CHAPTER 5

Forced oscillation technique and impulse oscillometry

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Conventional methods of lung function testing provide measurements obtained during specific respiratory actions of the subject. In contrast, the forced oscillation technique (FOT) determines breathing mechanics by superimposing small external pressure signals on the spontaneous breathing of the subject [1]. FOT is indicated as a diagnostic method to obtain reliable differentiated tidal breathing analysis. Because FOT is performed without closure of a valve connected to the mouthpiece, and without maximal or forced respiratory manoeuvres, it is unlikely that FOT itself will alter airways smooth muscle tone [2].

FOT utilises the external applied pressure signals and their resultant flows to determine lung mechanical parameters. These pressure–flow relationships are largely distinct from the natural pattern of individual respiratory flows, so that measured FOT results are, for the most part, independent of the underlying respiratory pattern. Therefore, oscillometry minimises demands on the patient and requires only passive cooperation of the subject: maintenance of an airtight seal of the lips around a mouthpiece and breathing normally through the measuring system with a nose-clip occluding the nares. Potential applications of oscillometry include paediatric, adult and geriatric populations, comprising diagnostic clinical testing, monitoring of therapeutic regimens, and epidemiological evaluations, independent of severity of lung disease. Oscillometry is also applicable to veterinary medicine.

The last two main sections Relevance of oscillometry in clinical practice and Oscillometry in the clinical pulmonary laboratory emphasise clinical aspects of application and interpretation of FOT rather than methodological details and technological solutions, which are discussed in the two sections that follow immediately below. Clinical application of FOT does not require mastery of the mathematical infrastructure of the technical methodology, and readers interested in the clinical use of FOT may find it more useful to begin with these clinical sections and refer subsequently to methodological and technological details.

Methodology of impulse oscillation technique

The mechanical basis of oscillometry concerns use of external forcing signals, which may be mono- or multifrequency, and applied either continuously or in a time-discrete manner. The impulse oscillation technique is characterised by use of an impulse-shaped, time-discrete external forcing signal.
The most useful aspect of applying FOT pressure pulses rather than pseudo-random noise (PRN) is improved time resolution of the measurement. The impulse oscillation technique allows measurement of up to 10 impedance spectra per second. This permits a useful analysis of intra-breath variation in impedance, comparable to that obtained with mono-frequency applications. However, a disadvantage of such high impulse rates is the inability to record longer respiratory time constants that may be more informative concerning respiratory abnormalities. For this reason, the common application of impulse oscillation utilises recordings of 5 impedance spectra (5 impulses) per second.

An additional benefit of impulse oscillation is the simplicity of the hardware needed to generate the forced signals, allowing smaller, more efficient electronic and mechanical structures with minimal power loss.

A unique aspect of applying pulses of pressure to the respiratory system is the fact that the entire energy of all applied pressure harmonics is applied within a very short time period. This causes a higher impact to the respiratory system compared with sinusoidal or PRN applied pressures, and may be perceived by some patients as a slightly unpleasant respiratory sensation during measurement.

**Peculiarities of aperiodic waveforms**

The impulse oscillation method applies aperiodic waveforms using an impulse generator that produces pressure pulses of limited magnitude and 30–40 ms duration. These pulses define specific amplitudes and phases of the inherent sinusoidal components. The time-course of such practical pressure pulses applied to the respiratory system is not a true Dirac-impulse, defined as having virtually infinite magnitude and infinitesimal time duration, which would provide a continuous spectrum of frequencies with the same amplitude. Thus, the terms "impulse-shaped" oscillations and "impulse pressures" are used to indicate realistic practical pressure pulses rather than mathematically defined impulses.

The short duration of the impulse-shaped waveform itself provides linearity of pressure and flow signals in the face of within-breath dynamic changes in the respiratory system. In contrast, the longer time needed with PRN to embed a range of periodic functions decreases time resolution, resulting in increased noise of calculated impedance related to any time-dependence of dynamic changes in the respiratory system.

The characteristic feature of any aperiodic waveform is the resulting continuous spectrum after transformation of its time course into the frequency domain, using a Fourier integral rather than a Fourier series, in the fast Fourier transform (FFT).

Thus, the advantage of continuous spectra is particularly important in abnormal respiratory systems with regional nonhomogeneities (fig. 1), where resistance, reactance and coherence spectra may manifest deviations from the normally smooth and uniformly continuous spectral courses.

In contrast, spectra resulting from FFT analyses of periodic multifrequency forcing such as PRN [3] are discontinuous. Discrete values of impedance are obtained with a frequency resolution determined by the frequencies of the included sinusoidal components. As a result, the course of such discrete spectra often may require post-processing to smooth the PRN spectra [3]. To improve interpretation of discrete PRN spectra, it is common to approximate the overall spectral range by smoothing with linear, quadratic or logarithmic functions. However, such smoothing inherently diminishes information contained in characteristic peaks and plateaus of impedance that may otherwise provide insight into superimposed parallel resonance phenomena, e.g. related to upper airway constriction.

Impulse power spectra of pressure and flow generated by the impulse oscillometry
system (IOS) are shown in figure 2 over a frequency range of 0.1–35 Hz. The energy distribution provides practical assessment of low (≤5 Hz), as well as high (>20 Hz) frequency ranges, with decreased amplitude at higher frequencies to minimise non-linearities due to acceleration of the moving air column [4]. Enhanced amplitudes at the

![Graph of respiratory resistance, reactance, and coherence](image)

**Fig. 1.** – Representative data for spectra of respiratory resistance ($R_{rs}(f)$; --), reactance ($X_{rs}(f)$; - - -) and coherence ($\gamma^2(f)$; - - - - -) are plotted, between 3 and 35 Hz, for a normal adult, during forced oscillation using pulse-shaped forcing generated by the impulse oscillometry system. Resonant frequency ($f_{res}$) is shown where the $X_{rs}(f)$ tracing crosses zero. The shaded area, below zero $X_{rs}$ and above $X_{rs}(f)$ tracing between 5 Hz and $f_{res}$, is the integral of $X_{rs}(f)$ from 5 Hz to $f_{res}$, and is designated the reactance area ($AX$). Regional nonhomogeneities may manifest deviations from the normally smooth and uniformly continuous spectral courses.

![Graph of power spectra of flow and pressure](image)

**Fig. 2.** – Power spectra of flow (—), and pressure (----), for the discrete pulse-shaped forcing signal generated by the impulse oscillometry system. Spectra plotted at frequencies 0.1–35 Hz. Pressure and flow power are highest at 3–20 Hz. Less power is needed at frequencies >20 Hz, because "competing" higher harmonics of the patient’s respiratory flow are very small at these frequencies.
lower frequencies limit the influence of higher harmonics of spontaneous breathing frequencies.

**Impulse oscillometry system**

The IOS measuring-head (fig. 3) is functionally similar to PRN systems designed for the determination of input impedance [1, 5–12]. The characteristic feature of the IOS [13] is the generation of recurrent aperiodic impulse-shaped forcing signals of alternating direction.

Flow is measured by a Lilly-type heated screen pneumotachograph with a resistance of 36 Pa·s·L⁻¹, providing a common-mode rejection ratio of >60 dB up to 50 Hz [12, 14, 15] for the combination of pneumotachograph and flow transducer system. At flow rates <15 L·s⁻¹ the heated pneumotachograph is linear within 2%. The proximal side of the pneumotachograph is connected to a pressure transducer. To guarantee suppression of technical influences and to avoid phase differences, both pressure and flow channels use matched transducers of the same type, SensorTechnics SLP 004D [16]. Pressure and flow signals are sampled at a frequency of 200 Hz and digitally converted by a 12-bit analogue-to-digital converter. Analogue anti-aliasing low-pass filtering is realised by a fourth-order Bessel filter at a border frequency of 50 Hz, providing a damping at Nyquist frequency of ~75 dB.

Tuning of the IOS impulse generator involves both volume displacement of the loudspeaker membrane and magnitude of the terminating resistor. The terminal resistor

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**Fig. 3.** – Schematic diagram of the impulse oscillometry system measuring-head and connectors: loudspeaker enclosure at top, connected to a y-adaptor at one upper arm, an exit for flow with terminal resistor at the second upper arm and a lower arm connected to the pneumotachograph. A mouthpiece is connected to the open side of the pneumotachograph. Pulsatile flows generated by the loudspeaker are shown as a lightly shaded thick line, part of which exits through the terminal resistor and part of which flows through the pneumotachograph and mouthpiece. The patient’s normal respiratory flow is shown as a shaded thick line from the mouthpiece though the Y-connector, exiting through the terminal resistor. The resistance of the terminal resistor is 0.1 kPa·s·L⁻¹ and the deadspace of the Y-connector/pneumotachograph/mouthpiece is ~70 mL.
provides a low-impedance pathway for normal respiratory flow, which, at the same time, is high enough to minimise loss of energy of superimposed impulses so that sufficient impulse pressure is transmitted into the respiratory tract. Both components determine the linear working range of the unit and range of input impedances, which can be measured to maintain international recommendations [16, 17]. A terminal resistor of $\sim 0.1 \text{ Pa}\cdot\text{s}\cdot\text{L}^{-1}$, in combination with a volume displacement of 40 mL, which is accelerated by the loudspeaker membrane in $<40$ ms, results in maximal peak-to-peak impulse pressures of 0.3 kPa and minimises interference of underlying higher harmonics of respiratory frequency that contribute "noise" to the oscillatory pressure and flow signal [10].

International recommendations for electromechanical performance are maintained in the IOS by use of advanced transducer technology and global mean spectral data derived from IOS are generally comparable to those obtained by the pseudo-random noise method of Ländser [6], Delecourt et al. [8] and Skloot et al. [18].

The measurement is performed as follows: while the subject spontaneously breathes ambient air via the tubing between mouthpiece and terminating resistor, the loudspeaker generator transmits brief pressure impulses via Y-adapter, pneumotachograph and mouthpiece into the respiratory tract; pneumotachograph and pressure transducer register the composite signals containing breathing activities and the forcing impulse signal for further processing.

Further processing of digitised impulse data. Flow and pressure channels contain both the underlying respiratory system flow and pressure, and the superimposed forced oscillation signals. By definition, respiratory input impedance is the transfer function or ratio of effective pressure ($P_{rs}$) and flow ($V_{rs}$), derived from the superimposed forced oscillations, after being discriminated from underlying respiratory pressure and flow and their harmonics. In the mathematical sense, all components are considered "complex", characterised by modulus and phase.

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\text{Multifrequency input impedance } \quad Z_{rs}(f) = \frac{P_{rs}(f)}{V_{rs}(f)} \quad \{0 < f \leq f_{\text{max}}\}
\]

Discrimination of superimposed forced oscillations from the underlying respiratory pressure and flow in the IOS is focused on individual impulses, based on pressure and flow sampling intervals that include both the impulse stimulus and the respiratory system reaction to the impulse. Figure 4a gives an example of such a sampling interval for flow.

A "baseline" straight line segment is inserted between the start- and end-points of separate sample segments of both pressure and flow. The baseline is a simple linear approximation of the underlying respiratory flow and pressure throughout the single impulse excitation. Baseline approximation has proved to be a useful and reliable technique to decrease the respiratory component of the composite signals for pressure and flow. Spline reconstruction, sinusoidal approximation of underlying respiratory pressure and flow or high-pass digital filtering were not as useful. Baseline correction and offset elimination, as can be seen in figure 4b, allow rectangular windowing prior to the FFT to effectively reduce spectral leakage and improve the signal-to-noise ratio.

Resolution of calculated pressure and flow spectra is increased by adding numerical zero values to the real sampling points of the corrected primary data segment. This procedure allows formation of exactly $2^n$ samples, compatible with FFT requirements. Choice of sampling interval as well as addition of zero values to this interval allow
adjustment of spectra concerning low-end border frequency as well as numerical resolution.

To further improve quality of calculated impedance data, impulses that do not fulfill defined reliability criteria are rejected. The critical segments of respiration are the phase transitions between inspiration and expiration. At these zero-crossings of pressure and flow, gradients of pressure and flow versus time are maximal, and the following principles are implemented to establish reliability. Slopes of baseline corrections for pressure or flow indicate dominance of the underlying respiratory pressure–flow pattern, and the
Impulse is rejected because separation of the superimposed impulse pressure and flow is not reliable. Absolute peak flow within the impulse segment must exceed 0.02 L·s⁻¹. Pulses with less flow are rejected because of very small flow values in the denominator of the input impedance Equation (1) [19] and the resulting mathematical errors. Finally, impulses that yield negative resistance values at any frequency after FFT are rejected.

**Impulse rate and sampling interval.** Impulse rate and selected sampling interval effects on calculated impedance have been evaluated in vitro as well as in calves of comparable size to adult humans [20, 21]. No significant effect of impulse rate was observed between 1 and 5 impulses per second.

In contrast, different sampling durations led to significantly different low-frequency respiratory system reactance ($X_{rs}$) results. Using 16 sampling points (80 ms) for data analysis, no useful information was obtained for $X_{rs} \leq 5$ Hz. Use of 32 sampling points (160 ms) per impulse for data analysis provided useful $X_{rs}$ data. However, sampling durations of 320 ms did not improve impedance results and coherence $\gamma^2 \leq 5$ Hz was significantly decreased, consistent with deterioration of calculated impedance quality due to interactions with spontaneous breathing signals. These findings underlie the current recommendation to use sampling intervals of 32 sampling points per impulse, corresponding to an optimised impulse rate of either 3 or 5 impulses per second.

**Coherence.** The coherence function is defined as the square of the cross-power spectrum divided by the product of the auto-spectra of pressure and flow at any forcing frequency. Ranging between 0 and 1, it is a measure of the available linearity [22].

$$\gamma^2(f) = \frac{|G_{yp}(f)|^2}{G_{yp}(f)G_{pp}(f)} \quad \{0 < f \leq f_{\max}\}$$

LÅNDSÉR et al. [6] found that when the coherence $\gamma^2 \geq 0.95$, PRN impedance data show a coefficient of variation CV% <10%. Subsequently, coherence value thresholds of 0.9 or 0.95 have been widely used to accept FOT data. However, if methods other than PRN forcing input signals or data acquisition are used, this original threshold value of coherence is not applicable. MILLER and PIMMEL [23] showed that estimated variance of calculated impedance is a function of coherence and the number of estimates averaged. Use of pseudo-random noise techniques commonly includes three measures of impedance of 16 s each [5]. Three replicate measures require coherence $\gamma^2 >0.9$ to yield an estimated standard error of 10%. In contrast, IOS commonly includes the average of >100 separate FFT analyses and, accordingly, requires less perfect coherence for the average data to provide an estimated standard error of <10%. For clinical purposes it is recommended to use a coherence value of $\gamma^2 \geq 0.6$ at 5 Hz for the acceptance threshold, provided that at least 100 FFT analyses are averaged. Coherence improves as a function of oscillatory frequency to $\gamma^2 \geq 0.9$ at 10 Hz and higher frequencies (fig. 1).

**Interpretation of oscillation mechanics**

Monofrequency oscillations provide a measure of total respiratory impedance ($Z_{rs}$) that includes airway resistance, and elastic and inertive behaviour of lungs and chest wall at one oscillation frequency. In contrast, multifrequency oscillation methods, such as pseudo-random noise or impulse oscillation provide measures of respiratory mechanical properties in terms of $Z_{rs}$, as a function of frequency ($f$), allowing the recognition of characteristic respiratory responses at different oscillation frequencies.
The resistive component of respiratory impedance, $R_{rs}$, includes proximal and distal airways (central and peripheral), lung tissue and chest wall resistance. Normally, central resistance dominates, depending on airway calibre and the surface of the airway walls, while lung tissue and chest wall resistance are usually negligible [7, 28].

$R_{rs}$ may be considered within normal limits if $R_{rs}$ at 5 Hz ($R_{rs5}$) is within $\pm 1.64 \, \text{sd}$ of the predicted value. $R_{rs5}$ values between 1.64 and 2 sd above predicted may be considered minor, $>2$ sd moderate and $>4$ sd above predicted severe obstruction.

In previous reports the calculation of per cent predicted has been used. $R_{rs5}$ values that did not exceed 150% predicted, defined in bronchial challenge comparing changes in $R_{rs5}$ to a 20% decrease in forced expiratory volume in one second (FEV1) and 50% increase in airway resistance ($R_{aw}$), were considered within normal limits [29–31]. However, it is now recognised that a 20% decrease in FEV1 is a substantial abnormality, and normal limits for $R_{rs}$ might be more profitably defined in their own right, without requiring a specific relationship to arbitrary spirometric criteria.

In healthy subjects, $R_{rs}$ is almost independent of oscillation frequency [7, 32, 33], but may increase slightly at higher frequencies due to the upper airways shunt effect [6, 26].

When proximal (central) or distal (peripheral) airway obstruction occurs, $R_{rs5}$ is increased above normal values. The site of airway obstruction is inferred from the pattern of $R_{rs}$, as a function of oscillation frequency, adjusting as necessary for subject age [2, 25, 34–40]. Proximal airways obstruction elevates $R_{rs}$ evenly independent of oscillation frequency [32].

In distal airways obstruction, $R_{rs}$ is highest at low oscillation frequencies and falls with increasing frequency. This negative frequency-dependence of $R_{rs}$ has been explained in terms of intrapulmonary gas flow redistribution, due either to peripheral pulmonary nonhomogeneities or to changes in peripheral elastic reactive properties [6, 8, 34, 35]. As peripheral resistance increases, $R_{rs}$ becomes more frequency dependent [26, 36–38]. Frequency dependence of $R_{rs}$ may be a normal finding in small children [39, 40] and may be greater than in adults in the presence of peripheral airflow obstruction [8].
capacitance ($C_a$).

$$X_{rs}(f) = \frac{1}{\omega^2 C_a} \omega = 2\pi f \quad \{0 < f \leq f_{\text{max}}\} \quad (4)$$

Most importantly, in medicine, it is emphasised that respiratory $C_a$ is not identical to compliance. The component of $X_{rs}$ associated with $C_a$ is defined to be negative in sign. It is most prominent at low frequencies. In contrast, the component of $X_{rs}$ associated with inertance is always positive in sign and dominates at higher frequencies. Thus, interpretation of $X_{rs}$ is primarily influenced by the oscillation frequency range under consideration.

Low frequency capacitive $X_{rs}$ essentially expresses the ability of the respiratory tract to store capacitive energy, primarily resident in the lung periphery. In both fibrosis and emphysema this ability is reduced: in fibrosis because of the stiffness of the lung; in emphysema because of hyperinflation and loss of lung elastic recoil. Distal capacitive reactance at 5 Hz ($X_{rs5}$) manifests increasingly negative values either in restriction or in hyperinflation. Thus, $X_{rs5}$ characterises the lung periphery, but is nonspecific as to the type of limitation. Additional information is needed to differentiate peripheral obstruction from peripheral restriction. This is not usually problematic in clinical practice.

Capacitive and inertive elements have been modelled by a number of authors [2]. Many simplifications have been attempted that include serial and parallel circuit elements, to define an approximation of a normal $X_{rs}$ spectrum with a zero-crossing exactly at resonant frequency and positive slope throughout. The frequency range utilised in multifrequency oscillometric forcing signals should allow for determination of the serial resonance of the respiratory system under investigation [5].

**Resonant frequency.** Resonant frequency ($f_{\text{res}}$) is defined as the point at which the magnitudes of capacitive and inertive reactance are equal.

$$\omega_0 I = \frac{1}{\omega_0 C_a} \quad \omega_0 = 2\pi f_{\text{res}} \quad (5)$$

$$f_{\text{res}} = \frac{1}{2\pi \sqrt{I \cdot C_a}} \quad (6)$$

Because $f_{\text{res}}$ can vary over a considerable range and, thereby, appear in close proximity to oscillation frequencies dominated by either capacitative or inertive properties, this parameter should not be directly interpreted in terms of a particular mechanical property of the respiratory system. However, it is a convenient marker to separate low-frequency from high-frequency $X_{rs}$. Thus, low-frequency capacitive $X_{rs}$ is dominant at oscillation frequencies below $f_{\text{res}}$, while high-frequency inertive $X_{rs}$ is dominant at frequencies above $f_{\text{res}}$. In normal adults, $f_{\text{res}}$ is usually 7–12 Hz [33]. In healthy young children, $f_{\text{res}}$ is larger than in adults and increases with decreasing age.

In respiratory disease, both obstructive and restrictive impairments of the distal respiratory tract cause $f_{\text{res}}$ to be increased above normal [7, 26, 36]. The relevance of $f_{\text{res}}$ is normally revealed in within-individual trends over time during bronchial or therapeutic challenge.

**Capacitive spectral range of reactance.** Thoraco-pulmonary elasticity is commonly viewed as a static property, and normally is investigated in the absence of resistive or inertive mechanical losses. However, in oscillometry, capacitive $X_{rs}$ is believed to comprise useful information concerning peripheral airways mechanical properties. In
practice, determination of peripheral capacitive $X_{rs}$ is determined at the lowest frequency
that is not highly interfered with by fundamental respiratory frequency and its harmonics
[41]. In the IOS method, $X_{rs5}$ is commonly utilised. In children breathing at high
respiratory frequencies, reactance at 10 Hz may be useful [42] in following bronchial and/or
therapeutic challenge.

Interpretation of $X_{rs5}$ is clearly different from that of conventional lung function test
parameters and, in particular, lung compliance. One striking feature of $X_{rs5}$ is its negative
value. The minus sign is derived from a general definition in natural sciences to
differentiate elastic properties from moments of inertia, the latter of which is always
positive. Therefore, the minus sign simply confirms a relationship with elastic properties.

Definition of abnormality has previously been based on increased negative readings
related to expected normal values of $X_{rs5}$. A difference $>0.15$ kPa·s·L$^{-1}$ is most definitely
agreed to imply abnormal lung function, independent of $R_{rs}$, although abnormal lung
function may be present with smaller differences.

**Capacitance versus dynamic pulmonary compliance.** Dynamic pulmonary compliance
is derived from the relationship between oesophageal pressure and changes in lung volume
[43]. In contrast, oscillometry assesses the elastic properties of the respiratory system from
the out-of-phase relationship of simultaneously recorded transrespiratory pressure ($P_{rs}$)
and central flow signals ($V''_{rs}$), measured from superimposed oscillations and transformed
into $X_{rs}$. Therefore, the term capacitance, $Ca$, an equivalent of capacitive phase
information between the primary signals $P_{rs}$ and $V''_{rs}$ should be used. The frequency range
for such measures is always below $f_{res}$.

In pulmonary fibrosis, dynamic lung compliance ($C_{Ldyn}$) is decreased below normal. In
a similar manner, oscillometry yields a decreased estimate of $Ca$, due to negative
displacement of low frequency $X_{rs}$. Both dynamic lung compliance and $Ca$ reflect elastic
limitation and they trend together. Previous oscillometry studies have reported less
sensitivity than dynamic lung compliance in the early stages of restrictive disease [7, 17].

In contrast, pulmonary hyperinflation is associated with loss of lung elastic recoil and
increased $C_{Ldyn}$. Because of the loss of lung elastic recoil, peripheral airways are not
supported externally by lung recoil and the resultant partial peripheral airway
obstruction prevents the applied oscillometric signals from reaching peripheral
compliant areas. In this way, loss of lung elastic recoil indirectly causes a decrease in $Ca$, with associated increased negative magnitude of low frequency $X_{rs}$, [26, 36]. Indeed,
low frequency $X_{rs}$ is particularly sensitive to pulmonary hyperinflation, and while $R_{rs5}$
may be nearly normal or only moderately increased, $X_{rs5}$ is highly abnormal [44].

**Reactance area.** The index designated reactance area ($AX$) is a quantitative index of total
respiratory reactance $X_{rs}$ at all frequencies between 5 Hz and $f_{res}$. The integration of these
negative values of $X_{rs}$ [45] creates an area between the reactance zero axis and $X_{rs}$,
providing an integrative function to include changes in the magnitude of low-frequency
reactance $X_{rs}$, changes in $f_{res}$ and changes in the curvature of the $X_{rs}(f)$-tracing. It is
represented graphically in figure 1 as the area under the zero axis of the reactance graph
above the $X_{rs}(f)$ tracing.

$$AX = \int_{f_{res}}^{\infty} X_{rs}(f) \cdot df$$

This integrative index provides a single quantity that reflects changes in the degree of
peripheral airway obstruction and correlates closely with frequency dependence of
resistance [18].
**Inertive spectral range of reactance.** During resting breathing at normal respiratory frequencies, transrespiratory pressure is dissipated in resistive and elastic losses, whereas inertive pressure losses are negligible [46]. In contrast, during forced oscillation, when oscillatory frequencies are more than 10-times greater than normal respiratory frequency, inertance ($I$) contributes significantly to dissipation of the externally applied pressures [16, 46]. As noted above, the inertive spectral range of $X_{rs}$ is at frequencies above $f_{res}$. These frequencies reflect mechanical properties of the proximal conducting airways. However, specific clinical interpretation of $X_{rs}$ in this range is limited due to the wide variety of influences that may appear in the upper respiratory tract and resultant resonant effects that may change $X_{rs}$ unpredictably. Changes in central airway calibre correlate more strongly with resistive parameters and are less well represented in the inertive spectral range.

Finally, it should be noted that oscillometric reactance occasionally demonstrates a low-to-mid frequency plateau in the $X_{rs}$ ($f$) tracing, which is suggestive of possible upper airway obstruction [47–50].

**Variability of oscillometric parameters**

The majority of oscillometric parameters can usefully be assessed using the coefficient of variation (CV%). Short-term variability should not exceed 10%, for magnitude of $Z_{rs}$ and $R_{rs}$ at frequencies $\geq 5$ Hz [17]. Variability of $X_{rs}$ is larger, because of physiological and numerical characteristics. $X_{rs}$ can be positive or negative and is commonly close to zero. As a result, the calculation of CV% is not suitable to estimate the variability of most of the $X_{rs}$ values. Therefore, it is recommended to estimate variability of $R_{rs}$ and $X_{rs}$ using standard deviation, 95% percentiles for normally distributed values or calculating the absolute difference (range) between minimum and maximum of the $X_{rs}$ parameters [20, 51].

**Methodological versus biological variability.** Low methodological variability in measures of impedance ($Z_{rs}$) has been shown using physical models with rather high reproducibility [20]. Biological variability is much more complex and incorporates intra-breath and intra- and inter-subject variability. Intra-subject variability of consecutive measurements within a specified time period, including circadian variability, day-to-day variability and variability associated with changes in diseased airways has been reported previously [52–56].

Intra-breath variability is of specific physiological interest. Commonly, $Z_{rs}$ is determined as an average over a number of consecutive breathing cycles within 15–30 s. However, flow- and volume-dependence of $R_{rs}$ and $X_{rs}$ within each breathing cycle may be apparent during both inspiration and expiration, and have been shown in a number of investigations to reflect specific pathophysiological characteristics [57–61].

**Special application of impulse oscillometry system to animals**

Application of the impulse oscillation technique has been described in different animal species. The standard IOS device, originally developed for humans, has been validated carefully in calves aged up to 6 months and weighing 35–150 kg [20, 27, 62] and in pigs [63, 64]. For large animals, such as horses or adult cattle, a specially designed IOS unit has been developed, which is capable of analysing larger flow and volume characteristics. While no data are available in adult bovines, methodological validation and clinical application of IOS in horses has been reported [65–67] and is still in progress.
Oscillometry in spontaneously breathing conscious animals requires the imposition of applied pressure signals via a rigid mask. Without correcting measured impedance for the facemask, the limit of frequencies that can be clinically analysed is <15 Hz. Higher frequencies are substantially influenced by the capacitance of the facemask itself [27].

The most useful frequency range for clinical evaluation of respiratory impedance differs in different species, primarily dependent on animal size. The lower the specific frequency is, the more sensitive the measurements to the periphery of the respiratory system are. For example, while the resonant frequency is between 5–12 Hz in calves, depending on body weight, it is <5 Hz in horses. Accordingly, frequencies that reflect the lung periphery in horses are lower than in calves.

In agreement with results in human medicine, peripheral airway obstruction is characterised by a marked increase in magnitude of low frequency respiratory reactance ($|X_{rs}|$) and in $f_{res}$. In addition, the resistance spectrum of $R_{rs}$ shows increased negative frequency dependence and increase in low frequency $R_{rs}$ (<5 Hz). Upper airway narrowing is characterised by a parallel increase in $R_{rs}$ at all frequencies with no change in the frequency dependence of $R_{rs}$. No significant changes occur in reactance with upper (large) airway narrowing.

Relevance of oscillometry in clinical practice

This section offers a perspective on clinical use of the FOT method of determining $Z_{rs}$ that may be summarised as follows:

1) FOT provides useful clinical information that prominently includes functional assessment of small, peripheral airway behaviour beyond that available from commonly used pulmonary function tests (PFT).
2) Because of its sensitivity to peripheral airway function, FOT in its own right, apart from other PFT results, provides useful guidance in clinical patient management.
3) The prominence of peripheral airway functional assessment provided by FOT derives both from $X_{rs}$ as well as $R_{rs}$.
4) The importance of $X_{rs}$ is amplified by recognition of different $X_{rs}$-characteristics at low, i.e. below resonant frequency ($<f_{res}$), and high ($>f_{res}$) oscillation frequencies.

The last issue is considered in detail in the foregoing technological sections.

Briefly, it is noted here that original technical descriptions of FOT included calculation of the magnitude ($|Z_{rs}|$) and phase ($\phi$) of $Z_{rs}$, i.e. polar coordinates [1, 5]. This engineering description gave way to clinical research descriptions of $R_{rs}$ and $X_{rs}$ in Cartesian coordinates. As noted in the technology section, $X_{rs}$ relates to peripheral airway properties at oscillation frequencies $<f_{res}$, and to central conducting airways at frequencies $>f_{res}$. The use of the magnitude of $X_{rs}$ ($|X_{rs}|$) rather than $X_{rs}$ itself in algebraic manipulation of reactance data is emphasised, because this increases sensitivity to changes in peripheral airway mechanical properties, as demonstrated later in this section in reference to previously reported studies.

The section that follows includes discussion of monofrequency, pseudo-random noise and pulse-shaped pressure oscillations, as these three methods are currently in common use. The general principles apply to all methods of FOT for the most part where issues concern specific use of multifrequency rather than monofrequency or IOS rather than PRN this difference is stated explicitly. Previous published reviews have discussed theoretical and modeling aspects of FOT [2, 45, 68]. The present discussion does not include an exhaustive review of clinical research investigations from the Barcelona group [69–73], Leuven [6, 29, 32, 36, 39, 74–78], London [7, 79–81], Paris [8, 82–86] and
Vandoeuvre-les-Nancy [25, 87–91], which have all helped to provide the essential infrastructure for clinical application of oscillometry. Instead, the authors focus on published studies in relation to current work that permit practical establishment of oscillometry in the routine clinical pulmonary function laboratory. Furthermore, because the authors have worked more intimately with IOS, illustrative examples of current work with this technology are included.

The relative advantages of each type of FOT may be summarised by noting that the simplest form for clinical practitioners is monofrequency sinusoidal pressure application [2, 68]. Measurement of $R_{rs}$ with this method is applicable to patients with sleep apnoea and those using continuous positive airway pressure or mechanical ventilation.

Multifrequency FOT provides further characterisation of respiratory mechanics, including variation of $R_{rs}$ and $X_{rs}$ with oscillation frequency. PRN FOT has been applied to the description of patients with asthma, bronchitis, emphysema, diffuse interstitial lung disease and thoracic wall deformities, and to assess bronchial or therapeutic challenge [6, 29, 32, 36, 74–78]. Multifrequency FOT using PRN imposes a more gentle forcing signal perturbation than IOS, and has not been noted to provoke bronchoconstriction. IOS differs from PRN by utilising brief pressure pulses of 30–40 ms duration. These pulses result in respiratory pressure responses that may be perceived as a slightly unpleasant respiratory sensation in some subjects. The brief pressure pulses provide convenient time-trend analyses and within-breath changes of $R_{rs}$ and $X_{rs}$ not available with PRN. IOS is most familiar to the current authors, and therefore, this and the following section relate current clinical work with IOS to previously published reports of both PRN and IOS.

The clinical relevance of FOT may be assessed, as with any test of physiological function, in terms of its utility in diagnosis. Two general approaches are considered: first, the use of FOT as part of an initial complete diagnostic evaluation, including spirometry, body plethysmography, and gas distribution and exchange measures; secondly, the use of FOT as a means of monitoring response to treatment can include both bronchial and therapeutic challenge.

Summary information is presented here concerning the utility of FOT in assessing severity of lung disease, degree of airway reactivity, reversibility of airflow obstruction, and stratification of breathing mechanics between central and peripheral airways.

Current clinical relevance of FOT relates significantly to the broad range of patients that may conveniently be evaluated. In contrast to standard PFT requiring maximal coordinated efforts, FOT requires only normal quiet breathing with the lips tightly closed to avoid airflow leak, and the wearing of a nose-clip. For this reason, children can be easily studied, often as early as 3 yrs [8, 19, 92–94]. Similarly, elderly subjects, those with severe airflow obstruction or those with neuromuscular disease who find maximal forced respiratory efforts difficult to perform are able to breathe normally for FOT testing [95–98]. Portability of commercial FOT instruments permits lung function testing at the bedside or, for occupational lung disease studies, at the place of work [18].

FOT places minimal performance demands upon the patient, often described as passive cooperation. However, the operator must take considerable care with the test procedure. Because of the freedom offered to patients by simply breathing normally, moment-to-moment changes in respiratory resistance may be anticipated. Accordingly, a minimum of three technically acceptable FOT tests of 20–30 s duration or longer should be performed. The mouthpiece of the FOT instrument must be supported at a position to ensure maintenance of a neutral relaxed head and neck posture, avoiding body postures that might affect $Z_{rs}$. Children should be seated in an appropriately-sized chair to comfortably support their legs and adults should avoid crossing their legs, which requires abdominal muscle contraction that may lead to end-expiratory lung volumes below relaxation volume. Patients should be comfortably relaxed to maintain a constant body
position without muscular effort. In contrast, firm contraction of the facial muscles is necessary to support airtight closure of the lips about the mouthpiece. It is also desirable that FOT testing be performed in a quiet examination room, sufficiently far from others undergoing spirometry so as to be undisturbed by vigorous operator instructions for spirometry. The operator must review each FOT test immediately to ensure adequate recording time free of artefacts; a minimum of 20 s of consecutive artefact-free recording time is advisable. Lack of attention to these fundamental principles may result in highly variable FOT tests in an individual that are not clinically interpretable. This is not a troublesome issue in experienced clinical investigators’ laboratories but it is an important consideration in clinical PFT laboratories who have not previously used FOT.

An important perceived concern about the clinical relevance of FOT is the availability of a normal database from which to judge results in a particular patient. Published reports of normative FOT data in children and adults are available, but the number and size of these studies represent a much smaller normal population than is available for spirometry [6, 32, 39, 74, 79, 80, 93]. Differences in techniques of FOT and more recently in mouthpiece design may allow some degree of uncertainty concerning ranges of normal expected values for both $R_s$ and $X_s$, in both adults and children. Nevertheless, the similarity of FOT data using monofrequency sine-wave oscillations, PRN or pulse-shaped multifrequency FOT over the past four decades supports the acceptance of clinically useful guidelines at this time. As expected, $R_s$ and $X_s$ are dependent on body size, and recent data suggest the possibility of racial/ethnic differences [99].

It is suggested that concern over precise definition of “normality versus abnormality” in an individual should not preclude clinical implementation of FOT at this time, because bronchial and therapeutic challenges are very helpful in assessing airway responsivity. If initial baseline $R_s/X_s$ data do not clearly identify abnormality relative to existing normative data, retesting after β-agonist inhalation will immediately identify increased airway responsivity, and sequential studies over time provide similarly useful guidelines for clinical patient management.

**Diagnostic evaluations**

The most obvious relationship with other PFT procedures concerns the widespread use of spirometry. At the outset, it must be emphasised that spirometry measures maximal forced respiratory efforts, while FOT measures quiet breathing. Accordingly, it is not appropriate to demand that FOT and spirometric parameters be closely correlated as a mandatory requirement for FOT to be considered valid. For example, children with asthma most commonly manifest normal spirometry [100] with no spirometric response to inhaled β-agonist [42], while they may manifest abnormal baseline FOT parameters that are responsive to therapeutic challenge [101]. At the other end of the spectrum, patients with advanced chronic obstructive pulmonary disease (COPD) commonly manifest marked dynamic airway compression during spirometry with little spirometric response to pharmacological treatment, but may often manifest significant FOT responses [45]. For these reasons, use of spirometry to define severity of obstructive lung disease or receiver-operating characteristic of true sensitivity and specificity of oscillometry must no longer be considered the optimal standard.

In some patients, spirometry cannot provide optimal clinical information. Patients with significant neuromuscular disease are unable to provide the motive force needed for clear interpretation of spirometric results [97, 98]. Patients with lung allograft transplantation have obvious thoracic wall limitations that preclude truly maximal respiratory efforts until many months after surgery, during which time it is often not possible to detect adverse events, such as infection or acute allograft rejection by
spirometry alone. It is common for forced vital capacity (FVC) and FEV1 to increase over the first 18–26 weeks post-lung transplantation [102]. Despite this apparent improvement in spirometric parameters, peripheral airway disease, if it occurs, will lead to substantial worsening of FOT parameters [103] or of gas distribution [104].

Spirometric determination of responses to bronchial or therapeutic challenge may be limited by the necessary deep inspiration immediately prior to maximal expiration, allowing for distinctly different FOT responses [105–108]. This disagreement between spirometric and FOT parameters during bronchial challenge may be readily documented by IOS during quiet breathing immediately before and after a deep inspiration, which commonly reveals immediate but transient bronchodilation in asthmatic subjects during bronchial challenge. Figure 5 illustrates a 70-s recording of tidal breathing and a deep inspiration with simultaneous display of calculated magnitude of impedance at 5 Hz ($Z_{rs5}$) using impulse oscillometry.

$R_{rs5}$ in this patient had increased markedly from 0.3 kPa·s·L$^{-1}$ at baseline to 1.2 kPa·s·L$^{-1}$ after cumulative inhalation of 0.25, 0.5 and 1.0 mg·mL$^{-1}$ methacholine, when FEV1 had changed by only 260 mL from a baseline of 2.73 L. $Z_{rs5}$ during normal breathing and following a deep inspiration with relaxed expiration shows that, at the onset of the IOS test, $Z_{rs5}$ is much increased, while after an inspiration to maximal lung volume, there is a marked fall in $Z_{rs5}$, which gradually "recovers" with time. Since deep inspiration to maximal lung volume must immediately precede the FEV1 measurement, patients like the one whose data are shown in figure 5 will manifest FEV1 responses to methacholine that are altered by the immediate decrease in airway smooth muscle tone following maximal inspiration [106, 107].

With these caveats it is suggested that FOT can provide useful supplementary information to spirometry that may not be tightly correlated with spirometric results. To put such FOT information into proper perspective, it is necessary to review commonly observed patterns of FOT results in lung disease (primarily airflow obstruction), and in response to bronchial and therapeutic challenge.

![Fig. 5. – Tidal volume and magnitude of respiratory impedance at 5 Hz ($Z_{rs5}$) plotted as a function of time during methacholine challenge. First 40 s are resting breathing. After 40 s, subject inspired to total lung capacity, followed by relaxation back to normal resting breathing. Note that $Z_{rs5}$ increases markedly during each exhalation. After the deep inspiration, $Z_{rs5}$ decreases transiently, with gradual return towards initial levels over the following 24 s. The moving average of $Z_{rs5}$ is shown by the dash-dot line.](image-url)
Oscillometry in relationship to other diagnostic pulmonary functional tests

An important body of work has related FOT to body plethysmography [29, 76–78]. A group led by Van Noord have reported high correlations between $R_{aw}$ and FOT parameters in patients with obstructive lung disease and between absolute total lung capacity (TLC) and FOT parameters in patients with diffuse interstitial lung disease. In further studies comparing plethysmography, spirometry and FOT to assess reversibility of airflow obstruction, Van Noord's group reported the distinctly lower sensitivity of FOT than plethysmography [77]. The importance of this and other work by the Van Noord group is discussed further in the following sections.

It is widely recognised that body plethysmographic resistance, $R_{aw}$ includes only the resistance of the extrathoracic and intrathoracic airways, while $R_{rs}$ includes that of the chest wall and lung tissue in addition to airway resistance. Resistance of the chest wall has been reported [75], but there has been limited clinical interest in this parameter because of the technical difficulty of the measurements. Another difference between $R_{aw}$ and $R_{rs}$ relates to the status of the glottic aperture: it is commonly assumed that the glottis is maximally open during panting, but Jackson et al. [109] have shown that this occurs only in totally unrestricted panting. During voluntary attempts to control panting frequency and tidal volume, there is significant adduction of the vocal cords. Similarly, during quiet breathing, normal subjects commonly manifest a small, but variable, degree of vocal cord adduction during expiration. In patients with obstructive lung disease, this phasic expiratory adduction, visualised during the course of bronchoscopy, does not appear to be systematically different from that observed in normal subjects. Thus, it is to be expected that average $R_{rs}$ will differ systematically from panting plethysmographic $R_{aw}$.

It is also well established that $R_{aw}$ is more prominently influenced by large airway than by small airway resistance. Thus, Smith and Dubois [110] reported a comparable increase in deadspace when compared to the decrease in $R_{aw}$ in response to scopolamine in normal subjects. In addition, Hensley et al. [111] reported similar changes in $R_{aw}$ and deadspace after inhaled atropine. These results are consistent with the idea that $R_{aw}$ is primarily influenced by large airways. In contrast, $R_{rs}$ is importantly influenced by small airway resistance, and, accordingly, it may be expected that FOT responses to interventions that improve peripheral airway obstruction will be more prominent than $R_{aw}$ responses. Because of the prominent effect of peripheral airway obstruction on FOT measurements, it may be expected that FOT indices of peripheral airway obstruction might correlate more closely with indices of gas distribution ("Closing volume" [104]) and areas of lung hyperinflation manifested by computerised tomography [112] than with plethysmographic or spirometric indices, although there are no published comparisons at this time.

Oscillometry as a clinical monitor of response to treatment

By way of summarising the clinical relevance of FOT, it is worth considering the special value of FOT as a means of monitoring response to interventions. FOT has been reported to show greater sensitivity to inhaled corticosteroid or to $\beta$-agonist inhalation [8, 113–115] than spirometry. Both inhaled corticosteroids and $\beta$-agonists improve small airways function, and FOT responses manifest prominent changes in indices of peripheral airway obstruction. In contrast, spirometric sensitivity to small airways function is less prominent. Accordingly, it is expected that FOT might provide useful indices of peripheral airway change in response to therapeutic interventions. Such use of FOT provides a clinically valuable monitoring tool to follow therapeutic changes in small
airways function over time. This use of FOT for therapeutic monitoring is not dependent on the use of FOT as an initial diagnostic evaluation.

Finally, as a matter of practical convenience, FOT is more readily utilised in the clinical pulmonary function laboratory than body plethysmography. This issue is relevant to recent interest in the therapeutic value of anticholinergics in patients with COPD. As noted above, anticholinergics result primarily in large airway bronchodilation, and changes in Raw and deadspace are considerable [110, 111]. Thus, effective airway cholinergic blockade decreases large airway bronchomotor tone and increases deadspace, with relatively little effect on small peripheral airways disease. Whereas body plethysmography may be considered a useful technique to monitor such treatment effects, it is substantially less convenient to use routinely than FOT.

Oscillometry in the clinical pulmonary laboratory

Clinical interpretations of FOT responses in patients have often been related directly to the application of a particular mechanical or electrical model of the respiratory system. Van Noord et al. [78] discussed their results in diffuse interstitial lung disease with respect to an electrical analogue of the respiratory system. They further confirmed earlier work (vide infra) that ascribed negative frequency dependence of resistance to peripheral airway obstruction [116, 117]. Engineering models of the respiratory system have provided predictions of FOT characteristics in normal human subjects, and changes in FOT parameters in lung disease. However, the fact that many of these predictions have been observed empirically does not constitute proof of validity of one or other engineering models. Rather, it provides evidence that under the particular conditions of the FOT measurements undertaken, the empirical results show patterns that would be intuitively expected in normal subjects and those with lung disease. Over the past 3 decades, a body of empirical evidence has accumulated that relates FOT results to particular lung diseases, indeed establishing patterns that are characteristic of lung disease. The following sections draw heavily upon this clinical research and codify FOT results with respect to obstructive lung disease, with very limited data in diffuse interstitial lung disease. These FOT data are not intended as validations of engineering models, but instead, to illustrate commonly observed patterns of FOT characteristics associated with lung disease.

Obstructive lung disease

The relationships of FOT to spirometry noted above have a common theme. Spirometry does not provide a clear indication of peripheral airway obstruction, despite the general information contained within the shape of the flow–volume curve, and values of mid-flow rates (forced expiratory flow between 25 and 75% of the forced vital capacity). Thus, the most striking characteristic of FOT in relation to spirometry is the relatively greater sensitivity of FOT to peripheral airway disease [2, 18, 25, 29, 32, 42, 45, 52, 68, 82].

Peripheral airway disease. The most well-known FOT result empirically observed in peripheral airway disease in adults is frequency dependence of resistance (fdr). Grimby et al. [116], using multiple replicates of monofrequency FOT, were the first to demonstrate the pattern of frequency dependence, wherein calculated Rs was greater at 3 Hz than at 5, 7 or 9 Hz in patients with chronic airflow obstruction (CAO). As calculated Rs decreased as oscillation frequency increased, patients with CAO might manifest nearly normal
values of $R_s$ at sufficiently high frequencies. For this reason, Grimby et al. [116] focused on low (3 Hz) monofrequency $R_s$ to avoid masking differences between patients with airflow obstruction and normal subjects [118]. Many subsequent reports [18, 32, 36, 74, 82, 117, 119] confirmed that subjects with early peripheral airways disease, including smokers, certain industrial workers and normal subjects after histamine infusion, manifested frequency dependence, even with normal values of low-frequency $R_s$ in smokers. Importantly, the abnormal frequency dependence of resistance occurred in the presence of normal spirometry in those subjects with early peripheral airways disease [18, 32, 117]. This body of clinical research is largely empirical, although it had been shown on autopsy many years earlier that cigarette smokers who died early in life had manifested peripheral airway inflammation on autopsy [120]. Similarly, there is now ample evidence of peripheral airway inflammation in patients with asthma, and, as will be illustrated below, frequency dependence of resistance occurs prominently in asthma.

The sensitivity of frequency dependence to peripheral airway disease is the first discriminant between methods of FOT in general: while monofrequency FOT is convenient to dissect within-breath patterns of change in $R_s$ [61, 68] or changes in $R_s$ during sleep-disordered breathing or in patients on mechanical ventilators [2], multifrequency FOT is most convenient to document frequency dependence of resistance in practical use in the clinical pulmonary function laboratory. Monofrequency FOT may be used at two or more single frequencies; however, multifrequency FOT uses different oscillation frequencies applied within a single burst to dissect patterns consistent with peripheral rather than central airway obstruction. This dissection is based upon established observations that pressure oscillations at frequencies >15 Hz are severely damped out before reaching peripheral airways, while those at frequencies <10–15 Hz penetrate much further to the lung periphery [25, 121].

The transition between "large central" airways and "small peripheral" airways is neither precisely fixed anatomically nor precisely defined in terms of airway lumen diameter. The illustrations in figures 6 and 7 reflect common patterns observed in children with asthma and in adults with COPD.

Figure 6 shows representative IOS tests pre- and post-salbutamol in a 6-yr-old patient

![Fig. 6. – Conventional plots of respiratory resistance ($R_s(f)$), as a function of oscillation frequency, in a 6-yr-old child with asthma. Note that frequency axis is shown between zero and 35 Hz, while data are plotted between 3–35 Hz. A vertical dotted line is shown at 5 Hz, the lower limit at which most impulse oscillometry system data are reported. ––: data prior to nebulised β-agonist bronchodilator; ----: data after bronchodilator.](image-url)
with mild asthma. $R_s$ is plotted as a function of oscillation frequency ($R_s(f)$-tracing). Note that prior to $\beta$-agonist, $R_s$ is 0.93 kPa·s·L$^{-1}$. $R_s$ falls steeply with increasing oscillation frequency to a minimum at 18 Hz, after which it increases with further increases in oscillation frequency. While Clement et al. [39] have shown that normal children manifest a mild degree of frequency dependence, the very large fall in $R_s$ between 5 and 15 Hz in figure 6 is consistent with abnormal peripheral airways function in a 6 yr old. This is confirmed by administration of nebulised $\beta$-agonist, after which $R_s$ decreased to 0.59 kPa·s·L$^{-1}$ (37% change). Note also that the fall of $R_s$ between 5–15 Hz post $\beta$-agonist is much less than pre $\beta$-agonist. Baseline and post $\beta$-agonist IOS data in this child may be compared with data in normal children of this age, who manifested <15% fall in $R_s$ from 5–15 Hz [122]. The response to $\beta$-agonist in figure 6 may also be compared with responses of normal nonatopic children who manifested an average change in $R_s$ after salbutamol of 19% [122]. Finally, it can be seen in figure 6 that $R_s(f)$ at frequencies >20 Hz decreased substantially after $\beta$-agonist. Adult patients with asthma show similar findings to those in figure 6. $R_s$ may be nearly independent of oscillation frequency in adult asthmatics after beta agonist.

Figure 7 illustrates an adult patient with COPD, pre- and post-nebulised $\beta$-agonist bronchodilator. ––: pre-bronchodilator; ----: post-bronchodilator. Note that $R_s(f)$ is unchanged after bronchodilator at frequencies >12 Hz.

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**Central airway obstruction.** Because of the frequency-dependent distribution of oscillatory pressures within the airway tree, FOT provides separate, although not entirely independent, indices of large and small airway responses. Thus, changes of resistance in the larger airways are manifest by FOT as uniform changes in $R_s$ at all oscillation frequencies, both low and high. An increase in resistance of the large airways was reported in a recent study of rescue workers at the World Trade Center site in New York [18]. Rescue workers with no history of cigarette smoking exposed to large-particle air
pollution at the World Trade Center site manifested, at baseline, uniformly increased $R_{rs}$ at all oscillatory frequencies studied between 5–35 Hz, as shown in figure 8, pre- and post-nebulised β-agonist.

Ironworkers with a history of cigarette smoking showed greater baseline increases in low-frequency $R_{rs}$, and, accordingly, a frequency dependence of resistance that is characteristic of peripheral airway obstruction [7, 18, 29, 36, 82, 116, 117]. Responses to nebulised β-agonist showed uniform decreases in $R_{rs}$ across all frequencies in nonsmokers, while smokers manifested larger decreases in $R_{rs5}$ than in $R_{rs20}$ [18].

**Nonresistive components of forced oscillation technique.** A second discriminant between mono- and multifrequency FOT concerns reactive components of applied pressure oscillations, reactance $X_{rs}(f)$-tracings, which appear prominently in multifrequency FOT. Reactance can be assessed by computer-assisted analyses utilising FFT; however, monofrequency FOT has not been widely adapted to conveniently calculate $X_{rs}$.

Just as with the interpretation of $R_{rs}$, oscillation frequency provides a means of examining different regions of the airway tree using $X_{rs}$ (vide infra): at low oscillation frequencies, elastic elements in peripheral airways are the dominant reactant to applied pressure, and reflect small airway mechanical properties. In airflow obstruction, small airways are functionally obstructed, due to peripheral airway inflammation in both asthma and COPD. This results in portions of the distal lung periphery that are "in the shadow" of effective obstruction of small airways. This pathological process leads to an increase in the magnitude of $X_{rs}$ at low frequencies. At high frequencies, accelerative forces are the predominant reactant to applied pressures and occur virtually exclusively in large airways where they are related to inertial properties. It should be noted that Van Noord et al. [78] reported qualitatively similar changes in $X_{rs}(f)$ tracings in patients with diffuse interstitial lung disease and obstructive lung disease. Accordingly, changes in low-frequency $X_{rs}$ are not specific to obstructive lung disease, but rather reflect peripheral airway disease. Mechanical interpretations of changes in low-frequency $X_{rs}$ in obstructive and restrictive lung disease are considered in detail in the methodology section.

![Fig. 8. – Respiratory resistance ($R_{rs}(f)$), plotted as a function of oscillatory frequency pre- (—) and post (----) -bronchodilator in an ironworker exposed to large-particle air pollution at the World Trade Center site. Note increased $R_{rs}$ at all frequencies, with no significant frequency dependence of resistance at baseline. After nebulised β-agonist, $R_{rs}(f)$ decreases in a parallel manner relative to baseline pre-bronchodilator.](image-url)
Figure 9 illustrates IOS $X_{rs}(f)$ tracings in the asthmatic child whose $R_{rs}(f)$ tracings pre- and post-nebulised β-agonist are shown in figure 6. Figure 9 shows that after β-agonist, $X_{rs}$ at 5 Hz ($X_{rs5}$) changes from -0.31 to -0.26 kPa·s·L$^{-1}$ and the frequency at which $X_{rs}$ is zero (resonant frequency = $f_{res}$, vide infra) changes from 18 to 17 Hz (6%). More strikingly, the overall curvature of the $X_{rs}(f)$ tracing changes from concave to the zero-X axis to being convex to the zero-X axis. This change in curvature is consistent with $X_{rs}(f)$ tracings described by Clement et al. [36], who reported that patients with airflow obstruction manifested a loss of the downward concavity of $X_{rs}(f)$ tracings that is commonly seen in normal subjects. β-agonist produced only small changes in $X_{rs5}$ and $f_{res}$ in figure 9; however, the change in the overall $X_{rs}(f)$ tracing curvature at frequencies below $f_{res}$ was dramatic.

Previous investigations have emphasised that low-frequency $X_{rs}$ and $R_{rs}$ are most sensitive to changes in peripheral airway function, and $X_{rs5}$ has been used as a primary efficacy variable [113–115, 122, 123]. However, in small children, respiratory frequency is commonly >20–30 breaths·min$^{-1}$, and, accordingly, the higher harmonics of fundamental respiratory frequency may encroach on the lowest FOT frequencies analysed [41, 68]. As a result, $X_{rs5}$ manifests relatively greater measurement noise. Some IOS studies in children have reported failure of $X_{rs5}$ to manifest significant changes after inhaled corticosteroids or β-agonists [42, 115, 124]. Marotta et al. [42] showed that the $X_{rs10}$ response to β-agonist, but not the $X_{rs5}$ response, manifested a significant difference between asthmatic and nonasthmatic atopic children. This was associated with less variability in $X_{rs10}$ responses compared with $X_{rs5}$. The absolute value of $X_{rs}$ ($|X_{rs}|$) changes differently as a function of oscillation frequency below and above $f_{res}$. At low frequencies of oscillation, below $f_{res}$, $|X_{rs}|$ decreases as oscillation frequency increases up to $f_{res}$. At $f_{res}$, $|X_{rs}|$ is zero. As oscillation frequency increases above $f_{res}$, $|X_{rs}|$ increases with further increases in oscillation frequency.

Because of this difference in the relationship between magnitude of $X_{rs}$ and oscillation frequency below and above $f_{res}$, a quantitative index of $X_{rs}$ magnitude at frequencies below $f_{res}$ was developed by integrating all negative values of $X_{rs}$ [18, 45, 52]. This index,

![Fig. 9. - Respiratory reactance ($X_{rs}(f)$), plotted as a function of oscillatory frequency pre- (---) and post- (----) bronchodilator. Same subject as figure 6. The integrated low-frequency reactance area ($AX$), is shown by vertical hatching pre-bronchodilator, and by diagonal hatching post-bronchodilator. This area is reduced by ~50% from pre- to post-bronchodilator, associated with marked change in curvature of the $X_{rs}(f)$ tracing. In comparison, there are small changes in $X_{rs}$ at 5 Hz and resonant frequency from pre- to post-bronchodilator.](image-url)
designated AX, provides an integrative function to include changes in the magnitude of low-frequency $X_{rs}$, changes in $f_{res}$ and changes in curvature of the $X_{rs}(f)$ tracing. AX includes $X_{rs}$ magnitudes at 5 Hz and slightly higher oscillation frequencies which manifest improved signal-to-noise ratio, as noted above for atopic asthmatic children [42]. It is represented graphically in figure 9 as the area under the zero $X_{rs}$ axis above the $X_{rs}(f)$ tracing. As discussed below, this integrative index provides a single quantity that reflects changes in the degree of peripheral airway obstruction and correlates closely with frequency dependence of resistance. In figure 9, AX decreases by 50% after $\beta$-agonist, closely comparable to the decrease in frequency dependence of resistance measured between 5 and 15 Hz in the same child shown in figure 6, when $R_5$-$R_{15}$ decreased from 0.36 kPa·s·L$^{-1}$ to 0.16 kPa·s·L$^{-1}$ after $\beta$-agonist.

The perspective presented here of AX in relation to peripheral airway function, results directly from the details presented in the methodology section, namely that low-frequency $X_{rs}$ essentially expresses the ability of the respiratory tract to store capacitive energy, which is primarily resident in the lung periphery. In contrast, at frequencies above $f_{res}$, $I$, which is primarily resident in proximal conducting airways, contributes significantly to the dissipation of externally applied pressures [6, 46]. Thus, oscillation frequencies above $f_{res}$ reflect mechanical properties of more proximal conducting airways. Because of these differences in mechanical properties reflected by low- and high-frequency oscillation, calculation of the arithmetic mean $X_{rs}$ is not likely to be optimally useful to assess pulmonary mechanical responses. Thus, VAN NOORD et al. [29] reported that the mean value of $X_{rs}$ change was less sensitive than FEV1 in assessing the effect of histamine. However, their graphic mean $X_{rs}$–frequency data reveal changes in the estimate of AX from ~0.15 at baseline, to 1.7 or 2.5 kPa·L$^{-1}$ when mean decrease in specific airway conductance ($sG_{aw}$) was 40% or 15% in FEV1. These increases in AX of 1,000–1,500% are comparable to those measured using IOS in the current author’s laboratory during methacholine challenge: the patient shown in figure 6 manifested an increase in AX from 0.34 at baseline to 7.5 kPa·L$^{-1}$ (>2,000% increase) after cumulative exposure to methacholine up to 1.0 mg·mL$^{-1}$. Furthermore, the study of VAN NOORD et al. [77] during assessment of reversibility of airflow obstruction by FOT, body plethysmography and spirometry reported that changes in mean $X_{rs}$ did not contribute significantly to discriminant function beyond spirometry, $R_{aw}$ and $R_{rs}$ at 6 Hz. In contrast, estimated AX, approximated from their graphic mean $X_{rs}$–frequency data, showed a 50% reduction after salbutamol, from ~3.1 to 1.5 kPa·L$^{-1}$. Both the baseline AX in patients with airflow obstruction and the AX decreases in response to $\beta$-agonist are comparable to those recently reported using IOS [101].

The empirical observations discussed above do not prove that any particular engineering model is a true representation of the lung, especially the diseased lung as emphasised by VAN NOORD et al. [78]. Nevertheless, FOT results predicted by models may correlate usefully with independent clinical physiological and pathophysiological evidence. Quite apart from engineering models, an intuitive understanding of $X_{rs}$ may be appreciated from the physical principles elucidated above and amplified in the foregoing discussion of methodology. The applicability of high frequencies to large central airways and low frequencies to peripheral airways is not a consequence of any particular engineering model, but is observed empirically both in $R_{rs}$ and $X_{rs}$.

Clinical interpretation of forced oscillation technique

As also noted in the methodology discussion of FOT, abnormalities of $X_{rs}$ are not specific to obstructive lung disease, because these same patterns have been reported in lung fibrosis [78]. In clinical diagnostic lung function testing including FOT, spirometry,
gas diffusion and body plethysmography, the problem is not usually distinguishing between obstructive and restrictive disease. The more important issue is the relative severity of pathophysiological abnormality. Furthermore, there is evidence to suggest that the early pathological lesion in lung fibrosis is inflammation of the small airways [125]. Thus, changes in $R_{rs}$ magnitude in lung fibrosis and in peripheral airflow obstruction may both reflect peripheral airway inflammation. If these nonspecific $R_{rs}$ abnormalities in lung fibrosis represent small airway inflammation, they may respond to anti-inflammatory treatment, analogous to the way asthmatic peripheral airway inflammation responds to corticosteroids. Such responses are more likely to be found in FOT parameters than in spirometry. Clinical interpretation may then be considered in the setting of response to treatment interventions.

Clinical interpretation of FOT can be related both to effects of airway smooth muscle tone and airway inflammation. Below, effects of anticholinergic, $\beta$-agonist or corticosteroid medications are represented, because these agents are most commonly utilised clinically. Commonly observed changes in FOT measures in patients with obstructive lung disease are illustrated. $R_{rs}$ is considered first.

$R_{rs}$ effects. While inflammation is a cellular process, it has mechanical consequences. These consequences may be considered in relation to bronchoconstriction, defined as increased tone of airway smooth muscles, and the common perception of bronchodilation defined as a decrease in smooth muscle tone.

When airway smooth muscle tone increases, $R_{rs}$ increases because of decreased airway lumen. Airway lumen is also decreased with inflammation or oedema in the walls of the airways. Therefore, $R_{rs}$ increases as a result of inflammation and oedema. Peripheral airways have much smaller lumina than central (large) airways, and inflammation/oedema in the walls of peripheral airways can reasonably be expected to have a proportionately larger effect on lumen size than inflammation/oedema in larger airways. In the discussion that follows, "low-frequency $R_{rs}$" will be denoted as $R_{rs}$ at frequencies <15 Hz and "high-frequency $R_{rs}$" as $R_{rs}$ at frequencies >20 Hz, with the latter term synonymous with large airway resistance.

If an intervention, such as inhaled anticholinergic, achieves bronchodilation with no effect on inflammation, it may be expected that large airway lumen will increase, with little effect on peripheral airway lumen. In this event, large airway $R_{rs}$ will decrease. Low-frequency $R_{rs}$ will decrease to a similar degree and little or no change in frequency dependence occurs. This is illustrated in a 55-yr-old patient with COPD in figure 10.

If an intervention such as inhaled $\beta$-agonist achieves bronchodilation with little or no effect on inflammation, it may be expected that peripheral airway lumina will increase, in addition to any release of bronchoconstriction in large airways. In this case, low-frequency $R_{rs}$ will decrease out of proportion to high-frequency $R_{rs}$.

In asthmatic patients, both high-frequency and low-frequency $R_{rs}$ may decrease, with relatively greater decrease in low-frequency $R_{rs}$ and associated decrease in frequency dependence of resistance as illustrated in figure 6.

In patients with COPD, a decrease in low-frequency $R_{rs}$ after $\beta$-agonist with little or no change in high-frequency $R_{rs}$ is commonly observed, as illustrated in figure 7. In COPD patients with lung hyperinflation, little or no decrease in $R_{rs}$ may occur after $\beta$-agonist inhalation, particularly if there is an associated fall in resting end-expiratory lung volume. If $R_{rs}$ remains the same after $\beta$-agonist while end-expiratory lung volume decreases, this represents "functional bronchodilation", because the same resistance pertains at lower operating lung volumes. Accordingly, failure of $R_{rs}$ to decrease in patients with COPD need not be considered as "no response" to $\beta$-agonist bronchodilator.

If an intervention such as inhaled corticosteroids achieves a decrease in inflammation
with no effect on airway smooth muscle tone, FOT responses might be expected to reflect a relatively greater impact due to decrease in peripheral airway inflammation with resultant increase in peripheral airway lumina. Such an effect results in a significant "dilation" of peripheral airways due to decreased inflammatory encroachment on peripheral airway lumina. Thus, a decrease in peripheral airway resistance can be expected, manifest as a greater decrease in low-frequency than in high-frequency $R_{rs}$, and concomitant decrease in frequency dependence.

In asthmatic patients, a decrease in large airway $R_{rs}$ (high-frequency $R_{rs}$) may also occur. In patients with COPD, there may be a decrease in low-frequency $R_{rs}$; however, little or no decrease in $R_{rs}$ may be manifest, especially if lung hyperinflation is present.

$X_{rs}$ effects. How then does decreased inflammation manifest itself in patients with COPD? As noted in the preceding section, describing nonresistive components of FOT, the magnitude of low-frequency $X_{rs}$ is increased in COPD due to functional peripheral airway obstruction, with resultant contraction of surface area of the lung periphery exposed to low-frequency oscillations. Indeed, low-frequency $X_{rs}$ is more sensitive to peripheral airway obstruction in COPD/emphysema than $R_{rs}$. In the presence of peripheral airway obstruction in patients with COPD, relatively small increments to airways resistance may occur because of the large cumulative cross-sectional diameter of all airways in the lower generations of airways, as manifest in the trumpet model of Weibel [126]. Accordingly, body plethysmographic measurement of airway resistance may be nearly normal, and only by measuring absolute thoracic gas volume is the abnormality manifest.

If peripheral airway inflammation is decreased by administration of inhaled corticosteroids, peripheral airway lumina increase and the patency of small airways expands in the direction of the lung periphery. As a result, a portion of the lung periphery comes "out of the shadow" of small airway obstruction and a larger surface area is presented to the low-frequency oscillations. This acts to decrease the magnitude of low-frequency $X_{rs}$. This is illustrated in figure 11a showing IOS tracings in a COPD patient at
baseline (—) and after 4 weeks of inhaled corticosteroids treatment (-----). $AX$ decreased from 3.0 to 1.3 kPa·L$^{-1}$ after inhaled corticosteroid treatment. In this patient, $R_{rs}$ and frequency dependence of the $R_{rs}(f)$ tracing show significant decreases, as illustrated in figure 11b; $R_{rs5}$ improved from 0.68 to 0.48 kPa·s·L$^{-1}$, $R_{rs15}$ from 0.41 to 0.35 kPa·s·L$^{-1}$. Furthermore, this patient with COPD manifests somewhat "responding" large airways, as his high-frequency $R_{rs}$ (at 30–35 Hz) also decreased by ~20%.

Figure 12 shows tracings in a COPD patient when stable at baseline and during the onset of an exacerbation. Figure 12a shows baseline reactance area $AX = 1.2$ kPa·L$^{-1}$, with increases to 1.6, 2.4 and 4.3 kPa·L$^{-1}$ over a duration of 9 days of exacerbation. $R_{rs5}$ increased significantly, but less dramatically from 0.51 at baseline to 0.54, 0.59 and 0.65 kPa·s·L$^{-1}$ during exacerbation, shown in figure 12b. Frequency dependence, calculated as the fall in $R_{rs}$ from 5 to 15 Hz, was 0.15 kPa·s·L$^{-1}$ when stable at baseline, and increased to 0.2, 0.23 and 0.31 kPa·s·L$^{-1}$ during exacerbation.
The close correlation between changes in $AX$ and changes in frequency dependence of resistance in individual patients shown in figures 6–12 are confirmed across individuals in the occupational study reported by Skloot et al. [18], who found a correlation of 0.92 between frequency dependence of resistance and $AX$ across a sample of ironworkers at the World Trade Center site, with variable exposure to cigarette smoking and large-particle air pollution, and resultant variability in both large and small airway obstruction. The close correlation between frequency dependence of resistance and $AX$ is consistent with both indices reflecting small airway function.

Coherence. Coherence, first introduced by Michaelson et al. [5], is defined as the auto- and cross-correlations of phase and amplitude of oscillatory pressure and flow components. It reflects, in an "engineering sense", the linearity of the respiratory system and, in a "biological sense", the variability of the respiratory system from time to time within the sample of data. Marked temporal variability of the respiratory system within a breath occurs commonly in COPD, where even during quiet breathing, dynamic...
compression of intrathoracic airways may occur. As a result, $R_s$ and $X_s$ may increase substantially during expiration.

Figure 13a illustrates a patient with severe COPD, with volume and $Z_{rs5}$ as functions of time. Figure 13b shows coherence plotted as a function of oscillation frequency, with separate tracings for average combined inspiration/expiration as well as for inspiration-only and expiration-only.

Figure 13a shows marked changes in $Z_{rs5}$ with respiratory phase, similar to those shown by Marchal and Loos [68]. There is a clear decrease in $Z_{rs5}$ at the onset of inspiration, keeping minimal values until end-inspiration. A marked abrupt rise in $Z_{rs5}$ occurs at the onset of expiration with elevated values including end-expiration. In figure 13b, the value of averaged coherence at 5 Hz, 0.4, is distinctly lower than at frequencies $\geq$10 Hz.

![Graphs of respiratory impedance and coherence](image-url)
Numerical calculations of coherence during the separate respiratory phases reveal that inspiratory-only and expiratory-only coherences are systematically greater than the combined coherence over the entire spectrum of oscillatory frequencies. The tracings in figure 13 are consistent with more uniformity of respiratory mechanics within the separate inspiratory and expiratory phases than for the combined total breath average. At 10 Hz, the coherence averaged across both respiratory phases is 0.7, while that for separate inspiratory and expiratory data are both 0.9, reflecting differences in respiratory mechanical parameters that pertain to the separate respiratory phases. Despite the very low coherence for combined inspiration/expiration, three consecutive 40-s impulse oscillography system recordings obtained within 5 min manifested an average respiratory resistance at 5 Hz of 1.08, 1.0 and 1.02 kPa·s·L⁻¹ and reactance area of 5.9, 6.1 and 6.2 kPa·L⁻¹. Thus, the within-phase uniformity of mechanical parameters reflected by separate inspiratory and expiratory coherences is borne out by standard deviations of <5% for triplicate measures.

### Summary

The aim of this chapter has been to describe the unique and clinically relevant information that forced oscillation technique (FOT) provides. This may be derived without mathematical mastery of technological principles of the equipment and/or of numerical models. It is emphasised that recognition of the change in respiratory mechanical parameters as a function of oscillation frequency is necessary to appreciate the outstanding value of FOT in its ability to assess peripheral airway function. This has been one of the major challenges in respiratory diagnostics up to the present time. The short duration of the FOT test, 20–30 s, makes it particularly useful as part of a diagnostic programme of lung function testing; it is not suggested that FOT be used in lieu of conventional pulmonary function testing, but rather in addition. FOT measures resting breathing while spirometry assesses maximal respiratory performance of the patient. The special value of FOT in terms of short-term response to bronchial and therapeutic challenge has been emphasised as well as its value in monitoring long-term trend responses to therapy.

The simplicity of FOT measurements and its minimal requirements on subject cooperation are in rather sharp contrast to its current limited clinical acceptance. Two primary reasons for the present limited application of FOT include the need for viewing respiratory mechanical parameters over a range of frequencies and the resultant central-peripheral specificity of oscillatory parameters, with specific emphasis on the reflection of peripheral airway function by low-frequency reactance. Indeed, lack of awareness of this ability of FOT to assess peripheral airway function has turned physicians to the use of multiple replicates of high-resolution computed tomography lung scans to assess small airway function. Other reasons for limited use of FOT currently may include the greater variability of FOT measures compared with spirometry. Despite such variability, use of at least three replicate FOT measures combined with therapeutic challenge can provide sensitive evaluation of small airway function.

The freedom allowed to the subject to breathe "naturally" imposes increased demands for vigilance on the operator, who must maintain a quiet environment for forced oscillation technique testing. Operators must also reassure subjects that their relaxation is needed, except for the facial musculature ensuring tight lip closure on the mouthpiece. Posture must be supported to maintain subject comfort and the
instrument mouthpiece must be brought to the subject to avoid stretching of the neck. Finally, the availability of results from a brief test must not lead the operator to accept a single measurement, but rather, the usual clinical testing procedure of at least three replicate measures is required.

**Keywords:** Forced oscillation technique, impulse oscillation technique, reactance, resistance, respiratory impedance.

**References**


