety and the accuracy of the test. Recommendations have been developed by an American Thoracic Society/European Respiratory Society Working Party [115] and the specific preparation measures for the FOT and details of the methodology have been described by DESAGER *et al.* [116]. The large values of Zrs in infants impose particularly strict performance requirements concerning the measurement set-up and the calibration procedure [117–119].

Most studies in infants deal with validation of the technique. The measurements of Zrs have shown to be reproducible with an average difference in Rrs from measurements made 15 min apart of 0.5±5.7% [118], and a reasonably good correlation has been reported between the results of FOT and those of the single-breath occlusion method [120]. The impact of the upper airway wall shunt [121, 122] and the nasal breathing [123] on Zrs has been evaluated. The nasal Z was shown to correlate with the clinical observation of nasal obstruction [123]. The feasibility of the FOT during artificial ventilation has been demonstrated in infants with bronchiolitis [124] and FOT has proved to be helpful in titrating optimal positive end-expiratory pressure [125]. In a prospective cohort study, low values of Grs6 measured during the neonatal period were reported to represent a significant risk factor for the occurrence of wheezing later in infancy [126]. FOT combined with FRC measurements detected lung function abnormalities in a minority of wheezing infants during a symptom-free interval [127]. Supporting previously clinical observations, the characteristic bronchodilator effects of nebulised salbutamol, phenylefrine, fenoterol and ipratropium bromide were confirmed using FOT [128]. No clinical or bronchodilating effect of furosemide was observed in intermittently infant wheezers [129]. Recently, methodological and clinical feasibility studies have employed special low and high-frequency test signals and these are addressed in the next section.

New developments

Applications of forced oscillation technique in monitoring respiratory mechanics

The FOT has recently been applied to follow the changes in respiratory mechanics during conventional mechanical ventilation (CMV), respiratory manoeuvres and sleep studies. Monitoring of Zrs may be a useful complementary tool in the adaptation of ventilator settings during invasive and non-invasive ventilation [130–135]. The FOT has also been used to improve the diagnosis of sleep disturbances [136] and to determine the optimal continuous positive airway pressure (CPAP) level required to treat obstructive sleep apnoea [137–140]. In sleep studies, changes of Zrs along the breathing cycle are followed, since obstructive sleep apnoeas/hypopnoeas are characterised by marked changes within the breathing cycle [138]. Separate analysis of inspiratory and expiratory impedance has also been suggested in the monitoring of the mechanically ventilated patients [130]. Single-frequency FOT has recently been proved an ideal tool to track Rrs or pulmonary resistance during a respiratory manoeuvre including a deep inhalation [141, 142], since it offers a good temporal resolution and the small amplitude oscillations do not interfere with the mechanical changes evoked by the manoeuvre.

The application of FOT in patients subjected to positive pressure requires a modification of the conventional FOT system based on a loudspeaker. Different approaches have been proposed to apply forced oscillations at elevated airway pressure [130, 133, 138, 143–145]. If the oscillations are applied through a nasal/face mask or ETT, further technical problems need to be taken into consideration. First, imperfect sealing around the mask or the ETT can cause air leaks, so providing a shunt pathway that leads to a misestimation of Zrs. Secondly, when using a full face mask in which the patient can breathe freely through the nose or the mouth, the actual route of breathing must be known, since the nasal impedance constitutes a significant fraction of Zrs [133]. Thirdly, for intubated patients, the high impedance and non-linear behaviour of the ETT pose a further problem, which can be circumvented by measuring the tracheal pressure [146]. An alternative approach is to correct the Zrs values for the effective impedance of the ETT [130] estimated *in vitro* using similar flow conditions to those of *in vivo* measurements.

Low-frequency oscillations

If the oscillatory signal is superimposed on spontaneous breathing, oscillation frequencies higher than 2–4 Hz must be used. However, the characteristic rheology of the respiratory tissues below 2 Hz can be revealed by investigation during voluntary apnoea, as has been shown using a modified set-up in normal subjects between 0.25–5 Hz [147] and in anaesthetised and paralysed patients from 0.25–32 Hz [146] or to 26 Hz [143]. The advantages of the low-frequency range are that the markedly different frequency dependences of the airway and tissue impedance allow the model-based separate estimation of their parameters [148], and that these parameters are more relevant to the mechanical properties manifested

during spontaneous breathing than those estimated with higher-frequency oscillations. Although the requirement of apnoea limits the applicability of the low-frequency FOT, there are special conditions where its advantages can be exploited. First of all, measurements during suspension of mechanical ventilation in anaesthetised and paralysed subjects for short intervals of oscillation [143, 146] allow the monitoring of the airway and tissue mechanics far more specifically than that offered by commercial respiratory monitors [135].

Another target population of the low-frequency FOT is infants, whose lack of cooperation permits lung function testing only in the sedated state. Here, activation of the end-inspiratory Hering-Breuer reflex can be used to evoke the apnoea needed for low-frequency FOT measurements [149]. The post-hyperventilation apnoea permits oscillatory measurements at lower transrespiratory pressures [150]. Further studies with this technique included the establishment of normal values of the mechanical parameters for this age group [151], the evaluation of bronchodilator [152] and bronchoconstrictor provocation tests [153], addressed the alterations in the mechanical properties in wheeze [154] and the contribution of the nasal pathways to Zrs [155].

A special version of the low-frequency FOT uses an optimal ventilatory waveform (OVW) to drive the respiratory system, the combination of mechanical ventilation and impedance estimation [144]. The OVW has been used in studies on the pulmonary and chest wall mechanics in normal subjects before and after bronchoconstriction [156], the broncholytic responses in asthmatics [157] and the inspiratory impedance in flow-limited patients [158].

The technical requirements imposed by the application of FOT during CMV or CPAP, which were addressed briefly above, pertain to all applications of the low-frequency FOT. Most importantly, any leak around the airway opening should be eliminated; a shunt that may not affect Zrs at the medium frequency range would substantially distort the low-frequency values.

High-frequency oscillations

Similarly to the inclusion of low-frequency components, the elevation of oscillation frequencies above ~100 Hz reveals new patterns of frequency dependence of Zrs, with the potential of estimating additional mechanical parameters [159–163]. In particular, at frequencies well above $f$res, Xrs crosses zero in the negative direction: this is called the first antiresonant frequency ($f$ar,1). Healthy subjects and patients with airway obstruction have been differentiated on the basis of both $f$res and $f$ar,1, and the forced spirometry indices have been shown to correlate better with $f$ar,1 than with the medium-frequency oscillation parameters [163]. The high-frequency Zrs is dominated by wave propagation processes in the airway tree and much less affected by tissue properties. Although the model-based analysis of these phenomena remains far from complete [159], current work suggests that $f$ar,1 carries information about airway wall compliance, which may be an important descriptor in the understanding of airway instability occurring in wheezing disorders in infancy [162].

Although the low-frequency and high-frequency oscillations reveal different mechanical characteristics of the respiratory system and, hence, require different modelling approaches, combined studies involving both oscillation ranges in the same subjects would certainly be useful, particularly in facilitating the interpretation of the medium-frequency Zrs data.

Finally, it should be noted that these new applications of FOT have been developed at research level by few laboratories and, therefore, the technical experience gained and the amount of data obtained are still limited.

Conclusions

Overall, the clinical diagnostic capacity of respiratory impedance measurement by forced oscillation technique is comparable to that of spirometry. With respect to the latter, the main weakness of respiratory impedance determination is that it does not enable the distinction between obstructive and restrictive lung disorders. The main advantages of the forced oscillation technique are that minimal cooperation of the patient and no respiratory manoeuvres are needed; therefore, the measurement of respiratory impedance should be considered whenever spirometry cannot be performed or appears to be unreliable. These qualities of the forced oscillation technique make it an ideal tool to study airway patency during sleep or to monitor the respiratory properties during mechanical ventilation. Additionally, the small amplitude oscillations do not influence the respiratory mechanical properties studied, and this is particularly important when assessing bronchoactive responses. The high time resolution that can be obtained when a single frequency is used makes forced oscillation technique the method of choice to study variations in mechanical properties within the respiratory cycle or temporal changes, such as those induced by a deep inhalation.

Chair and coordinator of the committee: E. Oostveen (University Hospital Antwerp, Belgium).

Appendix A: Glossary of symbols and abbreviations for impedance measurements

Abbreviation	Description	Unit
ao	Airway opening	
aw	Airway	
bs	Body surface	
es	Oesophageal	
f	Frequency	Hz
$f$res	Resonant frequency	Hz
FRC	Function residual capacity	L
G	Conductance (1/R)	L·kPa^{-1}·s^{-1}
Gaw	Airway conductance (1/Raw)	L·kPa^{-1}·s^{-1}
Grs	Total respiratory conductance (1/Rrs)	L·kPa^{-1}·s^{-1}
sGaw	Specific airway conductance (=Gaw/FRC)	kPa^{-1}·s^{-1}
in	Input	
L	Pulmonary system	
P	Pressure	kPa
R	Real part of Z or resistance	kPa·s·L^{-1}
rs	Respiratory system	
Raw	Airway resistance measured by body plethysmography	kPa·s·L^{-1}
sRaw	Specific airway resistance (1/sGaw)	kPa·s
Rrs$f$	Total respiratory resistance measured at frequency f	
ti	Tissue	
tr	Transfer	
V'	Airflow	L·s^{-1}
w	Chest wall	
X	Imaginary part of Z or reactance	kPa·s·L^{-1}
Z	Impedance	kPa·s·L^{-1}

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