Clinical Application of the Forced Oscillation Technique

Toshihiro Shirai¹ and Hajime Kurosawa^{2,3}

Abstract

The forced oscillation technique (FOT) is a noninvasive method with which to measure respiratory system resistance and reactance during tidal breathing. Recently, its clinical application has spread worldwide with the expansion of commercially available broadband frequency FOT devices, including MostGraph and Impulse Oscillometry. An increasing number of reports have supported the usefulness of the FOT in the management of asthma and chronic obstructive pulmonary disease (COPD). However, the FOT is not a surrogate test for spirometry, but should be used complementarily. Furthermore, reference values are not necessarily available and the interpretation of some measured data is controversial. There is a need to update the international statement for not only technical aspects but also the clinical use of the FOT. In this review, we summarize the previously published studies and discuss how to use the FOT in a clinical setting.

Key words: forced oscillation technique, impedance, mechanics, reactance, resistance

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Introduction

The forced oscillation technique (FOT) is a noninvasive method with which to measure lung mechanics (1). Forced oscillations are applied to the airway opening from the mouth to derive respiratory system impedance (Zrs), the spectral relationship between the resultant pressure and air-flow. The real part of impedance is called respiratory system resistance (Rrs), whereas the imaginary part is called respiratory system reactance (Xrs), which is supposed to reflect elastic and inertial properties of the lung. Since the first method using monofrequency FOT in the 1950s (2), many variants have been developed. Recently, the clinical application of broadband frequency FOT as a measurement of the lung function has progressed, and an increasing number of reported studies have examined its usefulness in the evaluation or management of obstructive lung diseases, including asthma and chronic obstructive pulmonary disease (COPD). Forced oscillations are superimposed on tidal breathing, avoiding the need for any special breathing maneuver or noticeable interference with respiration. The FOT provides more information on the lung than that obtained by forced expiration: spirometry. If reference values and proper inter-

pretation of the measured data are established, then this technique will be useful in older patients who have difficulty in performing spirometry and young children who cannot cooperate with the maneuver. However, the international statement of the FOT have not been updated since 2003 (1). In this review, we describe previous studies that used commercially available FOT devices, including MostGraph (Chest M.I., Tokyo, Japan) and Impulse Oscillometry (IOS) (MasterScreen IOS; Jaeger, Hoechberg, Germany), and discuss the problems in the clinical use and data interpretation of the FOT. Concerning the principles and more detailed information on the methodology, the reader is referred to other articles (1, 3).

Basic Indices of the FOT and Colored 3D Imaging

When the oscillatory signal is added through the mouth, Zrs is defined as the complex ratio of pressure to flow at the mouth. Zrs consists of its real part, called the Rrs, and the imaginary part (Xrs), with the following relationship: $(Zrs)^2 = (Rrs)^2 + (Xrs)^2$. Rrs reflects the dissipative mechanical properties of the lung (1) such as airway resistance (Raw) and respiratory tissue resistance (Rti). Xrs reflects the undis-

¹Department of Respiratory Medicine, Shizuoka General Hospital, Japan, ²Center for Environmental Conservation and Research Safety, Tohoku University, Japan and ³Department of Occupational Health, Tohoku University School of Medicine, Japan

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Correspondence to Dr. Toshihiro Shirai, toshihiro-shirai@i.shizuoka-pho.jp

Figure. Changes in spirometric and forced oscillatory parameters over a 4-year period in a patient with severe asthma successfully treated with omalizumab (modified from reference 4). Oscillatory parameters are expressed as whole-breath values. ALX: low-frequency reactance area, FEV₁: forced expiratory volume in 1 second, Fres: resonant frequency, FVC: forced vital capacity, Rrs: respiratory system resistance, R5 and R20: Rrs at 5 Hz and 20 Hz, respectively, R5-R20: the difference between R5 and R20, Xrs: respiratory system reactance, X5: Xrs at 5 Hz

sipative mechanical properties such as elasticity and inertia of the lung and air.

Oscillatory indices are expressed as the mean values of the whole data (whole-breath) and of each phase as inspiration or expiration. The difference between the inspiratory and expiratory phases (Δ) is also frequently used. Those basic indices can be easily obtained using both IOS and MostGraph. In addition, the latter visualizes the time course as well as the absolute values in colored 3D graphics, which are suitable to understand various respiratory condition such as bronchoconstriction in asthma, effects of the treatment, and so on, for both medical staff members and patients. Figure shows the changes in the spirometric and forced oscillatory parameters over a 4-year period in a patient with severe asthma who was successfully treated with omalizumab, an anti-IgE antibody (4). Colored 3D graphic images of MostGraph can generally be classified into 3 types (5). Rrs of the first pattern shows high values of the expiratory phases (blue or black at the top, i.e., ≥ 6 cmH₂O/L/s) and low values of the inspiratory phases (green or yellow at the bottom, i.e. approximately 2 cmH₂O/L/s) with a marked frequency dependence (increasing at lower frequencies) and respiratory cycle dependence (greater differences between the expiratory and inspiratory phases). Xrs shows greater (more negative) values (blue at the bottom, i.e., < -6 cmH₂O/L/s). This pattern is usually found in patients with COPD, but also in those with severe or uncontrolled asthma

(Figure, left panel). Rrs of the second pattern shows moderately high Rrs over the entire frequency and respiratory cycle (yellow, orange, or red, i.e., approximately 4 cmH₂O/L/s) with slight frequency and respiratory cycle dependence and Xrs changes (yellow), which is usually found in patients with asthma, but occasionally in those with COPD and healthy controls (Figure, middle panel). Rrs of the third pattern shows low Rrs (green, i.e., < 2 cmH₂O/L/s) and Xrs (yellow) with few within-breath changes, which is usually found in healthy controls, but also in patients with mild or controlled asthma, and sometimes in those with COPD (Figure, right panel). In the patient represented in Figure, there were few changes in spirometry, whereas Rrs and Xrs improved overall, with colored 3D image conversion from the first to the third patterns. Similar cases in which colored 3D imaging was useful have also been reported (6, 7).

Measurements

There are standard recommendations for measurements of the FOT (1, 5). In the hardware, after the reduction of the respiratory noise from the oscillation signals, the electric signals from the sensors of pressure and flow are processed with a computer. The time lag of the electric signal between the oscillatory pressure and flow must to be minimized (8). The dead space volume between the mouthpiece and the sensors should be minimized and fixed in order to avoid the

influence of inertia of the air.

The classical monofrequency FOT uses sinusoidal waves as oscillation signals. Recent apparatuses, such as MostGraph and IOS, use broad-frequency waves such as random noise and impulse wave, expanding the spectrum of 4-36 Hz (MostGraph) and 5-35 Hz (IOS), which enables one to measure the frequency properties of Rrs and Xrs in a short time. The available broad-frequency wave types are pyramidal wave (IOS), Hanning (MostGraph), and random noise (MostGraph). Pulse generation intervals are 0.2 sec (IOS) and 0.25 sec (MostGraph). A comparative study using phantom models found that the measured impedance values were confirmed to be closely consistent, but not identical, with more negative Xrs values in IOS than those in MostGraph (9).

In the sitting position with the neck in a comfortable neutral posture and wearing a nose clip, the subjects support their cheeks in order to eliminate upper airway shunting during the measurements. Cheek support by an operator, not the subject himself/herself, was found to result in different impedance values (lower Rrs and smaller Xrs) in patients with respiratory diseases, but not in healthy controls (10). The subjects are instructed to breathe quietly at a functional residual capacity level (tidal breathing) for approximately 30 seconds. In healthy subjects, slow breathing (0.7-fold respiratory rate) caused higher Rrs values, whereas greater tidal breathing (1.5-fold tidal volume) caused higher Rrs and greater (more negative) Xrs values (11). The time course of the lung volume should be monitored for at least 30 seconds. If the records other than normal spontaneous breathing, such as swallowing, glottis closure, leakage around the mouthpiece, incomplete sealing with the nose clip, irregular breathing, or acute hyperventilation, are found, the part or all of the measurements should be discarded. One of the criteria for the acceptability of breathing in the individual measurements is the coherence function, which is optionally reported in the apparatuses. The measurements should be repeated until three to five technically acceptable records are obtained. Taking these factors together, substantial attention should be paid to the measurements, albeit with easy tidal breathing.

Interpretation of the Measured Data

Rrs

Rrs indicates the total resistance of the respiratory system, including Raw, Rti, and chest wall resistance (Rcw). Since Raw is a major part of Rrs, Rrs is a sensitive parameter for Raw, and therefore, Rrs is frequently interpreted as an index of the airway caliber. In both IOS and MostGraph, the value of Rrs can be obtained at all oscillatory frequencies to be measured. Among those, Rrs at 5 Hz (R5) and 20 Hz (R20) are routinely used. Although both Rrs and the forced expiratory volume in 1 second (FEV₁) can be indices of airway obstruction, the FOT and spirometry are not the same mo-

dalities, and therefore, Rrs and FEV₁ are not necessarily identical or closely related. Indeed, in general, R5 only moderately correlates with FEV₁ in asthma and COPD (12, 13). R5 is higher in patients with COPD than in healthy controls, but not in those with asthma (12, 14).

To date, the usefulness of Rrs in airway hyperresponsiveness and bronchial reversibility tests has been frequently reported, but not satisfactorily established. In a study using an apparatus for the continuous methacholine inhalation method with simultaneous measurement of Rrs at 3 Hz (Astograph; Chest M.I.), FEV₁ was also measured at the baseline and immediately after a twofold increase of Rrs (15). In that study, the mean change in FEV₁ was -19.3%, suggesting a parallel change between FEV₁ and Rrs. If we apply this relationship to the airway reversibility tests, a 60% change in R5, presumed to be nearly equal to Rrs at 3 Hz, would correspond to a 12% change in FEV₁. Although the criteria to identify the Rrs response to bronchodilators in children are reported to be 20% to 40% (16), further studies are needed to establish those values in adults. We investigated the FOT parameters that would predict an improvement in patients with asthma in terms of FEV₁ after starting inhaled corticosteroid (ICS)/long-acting β_2 agonist (LABA) combination treatment in 31 untreated patients (17). In multivariate logistic regression analyses, more than 10% change in FEV₁ was independently predicted by R5 (adjusted odds ratio 15.9). The receiver operating characteristic (ROC) curve analyses also revealed that the area under the curve was higher for R5 (0.731) than for any other parameters. For the purpose of detecting a treatment effect or daily fluctuations, minimal clinically important differences in the FOT parameters should be established. R20 also correlates with FEV₁ in asthma, but more weakly than R5 (12, 13, 18). There was no correlation between R20 and delta N₂ in asthma (18), or between R20 and FEV₁ in COPD (12). There was no difference in R20 among patients with COPD, asthma, and healthy controls (12). In contrast to these, a study found that R20 had the most clinical significance, including the severity, impaired control, quality of life, and frequent exacerbation of the disease (19).

Frequency dependence of Rrs in patients with COPD was initially reported by Grimby and Takishima (20), which has been implicated as due to "non-uniform distribution of mechanical properties of the lungs to their overall mechanical behavior". To date, the difference from R5 to R20 (R5-R20) has been frequently used as a representative marker of the frequency dependence in the FOT. R5-R20 should be simply implicated as the extent of the frequency dependence. However, some researchers have interpreted R5-R20 as peripheral airway resistance because they consider R5 and R20 to reflect the total lung and central airway resistance, respectively (21, 22). With the exception of a few theoretical models of electric circuits, those hypotheses of R5-R20 as peripheral resistance do not have any physiological basis. Indeed, there is no statement in any official guidelines that supports this interpretation. The assumption of R5-R20 as

Table 1. Correlations between the Respiratory Impedance and Pulmonary Function Tests in 78 Patients with Asthma (Reference 18).

	%FEV ₁	FEV ₁ /FVC	%FEF25-75%	delta N ₂
R5 (cmH ₂ O/L/s)				
Whole-breath	-0.394*	-0.238*	-0.333*	0.247*
Inspiratory	-0.433*	-0.291*	-0.385*	0.251*
Expiratory	-0.368*	-0.201	-0.299*	0.258*
ΔR5	0.074	0.076	-0.005	-0.205
R20 (cmH ₂ O/L/s)				
Whole-breath	-0.268*	-0.115	-0.214	0.159
Inspiratory	-0.290*	-0.135	-0.229*	0.141
Expiratory	-0.240*	-0.083	-0.187	0.193
ΔR20	-0.053	0.139	0.042	-0.205
R5-R20 (cmH ₂ O/L/s)				
Whole-breath	-0.515*	-0.386*	-0.442*	0.284*
Inspiratory	-0.575*	-0.512*	-0.555*	0.367*
Expiratory	-0.447*	-0.285*	-0.352*	0.240*
Δ(R5-R20)	0.135	-0.034	0.042	-0.148
X5 (cmH ₂ O/L/s)				
Whole-breath	0.420*	0.339*	0.380*	-0.267*
Inspiratory	0.443*	0.355*	0.389*	-0.301*
Expiratory	0.413*	0.358*	0.391*	-0.274*
ΔX5	-0.139	-0.113	-0.106	0.082
Fres (Hz)				
Whole-breath	-0.478*	-0.388*	-0.421*	0.301*
Inspiratory	-0.503*	-0.435*	-0.456*	0.343*
Expiratory	-0.448*	-0.379*	-0.412*	0.288*
ΔFres	0.175	0.135	0.144	-0.116
ALX (cmH ₂ O/L/s x Hz)				
Whole-breath	-0.423*	-0.345*	-0.383*	0.259*
Inspiratory	-0.452*	-0.362*	-0.395*	0.306*
Expiratory	-0.414*	-0.358*	-0.390*	0.272*
ΔALX	0.088	0.065	0.067	-0.012

Values are the Spearman rank correlation coefficients.

ALX: low-frequency reactance area, Δ: difference between inspiratory and expiratory phases, FEF25-75%: forced expiratory flow between 25% and 75% of FVC, FEV₁: forced expiratory volume in 1 second, Fres: resonant frequency, FVC: forced vital capacity, R5 and R20: respiratory system resistance at 5 Hz and 20 Hz, respectively, R5-R20: the difference between R5 and R20, Xrs: respiratory system reactance, X5: Xrs at 5 Hz.

*p < 0.05.

peripheral resistance suggests that R5-R20 is always positive, but, in reality, R5-R20 is frequently negative. In addition, high R5-R20 values are physiologically detected in children mainly due to upper airway mechanics (23). In our study, R5-R20 and other pulmonary function values were investigated in 78 patients with asthma (18), and R5-R20, particularly inspiratory measurements, correlated with not only %FEV₁ but also the N₂ phase III slope of single-breath N₂ washout (delta N₂). We speculated that R5-R20 had a certain relationship with airway obstruction and ventilator unevenness (Table 1). Although it is clearly possible that patients with large R5-R20 have lesions at the peripheral airways as reported in patients with COPD (20), R5-R20 cannot be attributed to peripheral airway resistance.

Xrs

Xrs, presumed to reflect the summation of elastic and inertial properties, is the imaginary part of Zrs. In practical measurements, Xrs is frequency dependent. It is negative at a low frequency whereas positive at a high frequency. The point at which Xrs=0 is referred to as resonant frequency (Fres). Generally, more elastic properties are more negative Xrs whereas more inertial properties are more positive.

Therefore, elasticity and inertia balances each other at Fres. Fres and Xrs at 5 Hz (X5) is frequently used as a representative marker of Xrs. The low-frequency reactance area (ALX), which is the integral of X5 to the Fres, is also used. In patients with asthma, these three parameters were shown to significantly correlate with FEV₁ and delta N₂, suggesting that those three parameters are other markers of airway obstruction and ventilator unevenness (18) (Table 1). Although there are some differences in the details, the strongest correlation is generally found between Fres and FEV₁ in both asthma and COPD (12, 13, 18, 24). Interestingly, a previous study found hyperbolic relationships between Fres and FEV₁ in asthma (24). A linear relationship between a reciprocal Fres and FEV₁ was confirmed. In multiple regression analyses, we found that the delta N₂ was independently predicted by the forced vital capacity (FVC), Fres, and emphysema score (R²=0.57, p<0.0001) in 56 patients with COPD (25). However, it is not clear why Fres or other Xrs parameters have so significant relationships with the markers of airway obstruction or ventilatory unevenness.

The term expiratory flow limitation (EFL) is used to indicate that maximal expiratory flow is achieved during tidal breathing and it is characteristic of intrathoracic airway ob-

Table 2. Summary of the Measurements and Interpretation of FOT.

Measurements
<ul style="list-style-type: none"> ● Cheek support by an operator, not the subject himself/herself, results in lower Rrs and smaller Xrs in the patients. ● Slow breathing (0.7-fold respiratory rate) causes higher Rrs values, whereas greater tidal breathing (1.5-fold tidal volume) causes higher Rrs and greater (more negative) Xrs values.
Interpretation of the measured data
<ul style="list-style-type: none"> ● Compare the data between whole-breath, inspiratory, and expiratory phases, and the differences between the inspiratory and expiratory phases. ● Rrs, R5 in particular, reflects the airway caliber. ● R5-R20 is an indicator of the frequency dependence of Rrs, which is presumed to reflect ventilation inhomogeneity. ● X5, Fres, and ALX reflect an abnormality in lung parenchyma or airways. ● $\Delta X5$ reflects the expiratory flow limitation, a major determinant of dynamic hyperinflation and exercise limitation. ● Minimal clinically important differences have not yet been established. ● The FOT is not a surrogate test for spirometry, but should be used complementarily.
ALX: low-frequency reactance area, Δ : difference between the inspiratory and expiratory phases, FOT: forced oscillation technique, Fres: resonant frequency, Rrs: respiratory system resistance, R5 and R20: Rrs at 5 Hz and 20 Hz, respectively, R5-R20: the difference between R5 and R20, X5: Xrs at 5 Hz, Xrs: respiratory system reactance.

struction (26). This phenomenon is common in patients with severe COPD and a major determinant of dynamic hyperinflation and exercise limitation. Previous studies have indicated that $\Delta X5$ best reflects the EFL (27, 28), and $\Delta X5$ is referred to the EFL index. Dynamic airway narrowing during quiet breathing at rest has been visually detected in a patient with severe COPD by high-speed electron-beam computed tomography (26). The EFL index is useful for the differentiation between COPD and asthma (12, 14, 29). In multivariate regression analyses, a high EFL index (more than 0.55 cmH₂O/L/s measured with MostGraph) was independently predicted by the emphysema score, forced expiratory flow between 25% and 75% of FVC, functional residual capacity, and whole-breath R5 (30). Regarding the interpretation of Xrs, apparatus differences should be noted as we previously reported (9). In short, Xrs in IOS merely shifted to a negative direction compared to that in MostGraph, and, therefore, in IOS Xrs is more negative or less positive and Fres is higher than in MostGraph.

Taking these findings together, some FOT parameters are associated with spirometry. However, they are not identical. Therefore, the FOT is not a surrogate test for spirometry, but should be used complementarily. Table 2 shows a summary of the measurements and interpretation of the FOT.

Reference values

Reference values are available for the parameters of IOS in Japanese adults (31) and children (32), whereas the establishment of those for MostGraph is currently underway.

Asthma

There have been a number of studies comparing the effectiveness of ICS or ICS/LABA (33, 34). A recent study using IOS found that elderly patients with asthma showed higher

R5, Fres, and ALX, lower R5-R20, and more negative X5 than nonelderly patients (35). Although, in those reports, R5-R20 and Xrs parameters were implicated to reflect the small airway function, it should be implicated as the overall airway including central elements.

As another issue, the association of Zrs and eosinophilic airway inflammation has been studied. There is no correlation between fractional exhaled nitric oxide (FeNO) and Rrs or Xrs (18, 36). However, weak correlations were found between the alveolar nitric oxide concentration (CANO), a marker to reflect peripheral airway or alveolar inflammation, and whole-breath R5-R20, X5, and ALX using IOS (36, 37). We also investigated those relationships using MostGraph, and found significant correlations between CANO and $\Delta X5$, $\Delta Fres$, and ΔALX (18). Further studies are needed to establish those findings.

The difference in R5 and X5 between pre- and post-bronchodilator inhalation using MostGraph was significantly higher in asthmatic than in nonasthmatic children (23). The ROC curve analyses revealed that the difference in X5 (cut-off value: 0.46 cmH₂O/L/s) was the best predictor for FEV₁ reversibility. In another study using IOS in children, the ROC analysis showed that R5-R20 and ALX could discriminate controlled versus uncontrolled asthma, suggesting the usefulness of the FOT for assessing asthma control (38). An adult study using IOS also revealed that asthmatic patients showed higher R5-R20 and more negative X5 than subjects with asymptomatic bronchial hyperresponsiveness and healthy controls (39). On the other hand, a recent study using IOS found that R5-R20 was not associated with asthma severity, control, quality of life, or exacerbation, but R20 had clinical significance, suggesting the need for prospective longitudinal studies (19).

Concerning the quality of life in asthmatic patients, a study using IOS found that R20, X5, and dose of ICS, but

Table 3. Summary of the Practical Use of the FOT in Lung Diseases.

Asthma
<ul style="list-style-type: none">● Use FOT complementarily with spirometry.● Careful attention must be paid to both Rrs and Xrs.● Compare R5, a marker of the airway caliber, and Xrs with FEV₁.● The FOT may be useful in the bronchial reversibility test.● Do not use R5-R20, a marker of frequency dependence, alone.● No relationship to fractional exhaled nitric oxide exists.● The FOT parameters may improve despite no change in spirometry.
COPD
<ul style="list-style-type: none">● During measurements, the regular respiratory rate and tidal volume should be monitored.● The respiratory cycle and frequency dependence are more marked in COPD than in asthma.● Careful attention must be paid to both whole-breath and within-breath changes.● ΔX5 best reflects the expiratory flow limitation, a major determinant of dynamic hyperinflation and exercise limitation.● Compare FOT parameters with FVC, FEV₁, and inspiratory capacity.
Interstitial lung disease
<ul style="list-style-type: none">● A negative correlation between ΔX5 and VC or diffusing capacity when using IOS is often observed.● Inspiratory Fres best correlates with the FVC, FEV₁, diffusing capacity, and fibrosis score when using MostGraph.
Combined pulmonary fibrosis and emphysema
<ul style="list-style-type: none">● ΔX5 of MostGraph shows intermediate values between patients with COPD and those with interstitial pneumonia, suggesting that both emphysema and fibrosis affect the lung mechanics.
ALX: low-frequency reactance area, Δ: difference between the inspiratory and expiratory phases, FEV ₁ : forced expiratory volume in 1 second, FOT: forced oscillation technique, Fres: resonant frequency, FVC: forced vital capacity, Rrs: respiratory system resistance, R5 and R20: Rrs at 5 Hz and 20 Hz, respectively, R5-R20: the difference between R5 and R20, X5: Xrs at 5 Hz, Xrs: respiratory system reactance.

not FEV₁, significantly accounted for the Asthma Quality of Life Questionnaire in multiple regression analyses (40).

COPD

The 3D graphic images in MostGraph have an advantage to visualize not only frequency dependence but also respiratory cycle dependence (41-43). Since airway obstruction is more severe in the expiratory phase, Rrs becomes high and more frequency dependent and Xrs shifts to a more negative direction compared to in the inspiratory phase. These respiratory cycle dependence may be explained by the EFL (26), while frequency dependence has been implicated as an unevenness of the ventilation mechanics (44). However, it must be noted that the extent of both frequency and respiratory cycle dependence is not identical to the severity assessed by FEV₁. These phenomena are not always observed in severe patients (3, 45). Respiratory cycle dependence can also be indicated by variability in the FOT data. Especially in patients with COPD, it is greater during expiration than inspiration (43). In this context, the evaluation of drug effects, such as tiotropium may be more accurate during inspiration in patients with COPD (46).

An increased rate of tidal breathing (40 breaths/min) was shown to result in higher R5, R5-R20, and Fres, and more negative X5 in patients with COPD, but not in healthy controls (47). These changes reflect dynamic hyperinflation and are correlated with the severity of dyspnea.

Early detection of lung function changes in smokers is

important for the prevention of COPD. Approximately 60% of smokers showed higher Rrs and greater (more negative) Xrs, mainly in the expiratory phase, as observed in COPD patients (48). A case-control study of the lung function in the World Trade Center Health registry area residents and workers revealed that cases with persistent respiratory symptoms were more likely than control subjects to have elevated R5 and R5-R20 despite normal spirometry (49). These studies suggest the potential of the FOT.

A study using IOS found that R5-R20 alone, but not FEV₁, significantly accounted for the symptoms, impacts, and a total score of the St. George's Respiratory Questionnaire (SGRQ) in patients with COPD (50).

Interstitial lung disease (ILD)

A previous study using IOS showed the association between the presence of ILD and $\Delta X5$ in a multiple linear regression analysis, and a significant negative correlation between $\Delta X5$ and VC or diffusing capacity (51). In our study using MostGraph, however, inspiratory Fres best correlated with the FVC, FEV₁, diffusing capacity, and fibrosis score, but $\Delta X5$ showed no correlation (52). The discrepancy in the results of the studies may be attributed to different samples and FOT apparatuses. We confirmed that there was no difference in Fres between patients with ILD and those with mild to moderate COPD (53). However, Fres did not correlate with the emphysema score in patients with COPD. According to these findings, we speculated that Fres is a meas-

ure of increased lung elastic recoil resulting from fibrosis in ILD, suggesting that *Fres* is a marker of lung stiffness in ILD.

Combined pulmonary fibrosis and emphysema (CPFE)

R20 was significantly lower in patients with CPFE than in those with interstitial pneumonia (IP) or COPD, irrespective of the severity of airflow limitation (53). ΔX_5 in patients with CPFE was significantly higher than in those with IP and lower than in those with COPD, suggesting that both emphysema and fibrosis affect the lung mechanics in CPFE, leading to different findings from IP or COPD alone.

Table 3 shows a summary of the practical use of the FOT in lung diseases.

Conclusion

The clinical application of the FOT as a measurement of lung function has progressed with the spread of commercially available devices, and increasing numbers of studies have examined the usefulness of the FOT in the evaluation or management of not only obstructive but also restrictive lung diseases. One of current limitations is the lack of established normative values in different populations and comparability between different devices. Furthermore, data interpretation is often difficult without physiological understanding, which is why confused interpretation such as the assumption of R5-R20 as peripheral resistance has disseminated. The FOT is not a surrogate test for spirometry, but should be used complementarily. Finally, there is a need to update the international statement of the technical aspects and clinical use of the FOT.

Author's disclosure of potential Conflicts of Interest (COI).

Hajime Kurosawa: Patent royalties, Chest M.I.; Honoraria, Nippon Bohringer Ingelheim Co., Ltd., Novartis Co., Ltd.

References

- Oostveen E, Macleod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J* **22**: 1026-1041, 2003.
- Dubois AB, Brody AW, Lewis DH, Burgess BF Jr. Oscillation mechanics of lung and chest in man. *J Appl Physiol* **8**: 587-594, 1956.
- Kurosawa H. Broadband forced oscillation technique. *Saishin Igaku (The Medical Frontline)* **68**: 1104-1111, 2013 (in Japanese).
- Shirai T. MostGraph. *Bunshi Kokyukibyogaku (Respiratory Molecular Medicine)* **19**: 67-69, 2015 (in Japanese).
- Shirai T, Mori K, Mikamo M, et al. Usefulness of colored 3D imaging of respiratory impedance in asthma. *Allergy Asthma Immunol Res* **5**: 322-328, 2013.
- Matsuno O, Komori C, Hang Y, Matsumoto T, Minamoto S. Effectiveness of omalizumab in a patient with severe asthma, low serum IgE level, and lack of sensitized allergens induced by oral steroid therapy: the usefulness of impulse oscillation for assessment of omalizumab therapy. *J Asthma* **49**: 839-842, 2012.
- Shimizu Y, Kamiyoshihara M, Okajo J, Ishii Y, Takise A. Tracheobronchial stenosis evaluated by inspiratory and expiratory three-dimensional computed tomography and impulse oscillation with three-dimensional color imaging in a patient with relapsing polychondritis. *J Biol Regul Homeost Agents* **28**: 325-331, 2014.
- Ohishi J, Kurosawa H. Time lag between oscillatory pressure and flow affecting accuracy of forced oscillation technique. *Bio Med Eng* **10**: 65, 2011.
- Tanimura K, Hirai T, Sato S, et al. Comparison of two devices for respiratory impedance measurement using a forced oscillation technique: basic study using phantom models. *J Physiol Sci* **64**: 377-382, 2014.
- Uchida A, Ito S, Suki B, Matsubara H, Hasegawa Y. Influence of cheek support on respiratory impedance measured by forced oscillation technique. *Springplus* **2**: 342, 2013.
- Sano S, Goto M, Ono M, et al. A basic investigation of MostGraph-01. The 8th MostGraph clinical research meeting. Tokyo, August 9, 2014 (in Japanese).
- Mori K, Shirai T, Mikamo M, et al. Colored 3-dimensional analyses of respiratory resistance and reactance in COPD and asthma. *COPD* **8**: 456-463, 2011.
- Tsuburai T, Suzuki S, Tsurikisawa N, et al. Use of forced oscillation technique to detect airflow limitations in adult Japanese asthmatics. *Arerugi (Japanese Journal of Allergology)* **61**: 184-193, 2012 (in Japanese, Abstract in English).
- Kanda S, Fujimoto K, Komatsu Y, et al. Evaluation of respiratory impedance in asthma and COPD by an impulse oscillation system. *Intern Med* **49**: 23-30, 2010.
- Niimi A, Matsumoto H, Takemura M, Ueda T, Chin K, Mishima M. Relationship of airway wall thickness to airway sensitivity and airway reactivity in asthma. *Am J Respir Crit Care Med* **168**: 983-988, 2003.
- Beydon N, Davis SD, Lombardi E, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med* **175**: 1304-1345, 2007.
- Akamatsu T, Shimoda Y, Suzuki T, et al. Forced oscillation technique as a predictor of asthma control improvement after starting ICS/LABA treatment. *ATS meeting in Denver 2015*.
- Shirai T, Mori K, Mikamo M, et al. Respiratory mechanics and peripheral airway inflammation and dysfunction in asthma. *Clin Exp Allergy* **43**: 521-526, 2013.
- Gonem S, Natarajan S, Desai D, et al. Clinical significance of small airway obstruction markers in patients with asthma. *Clin Exp Allergy* **44**: 499-507, 2014.
- Grimby G, Takishima T, Graham W, Macklem P, Mead J. Frequency dependence of flow resistance in patients with obstructive lung disease. *J Clin Invest* **47**: 1455-1465, 1968.
- Shi Y, Aledia AS, Galant SP, George SC. Peripheral airway impairment measured by oscillometry predicts loss of asthma control in children. *J Allergy Clin Immunol* **131**: 718-723, 2013.
- Bickel S, Popler J, Lesnick B, Eid N. Impulse oscillometry. Interpretation and practical applications. *Chest* **146**: 841-847, 2014.
- Murakami K, Habukawa C, Kurosawa H, Takemura T. Evaluation of airway responsiveness using colored three-dimensional analyses of a new forced oscillation technique in controlled asthmatic and nonasthmatic children. *Respir Investig* **52**: 57-64, 2014.
- Shibasaka A, Kurosawa H, Tamura G. Evaluation of airway narrowing by MostGraph and spirometry. Examination using a reversibility test. *Arerugi (Japanese Journal of Allergology)* **62**: 566-573, 2013 (in Japanese, Abstract in English).
- Mikamo M, Shirai T, Mori K, et al. Predictors of phase III slope of nitrogen single-breath washout in COPD. *Respir Physiol Neurobiol* **189**: 42-46, 2013.
- Kurosawa H, Kohzuki M. Images in clinical medicine. Dynamic airway narrowing. *New Engl J Med* **350**: 1036, 2004.
- Dellacà RL, Santus P, Aliverti A, et al. Detection of expiratory flow limitation in COPD using the forced oscillation technique.

- Eur Respir J **23**: 232-240, 2004.
28. Koulouris NG, Hardavella G. Physiological techniques for detecting expiratory flow limitation during tidal breathing. *Eur Respir Rev* **20**: 147-155, 2011.
 29. Paredi P, Goldman M, Alamen A, et al. Comparison of inspiratory and expiratory resistance and reactance in patients with asthma and chronic obstructive pulmonary disease. *Thorax* **65**: 263-267, 2010.
 30. Mikamo M, Shirai T, Mori K, et al. Predictors of expiratory flow limitation measured by forced oscillation technique in COPD. *BMC Pulm Med* **14**: 23, 2013.
 31. Shiota S, Katoh M, Fujii M, Aoki S, Matsuoka R, Fukuchi Y. Predictive equations and the reliability of the impulse oscillatory system in Japanese adult subjects. *Respirology* **10**: 310-315, 2005.
 32. Hagiwara S, Mochizuki H, Muramatsu R, et al. Reference values for Japanese children's respiratory resistance using the LMS method. *Allergol Int* **63**: 113-119, 2014.
 33. Nakaji H, Petrova G, Matsumoto H, et al. Effects of 24-week add-on treatment with ciclesonide and montelukast on small airways inflammation in asthma. *Ann Allergy Asthma Immunol* **110**: 198-203, 2013.
 34. Hozawa S, Terada M, Hozawa M. Comparison of the effects of budesonide/formoterol maintenance and reliever therapy with fluticasone/salmeterol fixed-dose treatment on airway inflammation and small airway impairment in patients who need to step-up from inhaled corticosteroid monotherapy. *Pulm Pharmacol Ther* **27**: 190-196, 2014.
 35. Inoue H, Niimi A, Takeda T, et al. Pathophysiological characteristics of asthma in the elderly: a comprehensive study. *Ann Allergy Asthma Immunol* **113**: 527-533, 2014.
 36. Matsumoto H, Niimi A, Jinnai M, et al. Association of alveolar nitric oxide levels with pulmonary function and its reversibility in stable asthma. *Respiration* **81**: 311-317, 2011.
 37. Williamson PA, Clearie K, Menzies D, Vaidyanathan S, Lipworth BJ. Assessment of small-airways disease using alveolar nitric oxide and impulse oscillometry in asthma and COPD. *Lung* **189**: 121-129, 2011.
 38. Shi Y, Aledia AS, Tatavoosian AV, Vijayalakshmi S, Galant SP, George SC. Relating small airways to asthma control by using impulse oscillometry in children. *J Allergy Clin Immunol* **129**: 671-678, 2012.
 39. Boudewijn IM, Telenga ED, van der Wiel E, et al. Less small airway dysfunction in asymptomatic bronchial hyperresponsiveness than in asthma. *Allergy* **68**: 1419-1426, 2013.
 40. Takeda T, Oga T, Niimi A, et al. Relationship between small airway function and health status, dyspnea and disease control in asthma. *Respiration* **80**: 120-126, 2010.
 41. Kurosawa H, Ohishi J, Shimizu Y, et al. A new method to assess lung volume dependency of respiratory system resistance using forced oscillation. *Am J Respir Crit Care Med* **181**: A1240, 2010.
 42. Ohishi J, Kurosawa H, Ogawa H, et al. Application of impulse oscillometry for within-breath analysis in patients with chronic obstructive pulmonary disease: pilot study. *BMJ Open* **1**: e000184, 2011.
 43. Yamauchi Y, Kohyama T, Jo T, Nagase T. Dynamic change in respiratory resistance during inspiratory and expiratory phases of tidal breathing in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* **7**: 259-269, 2012.
 44. Dellacà RL, Pompilio PP, Walker PP, et al. Effect of bronchodilation on expiratory flow limitation and resting lung mechanics in COPD. *Eur Respir J* **33**: 1329-1337, 2009.
 45. Di Mango AM, Lopes AJ, Jansen JK, Melo PL. Changes in respiratory mechanics with increasing degrees of airway obstruction in COPD: detection by forced oscillation technique. *Respir Med* **100**: 399-410, 2006.
 46. Kubota M, Shirai G, Nakamori T, Kokubo K, Masuda N, Kobayashi H. Low frequency oscillometry parameters in COPD patients are less variable during inspiration than during expiration. *Respir Physiol Neurobiol* **166**: 73-79, 2009.
 47. Nakagawa M, Hattori N, Haruta Y, et al. Effect of increasing respiratory rate on airway resistance and reactance in COPD patients. *Respirology* **20**: 87-94, 2015.
 48. Shinke H, Yamamoto M, Hazeki N, Kotani Y, Kobayashi K, Nishimura Y. Visualized changes in respiratory resistance and reactance along a time axis in smokers: a cross-sectional study. *Respir Investig* **51**: 166-174, 2013.
 49. Friedman SM, Maslow CB, Reibman J, et al. Case-control study of lung function in World Trade Center Health Registry area residents and workers. *Am J Respir Crit Care Med* **184**: 582-589, 2011.
 50. Haruna A, Oga T, Muro S, et al. Relationship between peripheral airway function and patient-reported outcomes in COPD: a cross-sectional study. *BMC Pulm Med* **10**: 10, 2010.
 51. Sugiyama A, Hattori N, Haruta Y, et al. Characteristics of interstitial and expiratory reactance in interstitial lung disease. *Respir Med* **107**: 875-882, 2013.
 52. Fujii M, Shirai T, Mori K, et al. Inspiratory resonant frequency of forced oscillation technique as a predictor of the composite physiologic index in interstitial lung disease. *Respir Physiol Neurobiol* **207**: 22-27, 2015.
 53. Mori K, Shirai T, Mikamo M, et al. Respiratory mechanics measured by forced oscillation technique in combined pulmonary fibrosis and emphysema. *Respir Physiol Neurobiol* **185**: 235-240, 2013.