What can we learn about COPD from impulse oscillometry?

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***Highlights (for review)**

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- Impulse oscillometry (IOS) is the most commonly used forced oscillation technique
- Relatively little is known about its application in COPD
- lung resistance (R) and reactance (X) reflect airway geometry and compliance
- IOS indices relate to disease severity, bronchodilatation and bronchoconstriction
- Trials are required for the predictive value of IOS in relation to COPD exacerbations

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Future studies may be directed to assess if IOS in combination with spirometry is more sensitive at predicting future exacerbations. Perhaps AX might also be useful as a screening tool in early stage disease or to monitor long term decline in COPD.

Abbreviations:

AX: Area Under reactance curve between 5Hz and resonant frequency
COPD: Chronic obstructive pulmonary disease
FEF25-75: Forced expiratory flow between 25 and 75%
FEV1: Forced expiratory volume in 1 second
FVC: Forced vital capacity
FOT: Forced oscillation technique
Fres: Resonant Frequency
GOLD: Global Initiative for Chronic Obstructive Lung Disease
HRCT: High resolution CT scanning
IOS: Impulse oscillometry
R: Resistance
R5: Resistance at 5Hz
R20: Resistance at 20Hz
R5-R20: Heterogeneity of resistance
SRM: Standardised response mean
X: Reactance
X5: Reactance at 5Hz
Z: Impedance

Background:

Current COPD guidelines advocate using spirometry to assess airflow limitation in conjunction with symptoms and exacerbation history [1]. Spirometry involves a forced expiratory manoeuvre to measure dynamic lung volumes and expiratory flow. It has no comparable manoeuvre in real life, and hence is an artificial action. Cooperation may be difficult especially in patients who are breathless or susceptible to coughing. The forced expiratory flow between 25 and 75% (FEF25-75) of forced vital capacity (FVC) is thought to represent dynamic volume dependent small airway closure, but has marked inherent variability. Hence there is an unmet need for an alternative more patient friendly method to assess lung function in patients with COPD.
The forced mono-frequency oscillation technique (FOT) was first described in 1956 by Dubois [2] . Since then several FOT methods have been developed of which impulse oscillometry (IOS) is most commonly used in every day clinical practice. The application of IOS has been extensively described in asthma [3] .The purpose of this article is to critically appraise the potential role of IOS in COPD, where much less is known. It will focus on the more clinical applications of IOS, as this appertains to the general pulmonologist. This review will therefore not detail the physics of IOS or other FOT methods which have been covered elsewhere [4-6].

Basic principles of impulse oscillometry:

The currently used method of IOS was originally detailed in 1976 by Michaelson [7] and was then commercialised in 1998 [8] , available as the Jaeger Masterscreen IOS (Hoechberg ,Germany) .It has been widely adopted in paediatric pulmonology, but less so for adults ,aside as a research tool . IOS propagates a train of bi-directional, harmonic sound waves along the bronchial tree, from a source such as a loudspeaker. The oscillations are applied at a fixed square wave frequency of 5Hz, from which all other frequencies of interest are derived, typically multiples of 5Hz (between 5 and 35Hz) [9], each impulse lasting between 30 to 40ms . Measurements are made via a conducting tube to a mouthpiece with the cheeks held to obviate upper airway shunting. Forced oscillations are superimposed on top of tidal breathing to assess the frequency (Hz) dependence of the pressure/flow (as kPa/L/s or cmH_2O/L/s) relationship of respiratory impedance (Z), as in phase resistance (R) and out of phase reactance (X) components. A transducer attached to a pneumotachograph measures inspiratory and expiratory flow and pressure with

signal filtering used to separate breathing patterns from pressure and flow. It is performed using normal tidal breathing over a period of around 30 to 40s, and being effort independent is more physiological than spirometry. Conventionally the mean of whole breath values are used rather than separate inspiratory and expiratory moieties. As in spirometry three technically acceptable IOS manoeuvres are used.

In essence, IOS can be considered as bronchial sonar. Higher frequency waves travel shorter distances typically reflecting larger airways. Thus the resistance at 20Hz (R20) represents proximal resistance. Lower frequency waves travel further reaching the smaller airways <2mm in diameter after the eighth generation .Hence the resistance at 5Hz (R5) represents the total lung resistance. COPD and asthma will increase total resistance (R5) to a relatively greater degree than proximal resistance (R20). This is known as a frequency dependent change or heterogeneity of resistance evident as raised peripheral resistance (R5-R20). Nonetheless further validation is required to characterise heterogeneity of resistance and its relationship to the calibre of small and large airways.

Reactance can be considered as the out of phase component of respiratory impedance (with flow, but not volume), reflecting the balance between inertial and elastic properties of distensible airways. Typically this is measured at 5Hz (X5) or as the area under the reactance curve (AX) between 5Hz and the resonant frequency (RF),the latter representing the point at which opposing inertial and capacitive components cancel each other out . Conventionally AX is reported as a positive value for the area under the curve, even though in reality reactance per se becomes more negative (figure). AX represents low frequency reactance in smaller airways where elastance exceeds inertance, with increased values reflecting reduced lung compliance and stiffer lungs (Table). In asthma resistance and reactance tend to change in proportionate fashion, while in COPD reactance usually alters to a relatively greater degree than resistance.

IOS therefore provides more detailed information than spirometry on regional lung function and should be considered as being complementary to spirometry to comprehensively assess lung function in COPD. For example in patients with persistent asthma who had a preserved FEV1, the combined use of R5-R20 with FEF25-75 results in more predictive of impaired long term asthma control than either parameter used alone [10]. Although there are no defined reference values for COPD, we would propose pragmatic IOS cut offs for R5 > 0.5 kPa/L/s (>5.1 cmH_2O/L/s), R5-20 > 0.10 kPa/L/s (1.02 cmH_2O/L/s), AX > 1.0 kPa/L (>10.2cmH_2O/L) as being abnormal [11, 12]. Further cohort based studies are required to define proper reference values for COPD and asthma.

Relationship of IOS to disease severity:

The largest database involving IOS was the ECLIPSE cohort comprising 2054 patients with COPD (GOLD stage 2-4) and 233 healthy controls , in whom high resolution CT scanning (HRCT) was also performed [11]. R20 values were similar across GOLD stages 2-4 (0.29, 0.31, 0.31 kPa/L/s), but higher than controls (0.26 kPa/L/s). In contrast R5-R20 increased proportionately from GOLD stage 2 -4 (0.15, 0.20, 0.24 kPa/L/s), compared to controls (0.07kPa/L/s) .This in turn suggests that smaller rather than larger airways are the main determinant of increased lung resistance.

For AX there were increasing values across GOLD stages 2-4 (1.37, 2.25, 3.23 kPa/L) which were also higher than controls (0.38 kPa/L) along with a similar pattern for X5. Comparing GOLD 2 versus 4, equated to a 136% difference in AX and 60% in R5-20. Hence increased reactance (i.e. reduced compliance) predominates over increased resistance in relation to increasing COPD severity. There was a poor degree of correlation between R5-R20 or AX and HRCT low attenuation, inferring that the degree of emphysema is not closely related to either resistance or compliance.

In a cohort of 215 patients GOLD stages 1-4 ,values for AX (0.66 ,1.43 ,2.07, 2.5 kPa/L) mirrored the ratio of residual volume to total lung capacity (RV/TLC) (45.7,51.2,58.1,66.0 %) ,inferring the degree of air trapping is related to reduced lung compliance [12]. Studies have also shown a relationship between increasing AX and exacerbation frequency in COPD [11, 12]. A cross sectional evaluation of 94 COPD patients with moderate COPD revealed the strongest relationships for X5 in relation to FEV1 and specific airway conductance [13]. Multiple regression analysis of 75 patients with moderate COPD found that R5-R20 and X5 but not R20 were more closely related to health status and symptoms than either FEV1 or HRCT low attenuation [14] .In a screening study to detect early COPD , among 124 subjects who had positive spirometry criteria ,the presence of self reported symptoms was associated with higher values of R5-R20 ,X5 and AX [15].

A comparison of 36 asthma patients ,24 COPD patients and 24 healthy subjects showed values for R5-R20 and X5 in severe asthma were 0.13 kPa/L/s and -0.18 kPa/L/s respectively ; in moderate COPD 0.22 kPa/L/s and X5 -0.27 kPa/L ; and in controls 0.01 kPa/L/s and -0.12 kPa/L/s [16]. Thus, patients with COPD have a relatively higher level of peripheral airway dysfunction compared to those with

asthma in respect of both resistance and reactance. This is in keeping with pathological and radiological changes seen in small airways associated with disease progression in COPD [17, 18] .

Bronchodilator response and IOS:

Significantly greater changes were observed for R5 and RF, but not R20 or X5, when comparing responses to tiotropium 18ug and salmeterol 100ug in 32 patients with moderate COPD [19] . A trial in 16 patients with moderate COPD evaluated the effects of 4 weeks with open label tiotropium alone or with the addition of tulobuterol . Tiotropium alone produced significant improvements versus baseline in AX, R5 and R5-20, both drugs were better than tiotropium ,while R20 was unchanged [20] . For example with both drugs there were 56% ,46% and 38% changes in AX ,X5 and R5-R20 respectively, as compared to a 16% change in FEV1.
In an open label study 20 patients with moderate COPD received either tiotropium or glycopyrronium/indacaterol with IOS measured at baseline and 52 weeks [21] . Compared to baseline there were significant changes in R5, X5 but not R20 with glycopyrronium /indacaterol, while tiotropium afforded no improvements.
A double blind randomised cross-over trial involved 19 patients with severe COPD who received tiotropium or placebo for 2 weeks as add on to budesonide/formoterol combination taken during the preceding 4 weeks[22] . Compared to placebo the first but not last dose of tiotropium as triple therapy conferred significant improvements in X5, AX and RF, but not R5 or R20. Specific airways resistance but not RV/TLC also improved after single but not chronic dosing with tiotropium.
Taken together these data suggest that muscarinic and beta-2 receptors located in small airways (R5-R20, X5, AX) are relatively more important than large airways (R20) for mediating bronchodilator responses in COPD. Alternatively one might speculate that large airways disease per se is less important than small airway disease in COPD. Moreover increased lung compliance (as reduced AX values) in response to bronchodilators may reflect lung deflation, perhaps allowing the patient to breathe at a better mechanical advantage at a lower RV.

Bronchoconstrictor response with IOS:

Methacholine challenge was performed in 10 asthma and 25 moderate to severe COPD patients to achieve a 20% fall in FEV1. In asthma there was concordance between effects on resistance and reactance ,as a significant fall in X5 along with a

significant rise in R5 , while in COPD there was discordance in terms of a significant change in X5 but not R5 [23] .

12 moderate to severe COPD patients receiving beclometasone/formoterol combination at baseline were given the non selective beta-blocker carvedilol ,followed by formoterol withdrawal while continuing on carvedilol and belcometasone [24]. Compared to baseline, carvedilol produced a 1% change in R20, 21% in R5, 59% in X5, and 135% in AX. After formoterol cessation, only AX was associated with a further significant change amounting to a 210% increase from baseline. Hence large airways are not involved in beta-2 receptor mediated effects since R20 did not significantly alter in response to either addition of beta-2 antagonist or removal of beta-2 agonist. Furthermore the signal to noise ratio for bronchoconstriction with IOS was calculated as the standardised response mean, which is the ratio of the mean divided by the standard deviation, with a value of ≥0.8 indicating a sensitive test. The highest value was observed with AX at 1.74 versus R5 at 0.72, as compared to a value of 2.08 for FEV1. Thus measuring peripheral lung compliance as AX might be useful at detecting subtle changes in lung function in COPD, perhaps as a screening tool in early stage disease or to monitor long term decline. Nonetheless we would advocate that IOS should be used in conjunction with spirometry in order to make a comprehensive assessment of a given patient.

Future directions for IOS research:

There are fundamental gaps in the literature which warrant further investigation. Large prospective data sets are required to look at the possible predictive value of IOS for future moderate to severe exacerbations in high risk patients in GOLD groups C/D. Such studies should evaluate if lung stiffness (as AX) is more predictive than FEV1 or FVC.

Given the apparent lack of involvement of large airways (as R20) in mediating bronchodilator responses in COPD, it would seem logical to perform randomised controlled trials to investigate the impact of extra fine particle (ie<2um) inhaler formulations to see if putative improvements in small airway indices such as AX and R5-R20 might translate into superior longer term reductions in exacerbations, as compared to larger particle formulations.

Since there is a relatively poor signal with spirometry in COPD, IOS might prove to be more sensitive at detecting subtle differences in response to either bronchodilator or anti-inflammatory therapy, in order to explain commensurate reductions in exacerbations, improved symptoms and health status.

It also remains to be seen if IOS might be more suitable than spirometry for detecting early stage lung damage in COPD. Reference values and minimal important differences for IOS in COPD are required for use in clinical practice and interventional trials.

We believe the so called airway oscillometry (AOS) Tremoflo system (Thorasys, Montreal ,Canada) which uses a novel vibrating mesh, may fulfil the requirement for a more portable less expensive user friendly device. In turn this may make it more widely adopted in everyday clinical practice among adult pulmonologists.

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Figure Legend:

67 year old female, ex-smoker; COPD; BMI 23, FEV1 0.56L (31% predicted). IOS values are as follows: Resistance at 5Hz (R5) 0.85 kPa/l/s; Resistance at 20Hz (R20) 0.47 kPa/l/s; Heterogeneity of resistance between 5 and 20Hz (R5-R20) 0.38 kPa/l/s; Reactance at 5Hz (X5) -1.00 kPa/l/s; Area under the curve reactance (AX) 11.71 kPa/l; Resonant frequency (Fres).

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pneumotachograph measures inspiratory and expiratory flow and pressure with signal filtering used to separate breathing patterns from pressure and flow. It is performed using normal tidal breathing over a period of around 30 to 40s, and being effort independent is more physiological than spirometry. Conventionally the mean of whole breath values are used rather than separate inspiratory and expiratory moieties. As in spirometry three technically acceptable IOS manoeuvres are used.

In essence, IOS can be considered as bronchial sonar. Higher frequency waves travel shorter distances typically reflecting larger airways. Thus the resistance at 20Hz (R20) represents proximal resistance. Lower frequency waves travel further reaching the smaller airways <2mm in diameter after the eighth generation .Hence the resistance at 5Hz (R5) represents the total lung resistance. COPD and asthma will increase total resistance (R5) to a relatively greater degree than proximal resistance (R20). This is known as a frequency dependent change or heterogeneity of resistance evident as raised peripheral resistance (R5-R20). Nonetheless further validation is required to characterise heterogeneity of resistance and its relationship to the calibre of small and large airways.

Reactance can be considered as the out of phase component of respiratory impedance (with flow, but not volume), reflecting the balance between inertial and elastic properties of distensible airways. Typically this is measured at 5Hz (X5) or as the area under the reactance curve (AX) between 5Hz and the resonant frequency (RF),the latter representing the point at which opposing inertial and capacitive components cancel each other out . Conventionally AX is reported as a positive value for the area under the curve, even though in reality reactance per se becomes more negative (figure). AX represents low frequency reactance in smaller airways where elastance exceeds inertance, with increased values reflecting reduced lung compliance and stiffer lungs (Table). In asthma resistance and reactance tend to change in proportionate fashion, while in COPD reactance usually alters to a relatively greater degree than resistance.

IOS therefore provides more detailed information than spirometry on regional lung function and should be considered as being complementary to spirometry to comprehensively assess lung function in COPD. For example in patients with persistent asthma who had a preserved FEV1, the combined use of R5-R20 with FEF25-75 results in more predictive of impaired long term asthma control than either parameter used alone [10]. Although there are no defined reference values for COPD, we would propose pragmatic IOS cut offs for R5 > 0.5 kPa/L/s (>5.1 $cmH_2O/L/s$), R5-20 > 0.10 kPa/L/s (1.02 $cmH_2O/L/s$), AX > 1.0 kPa/L

(>10.2cmH_2O/L) as being abnormal [11, 12]. Further cohort based studies are required to define proper reference values for COPD and asthma.

Relationship of IOS to disease severity:

The largest database involving IOS was the ECLIPSE cohort comprising 2054 patients with COPD (GOLD stage 2-4) and 233 healthy controls , in whom high resolution CT scanning (HRCT) was also performed [11]. R20 values were similar across GOLD stages 2-4 (0.29, 0.31, 0.31 kPa/L/s), but higher than controls (0.26 kPa/L/s). In contrast R5-R20 increased proportionately from GOLD stage 2 -4 (0.15, 0.20, 0.24 kPa/L/s), compared to controls (0.07kPa/L/s) .This in turn suggests that smaller rather than larger airways are the main determinant of increased lung resistance.

For AX there were increasing values across GOLD stages 2-4 (1.37, 2.25, 3.23 kPa/L) which were also higher than controls (0.38 kPa/L) along with a similar pattern for X5. Comparing GOLD 2 versus 4, equated to a 136% difference in AX and 60% in R5-20. Hence increased reactance (i.e. reduced compliance) predominates over increased resistance in relation to increasing COPD severity. There was a poor degree of correlation between R5-R20 or AX and HRCT low attenuation, inferring that the degree of emphysema is not closely related to either resistance or compliance.

In a cohort of 215 patients GOLD stages 1-4 ,values for AX (0.66 ,1.43 ,2.07, 2.5 kPa/L) mirrored the ratio of residual volume to total lung capacity (RV/TLC) (45.7,51.2,58.1,66.0 %) ,inferring the degree of air trapping is related to reduced lung compliance [12]. Studies have also shown a relationship between increasing AX and exacerbation frequency in COPD [11, 12]. A cross sectional evaluation of 94 COPD patients with moderate COPD revealed the strongest relationships for X5 in relation to FEV1 and specific airway conductance [13]. Multiple regression analysis of 75 patients with moderate COPD found that R5-R20 and X5 but not R20 were more closely related to health status and symptoms than either FEV1 or HRCT low attenuation [14] .In a screening study to detect early COPD , among 124 subjects who had positive spirometry criteria ,the presence of self reported symptoms was associated with higher values of R5-R20 ,X5 and AX [15].

A comparison of 36 asthma patients ,24 COPD patients and 24 healthy subjects showed values for R5-R20 and X5 in severe asthma were 0.13 kPa/L/s and -0.18 kPa/L/s respectively ; in moderate COPD 0.22 kPa/L/s and X5 -0.27 kPa/L ; and in

controls 0.01 kPa/L/s and -0.12 kPa/L/s [16]. Thus, patients with COPD have a relatively higher level of peripheral airway dysfunction compared to those with asthma in respect of both resistance and reactance. This is in keeping with pathological and radiological changes seen in small airways associated with disease progression in COPD [17, 18] .

Bronchodilator response and IOS:

Significantly greater changes were observed for R5 and RF, but not R20 or X5, when comparing responses to tiotropium 18ug and salmeterol 100ug in 32 patients with moderate COPD [19] . A trial in 16 patients with moderate COPD evaluated the effects of 4 weeks with open label tiotropium alone or with the addition of tulobuterol . Tiotropium alone produced significant improvements versus baseline in AX, R5 and R5-20, both drugs were better than tiotropium ,while R20 was unchanged [20] . For example with both drugs there were 56% ,46% and 38% changes in AX ,X5 and R5-R20 respectively, as compared to a 16% change in FEV1.

In an open label study 20 patients with moderate COPD received either tiotropium or glycopyrronium/indacaterol with IOS measured at baseline and 52 weeks [21] . Compared to baseline there were significant changes in R5, X5 but not R20 with glycopyrronium /indacaterol, while tiotropium afforded no improvements.

A double blind randomised cross-over trial involved 19 patients with severe COPD who received tiotropium or placebo for 2 weeks as add on to budesonide/formoterol combination taken during the preceding 4 weeks[22] . Compared to placebo the first but not last dose of tiotropium as triple therapy conferred significant improvements in X5, AX and RF, but not R5 or R20. Specific airways resistance but not RV/TLC also improved after single but not chronic dosing with tiotropium.

Taken together these data suggest that muscarinic and beta-2 receptors located in small airways (R5-R20, X5, AX) are relatively more important than large airways (R20) for mediating bronchodilator responses in COPD. Alternatively one might speculate that large airways disease per se is less important than small airway disease in COPD. Moreover increased lung compliance (as reduced AX values) in response to bronchodilators may reflect lung deflation, perhaps allowing the patient to breathe at a better mechanical advantage at a lower RV.

Bronchoconstrictor response with IOS:

Methacholine challenge was performed in 10 asthma and 25 moderate to severe COPD patients to achieve a 20% fall in FEV1. In asthma there was concordance between effects on resistance and reactance ,as a significant fall in X5 along with a significant rise in R5 , while in COPD there was discordance in terms of a significant change in X5 but not R5 [23] .

12 moderate to severe COPD patients receiving beclometasone/formoterol combination at baseline were given the non selective beta-blocker carvedilol ,followed by formoterol withdrawal while continuing on carvedilol and belcometasone [24]. Compared to baseline, carvedilol produced a 1% change in R20, 21% in R5, 59% in X5, and 135% in AX. After formoterol cessation, only AX was associated with a further significant change amounting to a 210% increase from baseline. Hence large airways are not involved in beta-2 receptor mediated effects since R20 did not significantly alter in response to either addition of beta-2 antagonist or removal of beta-2 agonist. Furthermore the ~~best~~ signal to noise ratio for bronchoconstriction with IOS was calculated ~~expressed~~ as the ~~highest~~ standardised response mean, which is the ratio of the mean divided by the standard deviation, with a value of ≥0.8 indicating a sensitive test. The highest value was observed with AX at 1.74 versus R5 at 0.72, as compared to a value of 2.08 for FEV1. Thus measuring peripheral lung compliance as AX might be useful at detecting subtle changes in lung function in COPD, perhaps as a screening tool in early stage disease or to monitor long term decline. Nonetheless we would advocate that IOS should be used in conjunction with spirometry in order to make a comprehensive assessment of a given patient.

Future directions for IOS research:

There are fundamental gaps in the literature which warrant further investigation. Large prospective data sets are required to look at the possible predictive value of IOS for future moderate to severe exacerbations in high risk patients in GOLD groups C/D. Such studies should evaluate if lung stiffness (as AX) is more predictive than FEV1 or FVC.

Given the apparent lack of involvement of large airways (as R20) in mediating bronchodilator responses in COPD, it would seem logical to perform randomised controlled trials to investigate the impact of extra fine particle (ie<2um) inhaler formulations to see if putative improvements in small airway indices such as AX and R5-R20 might translate into superior longer term reductions in exacerbations, as compared to larger particle formulations.

Since there is a relatively poor signal with spirometry in COPD, IOS might prove to be more sensitive at detecting subtle differences in response to either bronchodilator or anti-inflammatory therapy, in order to explain commensurate reductions in exacerbations, improved symptoms and health status.

It also remains to be seen if IOS might be more suitable than spirometry for detecting early stage lung damage in COPD. Reference values and minimal important differences for IOS in COPD are required for use in clinical practice and interventional trials.

We believe the so called airway oscillometry (AOS) Tremoflo system (Thorasys, Montreal ,Canada) which uses a novel vibrating mesh, may fulfil the requirement for a more portable less expensive user friendly device. In turn this may make it more widely adopted in everyday clinical practice among adult pulmonologists.

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Figure Legend:

67 year old female, ex-smoker; COPD; BMI 23, FEV1 0.56L (31% predicted). IOS values are as follows: Resistance at 5Hz (R5) 0.85 kPa/l/s; Resistance at 20Hz (R20) 0.47 kPa/l/s; Heterogeneity of resistance between 5 and 20Hz (R5-R20) 0.38 kPa/l/s; Reactance at 5Hz (X5) -1.00 kPa/l/s; Area under the curve reactance (AX) 11.71 kPa/l; Resonant frequency (Fres).

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Table.

Comparison of spirometry and IOS in COPD

	Spirometry	IOS
Outputs	FEV1,FVC ,FEF25-75	R5, R20, X5, AX, RF
Signal to noise ratio	+	+
Patient friendly	-	+
Breathing pattern	Forced expiratory	Tidal
Reference values for COPD	+	-
Large/small airways	+/-	+
Cost	+	-
Portability	+	-
FDA approved	+	+

FEV1 :forced expiratory volume in 1s ,FVC :forced vital capacity ,FEF25-75:forced expiratory flow between 25 and 75% of FVC , R5 :resistance at 5Hz ,resistance at 20Hz ,X5 :reactance at 5Hz ,AX :area under reactance curve , RF :resonant frequency .Both methods should be used in complimentary fashion to fully assess lung function .

Figure

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