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Review Article

Forced Oscillations in Applied Respiratory Physiology: Clinical Applications

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Abstract

In the present study, a review of the literature that examines the widely used clinical applications of Forced Oscillation Technique (FOT) and Impulse Oscillometry (IOS) is attempted, in order to evaluate the contribution of the method to laboratory lung function testing. The typical modifications of respiratory impedance components and their diagnostic value are pointed out, as well as the parameters of optimal validity towards pathophysiology survey, but also the evaluation of effectiveness of treatment, for chronic obstructive pulmonary disease and bronchial asthma, in stable disease and exacerbations. Moreover, the current data to evaluate upper intrathoracic and extrathoracic airways obstruction is presented, but also to evaluate the state of diseases with restrictive and mixed (obstructive/restrictive) pathophysiology. Finally, there is an individual report about the correlation between the frequency and the intensity of abnormal oscillometric indices and common signs and symptoms of patients suffering from above diseases, but also the correlation between these indices and established values of spirometry and body-plythesmography. In this review, studies on pediatric populations are not included and all the data referred to, concern adult patients.

ABBREVIATIONS

COPD: Chronic obstructive pulmonary disease; FOT: Forced Oscillation Technique; IOS: Impulse Oscillometry

INTRODUCTION

Current evaluation and staging of respiratory diseases is based on conventional lung function tests, mainly spirometry and flow-volume curve. Primary element of those techniques, are some forced maneuvers, expressing the maximum volume and flow limits of breathing. Correspondence, however, between clinical and laboratory parameters of quiet breathing (dyspnea, gas exchange, arterial blood gases), and spirometric indices (FEV_1, FVC, PEF) has been seriously questioned by numerous studies [1-16]. For this reason, quiet breathing of the patients is not at all approached in conventional lung function testing.

Oscillometry (FOT and IOS), is sufficient to imprint with significant sensitivity almost the total number of parameters of respiratory mechanics during quiet breathing. At the same time, quiet breathing itself reinforces reliability of the measurements, as airways smooth muscles tone is not influenced by forced inspiratory maneuvers, and additionally, makes the testing easy to apply even in population groups which are impossible, for age or underlying pathology reasons, to perform efficiently the classical lung function tests. Finally, through respiratory physiology parameters evaluated by oscillometry, new, fine pathophysiological components of respiratory diseases emerge which, until today, are not taken under consideration in daily clinical practice.

Based on the above, presenting a review of the most principal clinical applications of Forced Oscillation Technique and Impulse Oscillometry is considered important, since it is here to evaluate the possibility of actual substantial contribution of the technique in lung function testing.

BRIEF REVIEW OF THE THEORETICAL PRINCIPLES

Three fundamental parameters have been classically used in respiratory physiology, in order to express respiratory system

motion throughout the respiratory cycle: volume (V), flow (V'), which is the first derivative of volume (V'=dV/dt), and acceleration (V''), which is the second derivative of volume ($V''=d^2V/dt^2$). Each of those parameters change throughout the respiratory cycle requires an amount of applied Pressure (P). Each pressure component, required for volume, flow and acceleration change, is determined by three coefficients respectively: respiratory system elastance (E_{rs}, which is the reciprocal of the respiratory system compliance-C_{rs}), respiratory system resistance (R_{rs}) and respiratory system inertial coefficient (I_{rs}). Thus, three pressure components emerge: elastic pressure: $P_{el}=E_{rs}V$, resistive pressure: $P_{res}=R_{rs}V'$ and inertial pressure $P_{in}=I_{rs}V''$. Contribution of each of the above parameters in the respiratory system motion, is expressed with Rohrer's respiratory system equation of motion: $\mathbf{P_{appl} = P_{el}+P_{res}+P_{in} = E_{rs}V+R_{rs}\ V'+I_{rs}V''}$ [17-20](equation 1), where P_{appl}, is the minimum required pressure, necessary for the respiratory system motion [20].

The conceptual core of Forced Oscillation Technique (FOT), is the application of pressure waves, which basically are pressure changes (positive and negative), on the opening of the airways, which are canalized to the respiratory tract of the subject during quiet breathing, forcing all the anatomic structures of the respiratory system to oscillatory motion, resulting in flow production. Each moment of the respiratory system oscillatory motion, elastic recoil forces, respiratory system resistance and inertial forces are surmounted, as it can be mathematically described by equation 1. Applied pressure can have either sinusoidal form with specific frequency [21] or multifrequency pressure waves in the form of Pseudorandom Noise Waveforms (PRN) [22], can be applied. The latest product of research in forced oscillations application on human respiratory system is Impulse Oscillometry (IOS) [23], where triangle shaped waveforms of 30-40 msec. duration (pressure pulses) are produced by an impulse generator.

Time functions of applied pressure and resulting flow, which can be mathematically expressed by equation $\mathbf{P_{appl}(t)= E_{rs}V(t)+R_{rs}V'(t)+I_{rs}V''(t)}$ [20], can be transformed into frequency functions, using an algorithm called Fast Fourier Transformation (FFT). Frequency functions P(f) and V'(f), can be expressed as angular frequency(ω) functions, when considering ω=2πf, where f is the oscillations frequency. The ratio of P(ω)/V'(ω) gives respiratory input impedance (Z_{rs}), expressing the total load imposed against the respiratory system motion, consisting of elastic and inertial forces, but also from the total respiratory system resistance. In case of multifrequency FOT or IOS, ratio P(ω)/V'(ω) refers to a frequency spectrum: $\{0 \le \omega \le \omega_{max}\}$, and thus multifrequency input impedance values can be measured: $Z_{rs}(\omega)= P(\omega)/V'(\omega), \{0 \le \omega \le \omega_{max}\}$ [24].

Cartesian complex form of $Z_{rs}(\omega)= P(\omega)/V'(\omega), \{0 \le \omega \le \omega_{max}\}$, gives the components of the respiratory system multifrequency input impedance, as follows: $\mathbf{Z_{rs}(\omega)= R_{rs} + jX_{rs}=R_{rs} + j(\omega I_{rs} - 1/\omega C_{rs})}$* [21], where $\mathbf{\omega=2\pi f}$, $\mathbf{\{0<f\le f_{max}\}}$ (equation 2). *Respiratory resistance (Rrs)* is the Ohmic component of respiratory impedance, including both airways' resistance (Raw), where $R_{aw} = (P_{alv}-P_{ao}) / V'$**, and respiratory system tissue-frictional resistance, due to the motion of the total respiratory system, including chest wall and diaphragm [21,25]. $\mathbf{X_{rs} = \omega I_{rs} - 1/\omega C_{rs}}$, is called ***respiratory reactance***, and expresses analogically to the reactance of a RIC electric circuit, both capacitive $\mathbf{(-1/\omega C_{rs})}$ and inertial $\mathbf{(\omega I_{rs})}$ properties of the system.

*Z_{rs}= respiratory system impedance, R_{rs}=respiratory resistance (ohmic component), j^2= -1 (imaginary numbers coefficient), X_{rs}= respiratory reactance.

** P_{alv}=alveolar pressure, $P_{a.o}$=pressure at the opening of the airways.

$\mathbf{C_{rs}}$, refers to the total respiratory system compliance, consisting of lung and bronchial wall compliance, the compliance of the chest wall/abdomen compartment, thoracic gas compression and the upper airways compliance (mouth cavity, pharynx etc.) [21,25]. $\mathbf{I_{rs}}$, refers to the total respiratory motion's inertial forces, produced by the motion of the air7column in the central airways and the motion of the total tissue mass of the respiratory system (parenchymal and not) [21,25].Considering the above, it is clear that total impedance of the respiratory system expresses the total load-"barrier", which is surmounted every moment of the respiratory motion.

Equation 2 is the original form of expressing respiratory system multifrequency input impedance, first propounded by DuBois et al. [21] and its conceptual core lies in the observation that through a linear approach and with one degree of freedom, the respiratory system behaves like an electrical circuit, consisting of resistors, capacitors and inductors [25]. However, that reasoning, even fundamental, is oversimplified, and, in fact, both capacitive and inertial components of X_{rs}, express energy storage capacity [26]. Thus, in modern theoretical approaches of Forced Oscillation Techniques, equation 2 appears slightly altered: $\mathbf{Z_{rs} = R_{rs} + j(\omega In - 1/\omega Ca)}$ with $\mathbf{\omega=2\pi f}$, $\mathbf{\{0<f\le f_{max}\}}$ [24] (equation 3). Term ***Ca (capacitance)*** expresses the sequence of elastic energy transport in the respiratory system throughout the respiratory cycle (inspiratory and expiratory phase) [20]. Term ***In*** (***Inertance)*** expresses the energy transport that is mediated by inertial forces in the respiratory system throughout the respiratory cycle, as the pressure configured by inertial forces ($\boldsymbol{P_{in}=I_{rs}V''}$), opposes the respiratory system motion at the beginning and until the middle of inspiration or expiration (when nullifies), resulting in the work of these forces to be negative, unlike the second half and until the end of inspiration or expiration when Pin tends to maintain respiratory system motion, resulting in inertial forces work being positive, and create energy efficiency for the respiratory system [20]. However, it must be pointed out that the above theory is based on the principle that in an "ideal" respiratory system, both elastic and inertial forces are conservative.

In figure 1, normal curves of R_{rs} and X_{rs} versus frequency are given. It can be observed that R_{rs} values are not affected by the frequency of oscillation, and remain almost stable throughout the frequency range. However, it has been referred that, due to the oscillatory motion of the mouth cavity and the extrathoracic airways, an amount of flow is produced which is included in the flow signal (V') and expresses the behavior of these structures as an impedance in parallel (Z_{uaw}) to the real total impedance of the respiratory system (Z_{rs}) [27-31]. As a result, a bias is established, described as the ***upper airways artifact***, expressed as a negative slope of curve $R_{rs}(f)$, which is called Frequency Dependence of

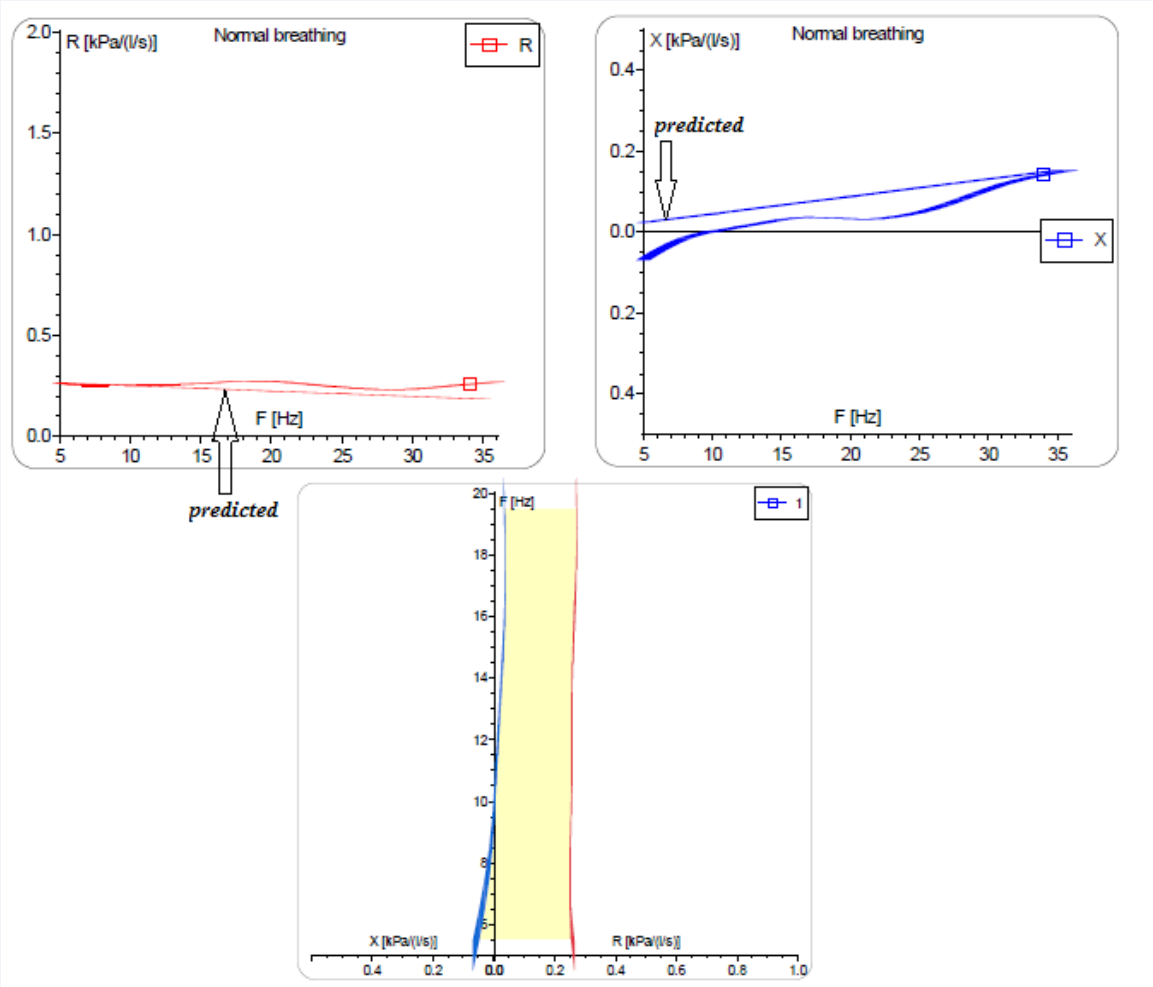

Figure 1 Resistance (R_{rs}) – frequency(f) [R_{rs}(f)] and reactance (X_{rs}) – frequency(f) [X_{rs}(f)] curves of a healthy non-smoker of 23 years of age are depicted. Graphs come from the archives of the Centre for Smoking and Lung Cancer Research of the Hellenic Cancer Society, where the CareFusion(Master screen – IOS) machine is used. R_{rs}(f) curve is almost rectilinear, frequency dependence of resistance is absent (fdr=0), which is confirmed by the following data: $R_{rs}5=R_{rs}20=0.26$ kPa/(L/s). Values of the rest parameters are: $X_{rs}5=$ -0.07 kPa/(L/s), $X_{rs}20=$ 0.03 kPa/(L/s), fres= 9.9 Hz, AX=0.14 kPa/L.

resistance(fdr), as well as shifting of the X_{rs}(f) curve to more negative values [32,33]. In order to neutralize this phenomenon, cheeks must be supported by the subject or the operator during the examination [33].

In contrast to the stable R_{rs} values throughout frequency spectrum, X_{rs} values can be either negative or positive, depending on the frequency range studied. It can be observed that when frequency gets a specific value, X_{rs} nullifies. That frequency of applied oscillations is called resonant frequency (f_{res}), and expresses the following relationship: $\omega_0 In=1/\omega_0 Ca$, $\omega_0=2\pi f_{res}$ [24]. Reactance area (AX) is the area under the X_{rs}(f) curve, which is defined by the two coordinate axes and curve X_{rs}(f), from its minimum rate (which is the point of intersection of the curve and axis y) to its rate in resonant frequency (f_{res}), which is the point of intersection of the curve and axis x.

So it is: $AX=\int_{5}^{f_{res}} \mathbf{X_{rs}}\,\mathbf{df}$

AX is a quantitative indicator of (i) respiratory system reactance in all frequencies between 5Hz and the resonant frequency (ii) value of f_{res} and (iii) curvature of the function X_{rs}(f). It has also been formulated that AX is a marker of airway closure, since, such closure results in impending diffusion of pressure waves more peripherally in the bronchial tree, a fact that is captured in the increase of the value of AX, expressing the increase of the "effective elastance" of the respiratory system [34].

It has been estimated that low frequency oscillations (f<20Hz) are spread in larger depth over generations of airways and reach more peripheral parts of the bronchial tree, while high frequency(f≥20Hz) pressure waves spreading is impeded in mid size airways and never reach periphery [32]. Consequently, R_{rs} and X_{rs} values at low frequencies, express the mechanical properties of the peripheral airways and, in general, those of the periphery of the respiratory system, whereas, R_{rs} and X_{rs} values at frequencies above 20Hz, express the mechanical properties of the central airways and the upper respiratory system.

Interpretation of oscillometric indices must be based on

both the actual values of the impedance components referred above and the frequency curves of R_{rs} and X_{rs} [20], which have been proved to be identical for both FOT and IOS [35]. In general, values of impedance components are considered normal, when they don't exceed 150% of the predicted values [24], calculated by prediction equations. However, in clinical practice, the fact that X_{rs} values variability is significantly higher than those of R_{rs} must be taken into account, and thus the above mentioned general criterion can safely be used only for the latter. Furthermore, there are few studies giving prediction equations for multifrequency FOT parameters, in which the most significant predictor of mean values of R_{rs} and X_{rs}, in frequency range 4 - *30Hz*, is height, with age and body weight factors to overall increase the power of the prediction equations, but individually, they are proved to be significantly weaker predictors [36-42]. Additionally, it must be pointed out that, to our knowledge, there are no published data of prediction equations for IOS parameters. Finally, ageing of the respiratory system is correlated with increased Functional Residual Capacity (FRC) and decreased total respiratory system compliance [43,44]. Thus, it is possible that in elderly subjects, mean value of R_{rs} throughout the frequency range ($R_{rs,mean\ 4\text{-}30}$) will appear slightly lower [45]. Moreover, low frequency R_{rs} and f_{res} values may appear slightly increased, due to the existing mild increase in peripheral resistance, observed in the elderly subjects [46].

After the previous brief review of the basic theoretical knowledge concerning physiology of respiratory system impedance and its components, description of the main, well characterized, modifications of those parameters observed in common respiratory diseases is attempted. Throughout analysis of the theoretical principles which frame FOT and IOS, can be found in a former study of the authors [20].

OBSTRUCTIVE SYNDROMES

Chronic Obstructive Pulmonary Disease (COPD).

Typical pattern of resistance(R_{rs}) and reactance(X_{rs}) modifications

Many studies in which FOT and IOS have been applied on patients with COPD [47-60], converge in configuration of a typical pattern for impedance parameters modifications, significantly altered from R_{rs} and X_{rs} values distribution in frequency spectrum which is observed in healthy adults (normal morphology of R_{rs} and X_{rs} frequency curves is presented in figure 1). R_{rs} values are significantly increased in frequencies lower than resonant frequency (f_{res}) and then, decreased as frequencies increase, until they are stabilized in frequencies higher than f_{res} where, pretty often, they are within normal limits [60]. This distribution of resistance values imparts a negative slope to R_{rs}(f) curve (figure 2), a phenomenon called frequency dependence of resistance(fdr) [47], and is quantified by the difference: *(i)* $\boldsymbol{R_{rs}4 - R_{rs}16}$, for ***FOT*** parameters and (ii) $\boldsymbol{R_{rs}5 - R_{rs}20}$ for ***IOS*** parameters. This difference is always a positive number for patients with COPD and expresses the location of obstruction, peripherally in the bronchial tree, since low frequency R_{rs} values are formed by peripheral airways resistance, while high frequency R_{rs} values are formed by larger, central airways resistance [20]. In addition, ***fdr*** has been correlated to increased non-homogeneity in the interaction of individual mechanical components of the respiratory system-which is expressed by the non-homogeneity of the individual time constants (***τ=CxR***, where ***C=compliance***, ***R=resistance***), but also with increased non-homogeneity in ventilation distribution [47,48].

Absolute values of X_{rs} in low frequencies increase significantly, and this results to the measured X_{rs} values becoming significantly more negative. The increase of f_{res} value is also significant and results to negative X_{rs} values, even in high frequencies. These quantitative changes lead to respective qualitative changes. Curve X_{rs}(f) shifts to more negative values, while reactance area (AX) is increased significantly and is strongly correlated with fdr [49] (figure 2).

The pattern analyzed above and presented in figure 2, is described in bibliography as peripheral airways obstruction pattern, or, more precisely, medium and small size airways obstruction, in which high frequency oscillations (f>20Hz) are impeded significantly [20,32]. Indeed, obstruction's location in COPD is peripheral, since the mechanisms causing it, influence mainly medium size and small size bronchi, whose wall is not supported by cartilage. Because of this fact, the walls of those pliable airways- already partially obstructed by secretions, edema and bronchoconstriction, coincide during expiration, which results to considerable increase of heterogeneity in ventilation distribution and individual time constants (τ). Those mechanical aftereffects are imprinted as a significant increase in low frequency R_{rs}, fdr, X_{rs} and AX values. Based on the above mechanism, COPD constitutes a disease-pattern for peripheral airways obstruction and, for this reason, the pattern presented in figure 2 is referred to as peripheral airways obstruction pattern, suggesting a special morphology for curves X_{rs}(f) and R_{rs}(f).

As COPD severity increases and presence of hyperinflation is more intense, resistance indices lose their sensitivity while reactance indices reflect more accurately lung function disorders. This phenomenon becomes more intense in emphysema, where resistance indices often lose their diagnostic value since they are found within normal limits in a number of times. In previous studies using FOT, Van Noord et al. [50] recorded more pathological resistance values in patients with bronchial asthma and chronic bronchitis than in patients with emphysema with a similar degree of airways obstruction, while Govaerts et al. [51] recorded Z_{rs}, R_{rs} and X_{rs} values within normal limits in patients with mild emphysema. However, low frequency X_{rs}, f_{res}, AX and fdr modifications are often impressive, as elastic work production capacity is significantly reduced because of reduction of lung elastance.

Apart from the significant changes of R_{rs}(f) and X_{rs}(f) mentioned above, a number of studies detect significant variations in impedance indices versus time, mostly between inspiratory and expiratory phase of the respiratory cycle. It has been detected that, in healthy subjects, $Z_{rs}5$, $R_{rs}5$, $R_{rs}20$ and $X_{rs}5$ values show significant variability between inspiration and expiration [52,53]. In a study by Kubota et al. [52], significantly increased values of $Z_{rs}5$, $R_{rs}5$, $R_{rs}20$ and ($R_{rs}5 - R_{rs}20$) and significantly more negative $X_{rs}5$ values were observed during expiration, in healthy population of 64 years average age, whereas a significant increase

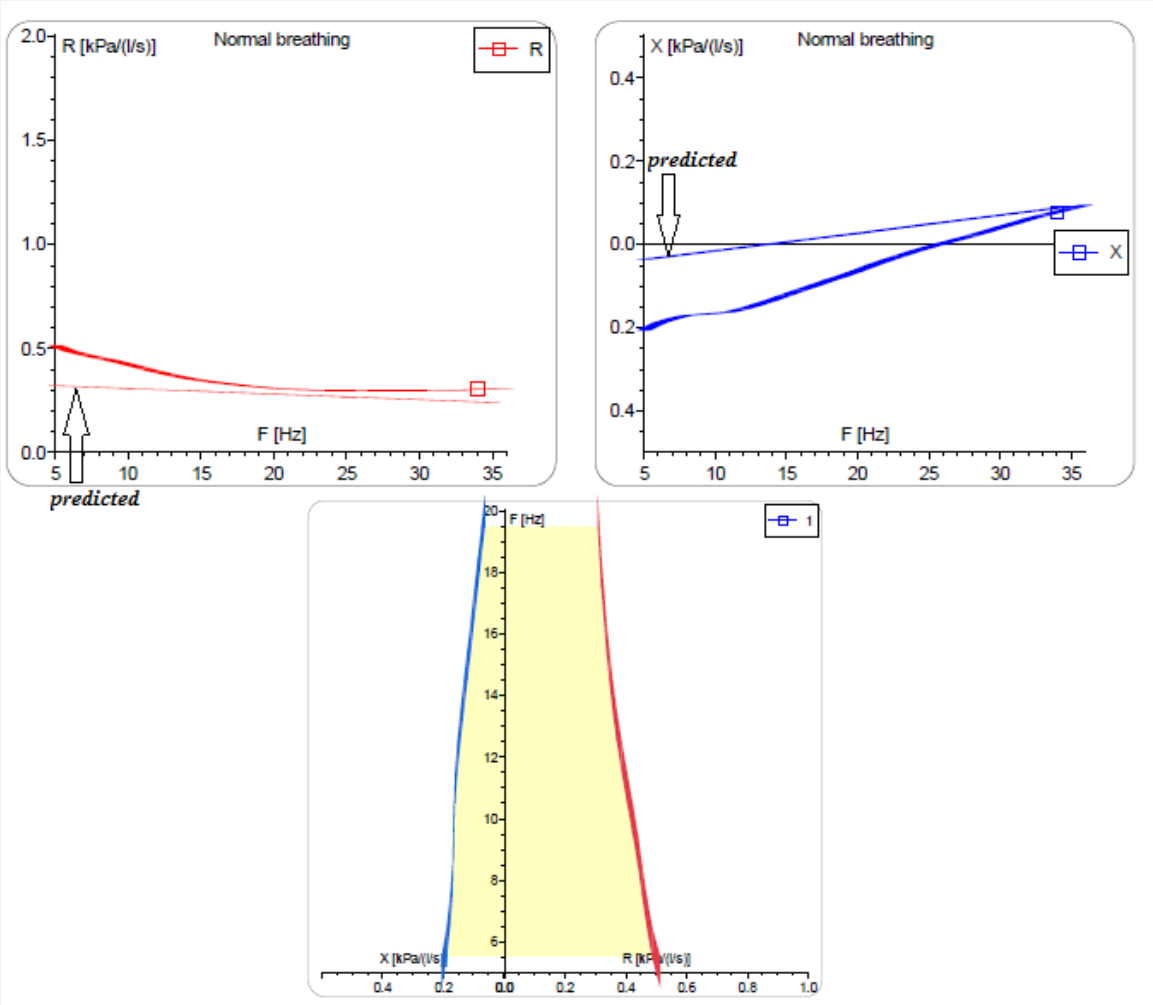

Figure 2 Rrs(f) and Xrs(f) curves of a 79 year-old COPD (GOLD stage III) male patient are depicted. Graphs come from the archives of the Centre for Smoking and Lung Cancer Research of the Hellenic Cancer Society, where the CareFusion(Master screen – IOS) machine is used. Significant increase of $R_{rs}5$ ($R_{rs}5$=0.51 kPa/(L/s)) as well as impressive fdr [67% increased (Rrs5 – Rrs20) value] can be observed. There is also significant increase of AX (AX=2.28 kPa/L), indicative of the significantly increased negative values of Xrs5= -0.21 kPa/(L/s)=-548% of the predicted value) as well as the impressively increased resonant frequency (f_{res}=25.8 Hz).

of expiratory $R_{rs}5$ and $R_{rs}20$ was observed in healthy population of 23 years average age. Nevertheless, in COPD patients, $Z_{rs}5$, $R_{rs}5$, $R_{rs}20$, ($R_{rs}5$ – $R_{rs}20$), f_{res} and AX values are significantly increased during expiratory phase [52-56], especially in the middle of expiration [53], in relation to both inspiratory values and the corresponding expiratory values of healthy population. Correspondingly, $X_{rs}5$ values are significantly more negative during expiration [52-56]. Modifications mentioned above have been connected with [52-56]: (i) variability in diameter of the glottis opening, (ii) performance of not absolutely passive expiratory effort, with consequent compression of the wall of intrathoracic airways, (iii) expiratory flow limitation and its variability during the respiratory cycle, especially for patients with COPD, but also (iv) dilation of the airways during inspiration, so that forced oscillations can reach more peripherally the bronchial tree and lung parenchyma, with consequent decrease of ventilation distribution non-homogeneity.

Assessment of COPD severity by oscillometric indices

The typical pattern for R_{rs} and X_{rs} values distribution to the frequency spectrum described above (figure 2), is obvious in early stages, and gets more intense along with deterioration of the disease. In a classic study of Clemént et al. [57], FOT is proved capable of separating healthy subjects (smokers and non-smokers) from COPD patients with respiratory complaints, regardless FEV_1 values (normal or abnormal). Indices with the highest diagnostic value were fdr and mean value of X_{rs} in frequency range 8-24Hz ($X_{rs,\ mean\ 8\text{-}24}$), the power of which was highest on patients with FEV_1<50% of the predicted value. In a study by Di Mango et al. [58] using FOT, R_{rs} mean value in frequency range 4-16Hz ($R_{rs,mean\ 4\text{-}16}$), differed significantly between healthy controls and patients with mild COPD having normal or abnormal FEV_1 values, while $X_{rs,\ mean\ 4\text{-}32}$ increase was non-significant. On the contrary, among patients with mild and moderate COPD, significant differences were observed only in fdr and $X_{rs,\ mean\ 4\text{-}32}$, while among moderate and severe COPD patients,

the only significantly altered parameter was $X_{rs,\ mean\ 4\text{-}32}$. COPD severity was evaluated according to the GOLD criteria. Similar conclusions were also reached by Kolsum et al. [59], who, by applying the IOS technique, put forward that $X_{rs}5$ changes are more indicative for the obstruction progress than $R_{rs}5$ changes. $R_{rs}20$ changes were not related to obstruction severity in the particular study.

The results of the above studies converge to the formation of a common denominator for the evaluation of COPD severity, based on impedance parameters. It appears that pathophysiology in early stage disease is better described by resistance components, while pathophysiology in late stage disease with a higher obstruction degree is better captured by X_{rs} components. The interpretation of this phenomenon is multidimensional. With the progress of the disease, obstruction increases and inflammation of small airways becomes more intensified, which results to their structural alteration and consequently leads to periphery non-homogeneity of time constants (τ), but also to flow limitation and non-homogeneity of ventilation distribution. Those facts are strongly correlated at the studies mentioned above, with increase of low frequency X_{rs} and fdr. Moreover, hyperinflation settled in late state disease, results in chest wall deformation, which introduces a restrictive factor in the lung to chest wall interaction. This fact, on the one hand affects the sensitivity of R_{rs} to a degree, and on the other hand, causes decrease of the chest wall and tissue compliance, which is reflected in capacitance values increase [58].

In the above studies, significant correlations were recorded among the parameters of spirometry, body-plethysmography and FOT which however, were moderate. In the Kolsum et al. [59] study, there were significant correlations among $R_{rs}5$, $X_{rs}5$, f_{res} and FEV_1, sG_{aw}, TLC, RV, IC*, while the parameter for which maximum strength of correlation was observed, was $X_{rs}5$. An important element of this study is that the patients, as far as progress of the disease is concerned, were attended for a whole year. FEV_1 changes were significantly correlated only with $X_{rs}5$ changes and not with $R_{rs}5$ and $R_{rs}20$ modifications over the year. FEV_1 decrease was correlated with the increase of $X_{rs}5$ negative values. The above mentioned correlations reinforce the interpretation mentioned above, as they prove that reactance parameters are better correlated both with obstruction and hyperinflation.

In a recent study of Crim et al. [60] with IOS technique, values of R_{rs}, X_{rs} and AX revealed two separate subpopulations of patients with clear characteristics, which may correspond to different COPD subtypes. In one case, an apparently healthy group of smokers with normal spirometry was characterized by increased AX values compared with the non smoking healthy group, a fact that seemed to reveal small airways obstruction in the specific group. A second group of subjects was characterized by normal R_{rs}, X_{rs} and AX values while COPD was present, according to the GOLD criteria. The above parameters were not correlated to the degree of obstruction in these subjects which appeared to have somewhat better spirometry.

*sG_{aw}= airways' conductance, where s $G_{aw}=1/sR_{aw}$, TLC: Total Lung Capacity; RV: Residual Volume; IC: Inspiratory Capacity

In this study [60], $R_{rs}5$, $X_{rs}5$, AX and f_{res} differed significantly among the populations being classified according to the GOLD criteria (stages I-IV), while $R_{rs}20$ was differed significantly among subpopulations of stage II and III, and, stage II and IV. Another important element of the study, is that 61% and 86% of the total COPD patients appeared to have normal $R_{rs}5$ and $R_{rs}20$ values respectively, while the corresponding percentage for $X_{rs}5$ and AX were 34% and 29%, facts that confirm the superiority of reactance and, at the same time, demonstrate the important lack of sensitivity of $R_{rs}20$ in evaluation of the disease.

An important component of COPD pathophysiology is the presence of Expiratory Flow Limitation (EFL). Single-frequency FOT in 5 Hz has proved to be an exceptionally sensitive and special method to evaluate EFL, as it offers the ability to record impedance indices variations within the respiratory cycle. Dellacá et al. [61], have evaluated EFL by applying sinusoidal pressure waves of 5Hz frequency. The parameters used were the difference of expiratory and inspiratory $X_{rs}5$ mean values ($X_{rs}5_{insp,mean}$ - $X_{rs}5_{exp,mean}$) and minimum expiratory ($X_{rs}5_{exp,min}$). The sensitivity and specificity of these parameters was 100%, using as threshold the following values: $X_{rs}5_{insp,mean}$ - $X_{rs}5_{exp,mean}$= =[2.53–3.12] $cmH_2O/(L/s)$ and $X_{rs}5_{exp,min}$=[(-7.38) – (-6.76)] $cmH_2O/(L/s)$. Thus, the above indices are demonstrated as absolutely efficient to evaluate both the moment the phenomenon begins and EFL severity, and supply yet another valuable information about clinical staging of COPD. Moreover, it has been detected that fdr is significantly higher in patients with a high degree of EFL than in patients with a lower EFL degree, as it estimated by the GOLD criteria [60,62,63]. Additionally, Ohishi et al. [53], using the IOS technique, detect significant increase in middle7expiratory $R_{rs}5$, $R_{rs}20$, $R_{rs}5$ $R_{rs}20$, f_{res} and $X_{rs}5$ values with the increase of COPD stage according to GOLD, a fact that can be correlated with the corresponding EFL increase.

Oscillometry in evaluating exacerbations of the disease: Correlation between intensity of the symptoms for patients with exacerbation of COPD and IOS indices was analyzed in a recent study of Haruna et al. [64] where dyspnea (MRC, SGRQ*) was more strongly correlated with ($R_{rs}5 - R_{rs}20$) and $X_{rs}5$ than with FEV_1. In this study, during recovery of 39 patients with exacerbation of COPD, significant changes of $X_{rs}5_{insp,mean}$ and $X_{rs}5_{exp,mean}$ were detected, while, on the contrary, R_{rs} modifications were not statistically significant. In a recent study by Stevenson et al. [65], the same parameters proved to be the most sensitive in evaluating the improvement of lung function of 22 hospitalized patients with COPD after exacerbation, while additionally, for patients whose $X_{rs}5$ was significantly improved, there was parallel but weaker improvement of FEV_1 and Inspiratory Capacity. In a study by Johnson et al. [66], the improvement of FOT indices was evaluated for patients with exacerbation of COPD after a 6 week bronchodilation therapy. $X_{rs}5_{insp}$ and $X_{rs}5_{exp,\ mean}$ showed significant improvement, while the first was strongly correlated with improvement of the symptoms and the patients' quality of life (HRQOL** index). However, no significant improvement of resistance parameters was recorded, a characteristic observed in all the above studies.

In conclusion, the parameters that appear to capture with greater sensitivity the patients' progress after exacerbation of COPD are ($R_{rs}5 - R_{rs}20$), $X_{rs}5$, $X_{rs}5_{insp,mean}$ and $X_{rs}5_{exp,mean}$ is

more strongly related to the improvement of the symptoms and HRQOL**, a fact that indicates that X_{rs} variations within the respiratory cycle are more sensitive to evaluate the lung function of those patients.

*SGRQ= St' George's Respiratory Questionnaire

** HRQOL= Health Related Quality Of Life

Bronchial asthma

Differentiations with COPD: The pattern of the changes of impedance indices versus frequency as formerly presented, also appears in patients with bronchial asthma. Nevertheless, because of hyper-reactivity and inflammatory infiltration of the wall of central and peripheral airways alike in bronchial asthma, significant changes are observed also in high frequency impedance parameters and thus fdr is less impressive [24,50,67,68] (figure 3).

In a recent study by Kanda et al. [67] using IOS, impedance modifications in asthmatic and COPD patients were evaluated, and significantly higher $R_{rs}20$ values were recorded in asthmatic patients compared to COPD patients and to the healthy control group. In addition, impressively increased were the values of parameters $R_{rs}5$ and $X_{rs}5$ recorded on asthmatic patients with normal spirometry (FEV_1/FVC), while $R_{rs}5$ was proved more sensitive than the ratio (FEV_1/FVC). In this specific study, increase in values of $X_{rs}5_{insp,mean}$ and $X_{rs}5_{exp,mean}$ (with $X_{rs}5_{exp,mean} > X_{rs}5_{insp,mean}$) observed along with increase of severity of the disease, was significant only for patients with severe COPD, whilst for asthmatic patients these variations were negligible, as was the difference of X_{rs}5exp,mean and X_{rs}5insp.mean. Moreover, ($R_{rs}5 - R_{rs}20$) and f_{res} were found significantly more increased in COPD patients than in asthmatic patients. Similar findings are detected by Paredi et al. [55] even though in this specific study the differences between $X_{rs}5_{exp,\ mean}$ and $X_{rs}5_{insp,\ mean}$ of asthmatics and COPD patients were not statistically significant. Additionally, in a study by Mori et al. [54], the above mentioned variations of inspiratory and expiratory $X_{rs}5$ were significantly different between asthmatic and COPD patients, regardless of age, sex, body weight and spirometrically assessed lung function. All the above indicate that, even if classical approach of impedance modifications versus frequency often presents similar findings for asthma and COPD, variability of $X_{rs}5$ within the respiratory cycle is significantly different between these two disease entities.

Assessment of asthma severity by oscillometric indices: In a study by Cavalcanti et al. [68], modifications of impedance parameters were evaluated, using FOT, on 84 adult asthmatic patients with progressive severity of obstruction. Severity of the disease was determined based on the patients' history and spirometric indices, and the patients were classified in groups based on these characteristics. X_{rs}, mean 4-32 differed significantly among the healthy controls, mild, moderate and severe asthmatics, while it was the only parameter able to achieve significant modifications comparing the mild and moderate stages. Mean value of respiratory system resistance extrapolated at 0 Hz (R0), R_{rs} mean 4-32, ($R_{rs}4$-$R_{rs}16$) and f_{res} differed significantly among all groups, except mild and moderate asthmatics. Significant correlations were detected between R_{rs} indices and spirometric indices. The best parameters for detecting and evaluating asthma were R0, ($R_{rs}4$-$R_{rs}16$) and X_{rs}, mean 4-32 having almost equal values of sensitivity (Se) and specificity (Sp): Se= (78-81)% and Sp= (76-80)%.

So in the Cavalcanti et al. [68] as in the Kanda et al. [67] study, low frequency resistance increase was able to detect a subpopulation of asthmatic patients with normal spirometry, a fact that may highlight the dominance of R_{rs} indices previously mentioned in evaluating early stages of the disease. In former studies [69,70], significantly increased peripheral resistance values have also been recorded in asthmatic patient populations with normal spirometry, reinforcing the status of this indication. In any case, the above studies [67-69] indicate the existence of a different subtype of asthma, with normal spirometry and increased peripheral resistance.

The pathophysiological substratum of the modifications described is complex and not fully clarified. The increase of peripheral resistance probably depicts pathophysiological processes which affects mainly the peripheral airways wall, such as thickening of the basement membrane due to subepithelial fibrosis, but also other effects of the small airways remodeling due to inflammation, which result to their calibre reduction caused also by edema and bronchoconstriction. X_{rs} modifications may reflect reduction of total respiratory system compliance which is caused by tissue element increase due to airways remodeling, and hyperinflation [67,68,71,72].

Patients' clinical presentation and quality of life are perhaps more important to evaluate the state of the disease. In a study by Takeda et al. [73], significant correlations are demonstrated among dyspnea severity (BDI*), asthma control state (ACQ**), asthma related quality of life (AQLQ***, SGRQ****), and $R_{rs}5$-$R_{rs}20$, $R_{rs}20$ and $X_{rs}5$ IOS indices, significantly stronger than the corresponding correlations with FEV_1.

Maybe these strong correlations, in combination with the pathophysiological substratum of the above indices modifications, detect new diagnostic and therapeutical directions, independent to the established staging of the disease.

Airways' Hyper Responsiveness (AHR): Inhalation of substances such as Histamine and Metacholine causes bronchoconstriction to patients with AHR. FEV_1 is considered by the American Thoracic Society as the best index to evaluate AHR [74]. Thus, the bronchial challenge test results are evaluated on the basis of the smallest change of FEV_1, indicative of AHR, which is defined in most studies as the 20 % decrease of its value after inhalation of a provocative dose ($PD_{20}FEV_1$), or concentration (PC_{20} FEV_1) of the above substances. Many studies have been conducted to assess the efficiency of oscillometry to evaluate AHR, but also the definition of the impedance parameter more strongly correlated with FEV_1 modifications.

*BDI= Baseline Dyspnea Index,

**ACQ=Asthma Control Questionnaire,

***AQLQ=Asthma Quality of Life Questionnaire,

****SGRQ=St' George's Respiratory Questionnaire.

In previous studies in which AHR was evaluated using FOT,

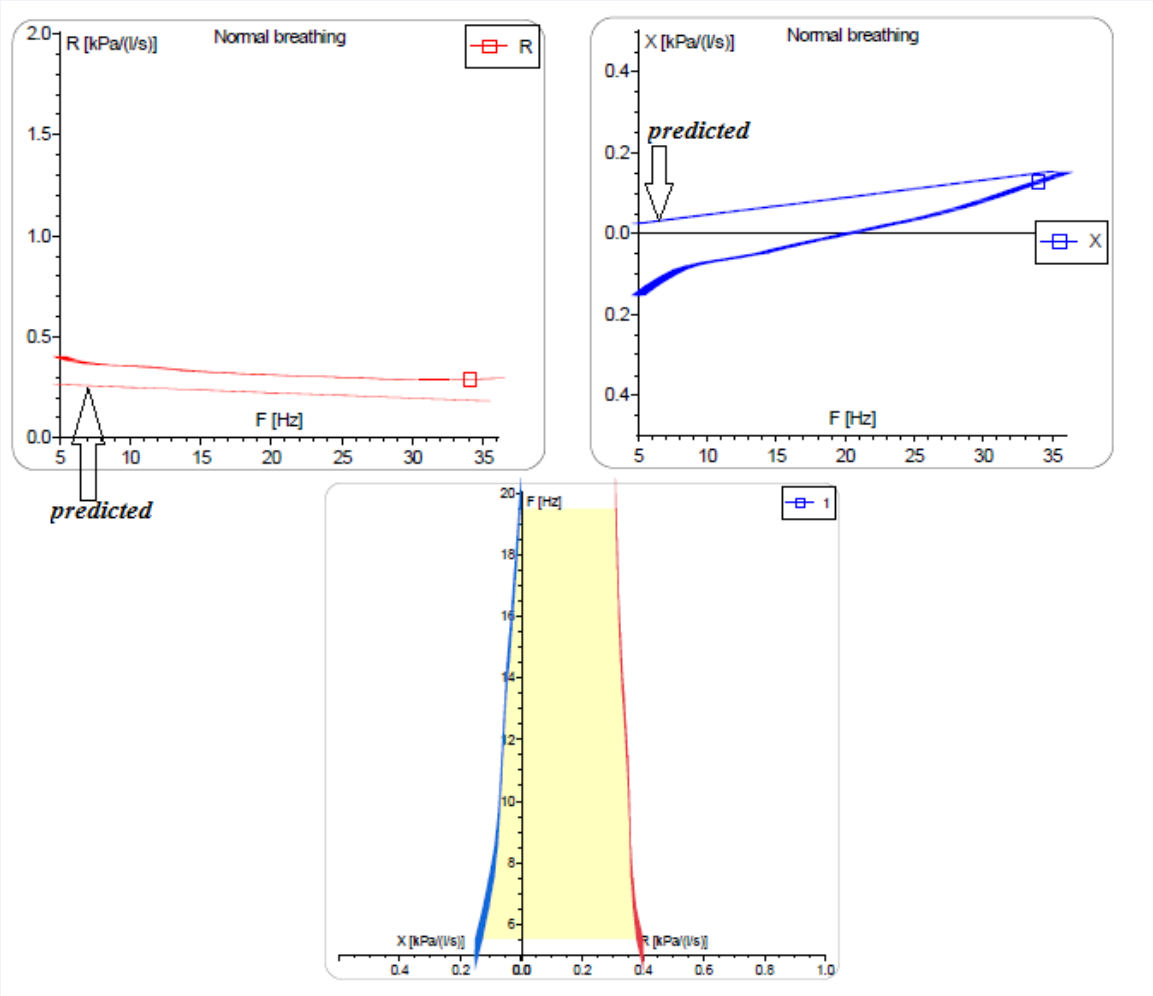

Figure 3 $R_{rs}(f)$ and $X_{rs}(f)$ curves of a 33 year-old male patient with bronchial asthma are depicted. Graphs come from the archives of the Centre for Smoking and Lung Cancer Research of the Hellenic Cancer Society, where the CareFusion(Master screen – IOS) machine is used. An almost rectilinear $R_{rs}(f)$ curve can be observed, due to the low rate of fdr [29% increased (Rrs5 – Rrs20) value], a fact that is explained by the following values of resistance: $R_{rs}5$=0.40 kPa/(L/s), $R_{rs}10$=0.35 kPa/(L/s), $R_{rs}20$=0.31 kPa/(L/s). Additionally, increase of resonant frequency and $X_{rs}5$ (f_{res}=20 Hz, $X_{rs}5$= -0.15 kPa/(L/s)) leads to significant increase of AX (AX=0.91 kPa/L).

PC_{40} $R_{rs}8$ [75] and PC_{47} $R_{rs}10$ [76] were significantly correlated with PC_{20} FEV_1 και PD_{20} FEV_1 correspondingly, while significant correlation was observed among PD_{35} $R_{rs}10$ [77], $PC_{60}R_{rs}8$ [78] and PC_{10} FEV_1. In a study by Van Noord et al. [79], sensitivity of $PD_{40}G_{rs}6$ (where $G_{rs}6$=1/ $R_{rs}6$), is proved significantly higher than that of $PD15FEV_1$, and the difference is demonstrated more intensively as AHR grade increases. Apart from resistance parameters, other indices have been proved exceptionally sensitive in evaluating AHR. Schmeckel and Smith [80], conducted Isocapnic Hyperventilation of dry Cold Air (IHCA) tests to mild asthmatic and healthy populations. IOS was proved more efficient to separate the two populations than spirometry, as the specificity of f_{res} was 100%*, but also $R_{rs}5$* appeared to have higher diagnostic value than FEV_1, with sensitivity and specificity of 88% and 89%, compared to 73% and 88% respectively. In a recent study by McClean et al. [81] using FOT, PD_{27} $G_{rs}6$ and, decrease of $X_{rs}6$ by 0.93cmH_2O/(L/s), was significantly related to PD_{15} FEV_1, while variability of the above was evaluated as similar. The sensitivity of PD27 $G_{rs}6$ and $X_{rs}6$ was 77% and 87% respectively, while specificity of both indices was 88%. In a study by Broeders et al. [82], FOT proved more pleasant for patients than spirometry, when fatigue (MIP**) of the latter was evaluated after bronchial challenge tests with Metacholine, conducted both ways. At the same time, $PC_{40}R_{rs}6$ was proved more sensitive than $PC_{20}FEV_1$, while smaller concentration of the drug was used and duration of the test was significant MEF_{50} ly shorter. Moreover, in a recent study by Mansur et al. [83] using the IOS technique, $R_{rs}5$ and $X_{rs}5$ modifications were significantly correlated with intensity of the metacholine induced dyspnea of 20 adult stabled asthmatics, while, at the same time, no correlation between FEV_1 and MEF_{50} modifications, and dyspnea was detected.

* the optimal cut-off level for f_{res} was determined as 3SD units while an optimal cut-off level of 2SD units was determined for $R_{rs}5$

** MIP=Maximal Inspiratory Pressure

It must be pointed out that variability of oscillometric indices

is greater than FEV_1 [84] and fidelity indexes have been proposed for the FOT data [84,85]. In all the above studies though, oscillometric data present sensitivity and specificity rates similar or greater than FEV_1, while they are evaluated as reliable in terms of repeatability [33]. At the same time, drug concentration is minimized and duration of the test is significantly reduced.

To conclude, even though pursuit of an optimum index for bronchial challenge tests continues, oscillometry proves to be a sensitive and special method, at least as much as spirometry. The element though that is of special interest, is that impedance indices capture more clearly the clinical presentation of the patient, even when conventional tests fail to correlate with it. At the same time, testing can become more pleasant and comprehensible by the patients when performed using oscillometry, a fact that should not be ignored in clinical practice.

Interpretation of supremacy of oscillometry as far as correlation with clinical findings is concerned, but also in terms of sensitivity and specificity rates, is based on the inherent capacity of the method to evaluate quiet breathing. It has been proved that because of the deep inspirations demanded in spirometry, the airways' smooth muscle tone is significantly altered [86-91]; this does not happen in quiet breathing which is asked by the patient to perform during oscillometry.

Evaluation of the reversibility of airways' obstruction: A number of former studies have reached to different and conflicting conclusions using FOT [33]. However, the results of more recent studies, for which the IOS technique was used, seem to invert this picture. In a study of Houghton et al. [26], sensitivity of $R_{rs}5$, f_{res} and FEV_1 proved to be similar in detecting bronchodilation after administration of 10μg Ipratropium Bromide, on mild asthmatic population. In the control group submitted in the same test, FEV_1, $R_{rs}5$ and $R_{rs}20$ altered significantly. In another study conducted by the same collaborators [92], sensitivity of impedance parameters varies depending on the severity of airways obstruction, as in mild asthmatics $X_{rs}5$ and f_{res} are proved more sensitive than FEV_1 at 20 μg of Salbutamole, while in moderate asthmatics sensitivity of $R_{rs}5$, $X_{rs}5$, f_{res} and FEV_1 was estimated similar at 10μg of Salbutamole. In this study [93], positive response of healthy controls to bronchodilation was detected by FEV_1 and MMEF at 100μg and $R_{rs}20$ at 200 μg of Salbutamole. In a latter study by Yaegashi et al. [94], $R_{rs}5$ and ($R_{rs}5$- $R_{rs}20$) modifications proved more sensitive than FEV_1 at 0.2mg of Pirbuterole. In a study by Park et al. [95], $R_{rs}5$ and ($R_{rs}5$- $R_{rs}20$) achieve the greatest sensitivity among impedance parameters in patients with mild asthma, which is comparable to that of FEV_1 at 100μg of Albuterol. In a recent study of Nair et al. [96], $R_{rs}5$ is significantly correlated with FEV_1, with 1 unit increase in $\%FEV_1$ corresponding to a 2.5% decrease in $\%R_{rs}5$ at 400 μg of Salbutamole. In this specific study, $R_{rs}5$ and $R_{rs}20$ modifications imprinted positive response of the healthy control group in bronchodilation.

The use of different response criteria in bronchodilation by the studies mentioned above surely must be noted (table 1), which indicates the lack of consensus as far as defining the optimum evaluation parameter is concerned. Moreover, in the majority of the studies, sG_{aw} and sR_{aw} parameters of body- plythesmography were equally or more sensitive than $R_{rs}5$ and more sensitive than FEV_1. In any case, and modifications are significantly correlated with FEV_1 changes and, in all the above studies they have at least the same sensitivity, while they are proved more sensitive and reliable to evaluate reversibility of bronchoconstriction than $R_{rs}20$.

Evaluation of the response to inhaled corticosteroids and omalizumab therapy: In a relevantly recent study by Gaylor et al. [97], response of asthmatic patients to ICS* treatment of 3-26 weeks duration was evaluated with IOS. Even if FEV_1 was not significantly improved during therapy, IOS indices were improved by 21-48% for all patients. In a recent study by Yamaguchi et al. [98], the response of patients with mild and moderate asthma was studied with two different therapeutic ICS regimens (HFA-BDP** , CFC-BDP***) during a twelve week therapy. AX and ($R_{rs}5$- $R_{rs}20$) IOS indices imprinted severity of the disease more accurately and their improvement was related to AHR decrease. At the same time they imprinted the superiority of HFA-BDP therapy, but also the pharmacokinetics differences between the two substances. Additionally, AX and ($R_{rs}5$-$R_{rs}20$) values week omalizumab therapy weeks) unlike FEV_1, $FEF_{25-75\%}$ and $R_{rs}20$, whose values stabilized within the first 4 weeks. In a recent study by Williamson et al. [99] using IOS, 36 asthmatic patients were classified according to the provided ICS therapy and FEV_1 values in two subpopulations, with mild to moderate asthma and severe asthma. Despite the fact that $R_{rs}5$,$R_{rs}5$-$R_{rs}20$,$X_{rs}5$ and f_{res} values increased among subpopulations of asthmatic patients, no statistically significant differences were observed. On the contrary, all the above indices were significantly different between severely asthmatic and healthy subjects, while only $R_{rs}5$ and f_{res} were significantly different among mild to moderate asthmatic patients and the healthy controls. Finally, among all subpopulations (healthy and asthmatic), $R_{rs}20$ values showed no significant difference.

It is illustrated from the above studies that even if $R_{rs}5$,$R_{rs}5$-$R_{rs}20$ and f_{res} start to improve early, their improvement continues throughout a long term ICS treatment, in contrast with $R_{rs}20$, whose values are stabilized early through treatment.

* ICS= Inhaled Corticosteroids

**HFA-BDP=Hydrofluoroalkane-134a beclomethasone di-propionate,

***CFC-BDP= Chlorofluorocarbon-11/12 beclomethasone dipropionate

Also, AX is proved the most sensitive index in terms of imprinting both early and late effects of long term treatment, but also the pharmacokinetics differences of therapeutic regimens. This fact indicates that both $X_{rs}5$ and f_{res} values improve significantly not only in early stages of the therapy, but through the whole duration of the therapy.

In a Saadeh et al. [100] study, the 3-4 week omalizumab therapy on moderate and severe asthma patients was evaluated. $R_{rs}5$ and AX were improved significantly, without respective improvement of FEV_1.The most sensitive index here was also AX, which was decreased from a 26.9 cmH_2O/L mean value before therapy, to 18 cmH_2O/L after therapy, while $R_{rs}5$ also showed significant decrease, from5.8 $cmH_2O/(L/s)$ before therapy to 4.8 $cmH_2O/(L/s)$ after therapy.

Table 1: IOS parameters modifications, indicative of positive response to bronchodilation, in healthy adults and patients with asthma.

	Houghton et al.[66]		Houghton et al.[67]			Yaegashi et al.[68]	Park et al.[69]	Nair et al.[70]	
	Healthy	**Asthma :** FEV_1= 94 (82-111)% pred.	**Healthy**	**mild asthma:** FEV_1= 96 (80-117) %pred.	**Moderate asthma:** FEV_1= 63 (49-77) %pred.	**Asthma:** FEV_1= 77.9±19.8% pred.	**Asthma:** FEV_1=81.9 ±1.7% pred.	**Healthy**	**Asthma:** FEV_1= 83.99 ±2.33% pred.
$R_{rs}5$	-5.97%	-7.65%	-9.4%	-7.9%	-13.5%	-16%	-0.13 kPa/(L/s)	-14.91%	-33.78%
$R_{rs}20$	-7.38%	-2.48%	-6.6%	-11.2%	-10.1%	-10.08%	-0.12 kPa/(L/s)	-15.68	-19.96
fdr						-60.9%			
f_{res}	-12.05%	-5.05%	-5.8%	-6.6%	-13.6%		-11.6 Hz		
FEV_1	+1.25%	+2.33%	+1.3%	+2.9%	+3.3%	+10.5% (0.2L)	+12%	+2.24%	+6.35%
MMEF	+8.88%	+6.28%	+3.68%	+8%	+4.7%				
sG_{aw}	+13.76%	+12.89%	+18.8%	+10.7%	+9.1%				

[66, 67] Modifications indicative of positive response to bronchodilation, were determined based on within-day variability (CV%) of the corresponding parameters.

[68] Modifications indicative of positive response to bronchodilation, were determined based on d-score calculation, a statistical method able to transform all the parameters of the table to dimensionless subjects, which is considered a useful tool in order to compare measurements with different metrics.

[69, 70] Modifications indicative of positive response to bronchodilation, were determined based on the mean ± 2 SD[69] and mean (SEM)[70] change before and after bronchodilation.

Abbreviations: fdr= $R_{rs}5$- $R_{rs}20$, sG_{aw}= airways' conductance, where $sG_{aw}=1/sR_{aw}$, SD = standard deviation, SEM=Standard Error of the Mean

Pathophysiological substratum of the modifications mentioned above is considerably complex. Gradual and impressive improvement of AX, ($R_{rs}5$-$R_{rs}20$) and $R_{rs}5$, indicates that inflammation of small peripheral airways regresses gradually and progressively during ICS therapy. Improvement of $R_{rs}20$, which imprints regression of the inflammatory process in larger, more central airways, does not follow this standard, as it is less impressive and stabilizes earlier in therapy process, in parallel with FEV_1 and $FEF_{25-75\%}$. This different behavior of the above indices, could be interpreted by the larger total surface of the small against the large airways, but also the differentiation in anatomical location of infiltration of the airways' wall, as CD45+ cells and eosinofils infiltrate mostly in the outer layers of small airways wall, while conversely, in larger airways infiltration is located internally, mostly in the mucosa, where contact with the drug is direct and faster [98,101,102]. Indications for progressive solution of the inflammation of peripheral airways are also reinforced by the gradual improvement of AHR during therapy, which was strongly related with improvement of AX and ($R_{rs}5$-$R_{rs}20$), in the study of Yamaguchi et al. [98] Additionally, it has been detected that correspondence of small airways to both drugs and allergens is higher than correspondence of the large airways to them [98,101,102], fact that indicates that even after some time interval under ICS therapy, AHR of small airways may be maintained to higher levels than it does in larger airways, causing bronchoconstriction, which the above mentioned indices imprint.

UPPER INTRATHORACIC AIRWAYS OBSTRUCTION

In a relatively recent review of Smith et al. [24], a typical pattern for impedance indices modifications in the presence of central intrathoracic airways' obstruction is mentioned. R_{rs} indices are presented significantly increased regardless frequency (5-35 Hz), and as a result, curve $R_{rs}(f)$ becomes almost rectilinear, outside normal limits. This phenomenon reflects the location of the obstruction, as high frequency resistance increase leads to equalization of its values with those of low frequency resistance and counterbalances the upper airway shunt (figure 4).

This pattern is also confirmed by a Skloot et al. [49] study, who applied the IOS technique on smokers and non smokers professional ironworkers at risk of developing respiratory abnormalities. The smoking population presented the typical pattern of modifications observed in patients with peripheral airway obstruction, described below. From the non-smokers, those who did not use appropriate respiratory protection and were at risk of developing large airways dysfunction, presented significantly increased high frequency resistance values ($R_{rs}20$), but also higher total resistance values than those using respiratory protection, while R_{rs} increase was more homogeneous throughout frequency spectra and more independent from frequency compared to the smoking population. In addition, fdr was not significantly different between the two non7 smoking subpopulations (using and not respiratory protection).

Conversely from the resistance values that appear abnormal throughout frequency spectrum (5-35Hz), X_{rs}, AX and f_{res} values are normal, and this results to curve $X_{rs}(f)$ to present normal morphology [24,49] (figure 4).

Even though the existing studies are few, it appears that they converge to a typical pattern for impedance parameters modifications when upper intrathoracic airways' obstruction is present and detect that the optimum parameter for evaluation of the severity of the obstruction, is high frequency R_{rs} ($R_{rs}20$ of IOS) while X_{rs}, f_{res} and AX indices do not present the same validity.

Extrathoracic airways obstruction

In a study by Van Noord et al. [103], in which were included

patients populations with a number of diseases (mostly malignancies) that are characterized by extrathoracic airways' obstruction, R_{rs} and X_{rs} modifications followed the peripheral airway obstruction pattern. The authors put forward that the FOT capacity to define the obstruction location is limited, because of identical modifications.

Nonetheless, in the specific study, the phenomenon was partially attributed to upper airway artifact, as when testing was repeated with the cheeks supported by the subjects, the modifications described in the peripheral obstruction pattern were significantly reduced, but not disappeared.

In a latter study by Horan et al. [104], the process of 10 patients with neurologic injury who had previously undergone tracheostomies was evaluated with IOS technique. Measurements of impedance parameters were made before and after bronchoscopic tracheostenosis dilatation procedures. $R_{rs}5$, $Z_{rs}5$ and f_{res}, were significantly correlated with the diameter of the tracheal stenosis, with f_{res} presenting the strongest correlation, while X_{rs} failed to correlate. For every increase of 1 mm in the diameter resulting from dilatation of the stenosis, there was an average decrease in f_{res} of 2.8 Hz and a reduction of Z_{rs} of 0.11 kPa/L/s., with these two indices proved to be the most reliable to evaluate tracheostenosis. What is interesting, is that even though R_{rs} values distribution to the frequency spectra before the bronchoscopic intervention followed the peripheral airway obstruction pattern, confirming the Van Noord et al. [103] study findings, X_{rs} values distribution and X_{rs} (f) curve presented different morphology. Impressive increase of low frequency X_{rs} absolute values was recorded, presenting a plateau in frequencies 6-13 Hz, which was followed by monotonically increasing curve. F_{res} was impressively increased, while X_{rs} values remained outside normal limits and negative throughout frequency spectrum.

Even though the existing studies are few and it cannot be illustrated that they converge to a typical impedance variation pattern, it seems that f_{res} evaluates more efficiently the extent of obstruction, while probably morphology of X_{rs}(f) curve demonstrated by Horan et al. [104], constitutes a special element of this dysfunction. However, specificity of oscillometric indices for these forms of obstruction has not yet been evaluated with precision and many more studies are demanded to be done to this direction.

DISEASES WITH RESTRICTIVE AND MIXED (OBSTRUCTIVE/RESTRICTIVE) PATHOPHYSIOLOGY

Few studies have been conducted applying FOT on patients with restrictive syndrome, and no study was found having applied IOS on such patients. In a study of Van Noord et al. [105] R_{rs} and X_{rs} modifications were evaluated on 54 patients with Diffuse Interstitial Lung Disease. R_{rs} did not present significant modifications from the normal pattern. For patients with TLC<50% of the predicted value

though, an increase on low frequency R_{rs}, and fdr were observed. X_{rs} values were significantly increased, especially in low frequencies, in all patients with TLC<80% (figure 5). In another study by Van Noord et al. [106], patients suffering from diseases with restrictive and mixed respiratory pathophysiology (ankylosing spondylitis, kyphoskoliosis), were estimated in terms of impedance modifications. Low frequency X_{rs} values were also here significantly more negative. A significant increase of low frequency R_{rs} values was also observed, with corresponding increase of fdr. Resistance and reactance indices modifications were significantly correlated with restrictive syndrome severity. The same pattern was recorded by Zerah et al. [107] studying R_{rs} and X_{rs} modifications on populations with different levels of obesity and restrictive syndrome. R_{rs} and fdr increase was correlated with lung volume decrease and BMI (Body Mass Index) increase in the different stages of obesity. Both capacitance and inertance were significantly decreased when BMI increased.

The results of these studies, demonstrate the existence of a pattern, identical to the one seen in peripheral airways obstruction. However, this pattern is disproved by a Wesseling et al. [108] study, for which patients with numerous systemic and neuromuscular diseases with restrictive respiratory pathiphysiology (myasthenia Gravis, Duchenne's muscular dystrophy a.o.) were examined. In this study, lack of fdr was detected and R_{rs}, f_{res} and X_{rs} values were found within normal limits while R_{rs}(f) and X_{rs}(f) curves presented morphology similar to those found in healthy adults, a pattern the authors suggest as differential diagnosis and obstruction exclusion tool for patients with neuromuscular diseases. Moreover, in a Van den Elshout et al. [109], study in which impedance indices modifications were evaluated in patients with COPD, bronchial asthma, interstitial lung disease and sarcoidosis, the conclusion that increased low frequency resistance values and associated fdr, specify obstruction rather than clear restrictive syndrome was reached.

Recent studies by Faria et al. [110,111] on patients with

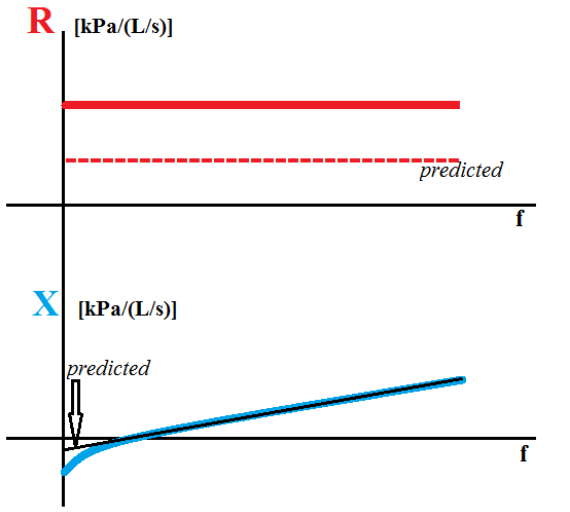

Figure 4 A graphical representation of indicative R_{RS}(f) and X_{RS}(f) curves appearing in presence of upper intrathoracic airway obstruction is given. A homogenous, significant increase of respiratory resistance throughout frequency spectrum (absence of fdr) can be observed, which is explained by the nullification of the upper airways' artifact due to the increase of high frequency resistance (R_{RS}20) values. Hence, R_{RS}(f) curve appears almost rectilinear and out of the normal limits throughout frequency spectra. Contrarily, X_{RS}(f) curve's morphology as well as reactance values remain within normal limits throughout frequency spectrum.

sarcoidosis [110] with presence and absence of peripheral airways obstruction (spirometric findings) and patients with rheumatoid arthritis [111], highlight the significant diagnostic value of $Z_{rs}4$, $R_{rs,mean4-16}$ and $X_{rs,mean4-16}$ indices in evaluating lung function of such patients. Resistance values were found significantly increased throughout frequency spectrum in relation to healthy controls. However, significant and almost stable fdr was demonstrated on patients with sarcoidosis, regardless severity of peripheral airways' obstruction (FEV_1 and FEV_1/FVC indicative values), finding that was not observed on patients with rheumatoid arthritis (FEV_1 and FEV_1/FVC within normal limits), where resistance increase was almost stable and independent of frequency. In addition, significantly Xrs, mean4-16 more negative values were observed on patients with sarcoidosis in relation to healthy controls, and this difference was independent of obstruction severity. However, for both patients with sarcoidosis and rheumatoid arthritis, $X_{rs}(f)$ curves were not significantly different from those of the healthy controls, just as f_{res} values. Finally, significant increase of $Z_{rs}4$ values in both groups of patients was observed.

Pathophysiological substratum of the results of the above studies, although complex, gives an overall picture of the respiratory system mechanics modifications. It appears that reduction of lung volumes has an important role in resistance increase. FRC changes have strongly been related to sR_{aw} and sG_{aw} modifications, while common denominator in this correlation has proved to be the elastic recoil pressure(P_{el}), which tends to increase airways diameter at high and respectively reduce it at low lung volumes (when Pel values are significantly reduced) [25]. FRC reduction also seemed to interpret more sufficiently R_{rs} increase in the studies in which it was observed, as modifications of the two parameters significantly correlated. Significant low frequency R_{rs} increase and fdr presence in healthy subjects has been observed, when measurements are made in supine position in relevance to sitting position, which is attributed to FRC decrease in the first [113,114], but also when rib cage strapping is applied [115]. This restriction effect is reversed when subjects breathe 1L over their actual FRC, as low frequency R_{rs} values come back to normal and fdr disappears [89]. In addition, in the Zerah et al. [81] study, significant correlation was observed between FEF50 and fdr, fact that illustrates the significant influence of obstruction in peripheral resistance increase on obese patients.

In neuromuscular diseases, fdr absence was attributed to the proportionate Rcw (increase) and Ccw (decrease) modification, which result to homogeneity conservation of time constants (τ) of the chest wall, but also conservation of the relation of time constants between the rib cage and the abdomen-diaphragm compartment. This interpretation may also cover the lack of significant X_{rs} and $X_{rs}(f)$ modifications on the specific patients. As for the other patients populations (fibrosis, ankylosing spondylitis, kyphoskoliosis and obesity), where X_{rs} and $X_{rs}(f)$ presented significant alterations, the latter probably reflect the significant reduction of the chest wall and lung compliance.

As for sarcoidosis, significant fdr cannot be exclusively attributed to obstruction, as not significant increase to patients with spirometricaly confirmed peripheral airways obstruction was observed. These changes possibly illustrate individual time constants(τ) non-homogeneity (which is induced by lung parenchyma disorders), but also ventilation distribution disorders, even for patients with normal spirometry. Additional expression of mechanical non-homogeneity and reduction of the respiratory system dynamic compliance is the significant Xrs, mean4-16 value increase. Moreover, resistance values homogenous increase throughout frequency spectrum possibly indicates the presence of upper airways obstruction.

Detection of abnormal impedance values in patients with rheumatoid arthritis and normal spirometry is important because, in the Faria et al. [111] study, 90% of these patients presented daily symptoms from the respiratory system. Homogeneously increased resistance values possibly express lung parenchyma disorders, such as obliterative bronchiolitis and rheumatoid nodules, which lead to airways (both peripheral and upper) diameter reduction. Increased $Z_{rs}4$ values express total mechanical load of the respiratory system, and most likely express in a better way symptoms like fatigue and dyspnea, but also these patients influenced quality of life. However, it seems that mechanical homogeneity of the respiratory system is not disturbed to a great extend, at least in the early stages of rheumatoid arthritis lung disease, since frequency dependence of resistance and reactance values alike are within normal limits, which was also a characteristic of the neuromuscular diseases mentioned above. However, in the latter, resistance values were within normal limits throughout frequency spectrum, whereas the pattern observed at the above mentioned group of patients with rheumatoid arthritis is identical to that occurs in presence of upper intrathoracic airways obstruction (figure 4).

To conclude, it can be formulated that in the early stages of a "strictly" restrictive syndrome, R_{rs} values are within normal limits throughout the frequency spectrum, a pattern identical to that of healthy adults. $X_{rs}5$ values may possibly be presented more negative and out of normal limits, in parallel with $X_{rs}(f)$ curve shifting to more negative values and, f_{res} and AX increase, pattern also observed in peripheral airways obstruction, as analyzed in previous units. Reactance parameters modifications increase along with disease severity increase and become more impressive in severe syndromes. It is most likely that those indices modifications come before resistance parameters modifications and are more reliable in evaluating early stages. In severe restrictive syndrome cases where R_{rs} abnormal values and significant fdr are observed, they probably reveal the emerging obstructive component of the disease, and simultaneously follow the time course of the disease progress, reflecting the increase of non-homogeneity of individual time constants (τ) and ventilation distribution.

In neuromuscular diseases with restrictive syndrome, pathophysiological modifications in the disease course represent opposing forces whose components are impedance parameters, so consequently, the latter remain within normal limits. Perhaps, the latter observation can become a useful diagnostic tool for the specific diseases.

The contribution of oscillometry is proved to be especially important in the evaluation of pulmonary pathology for patients with sarcoidosis and rheumatoid arthritis, since impedance indices interpret early clinical manifestations of the diseases,

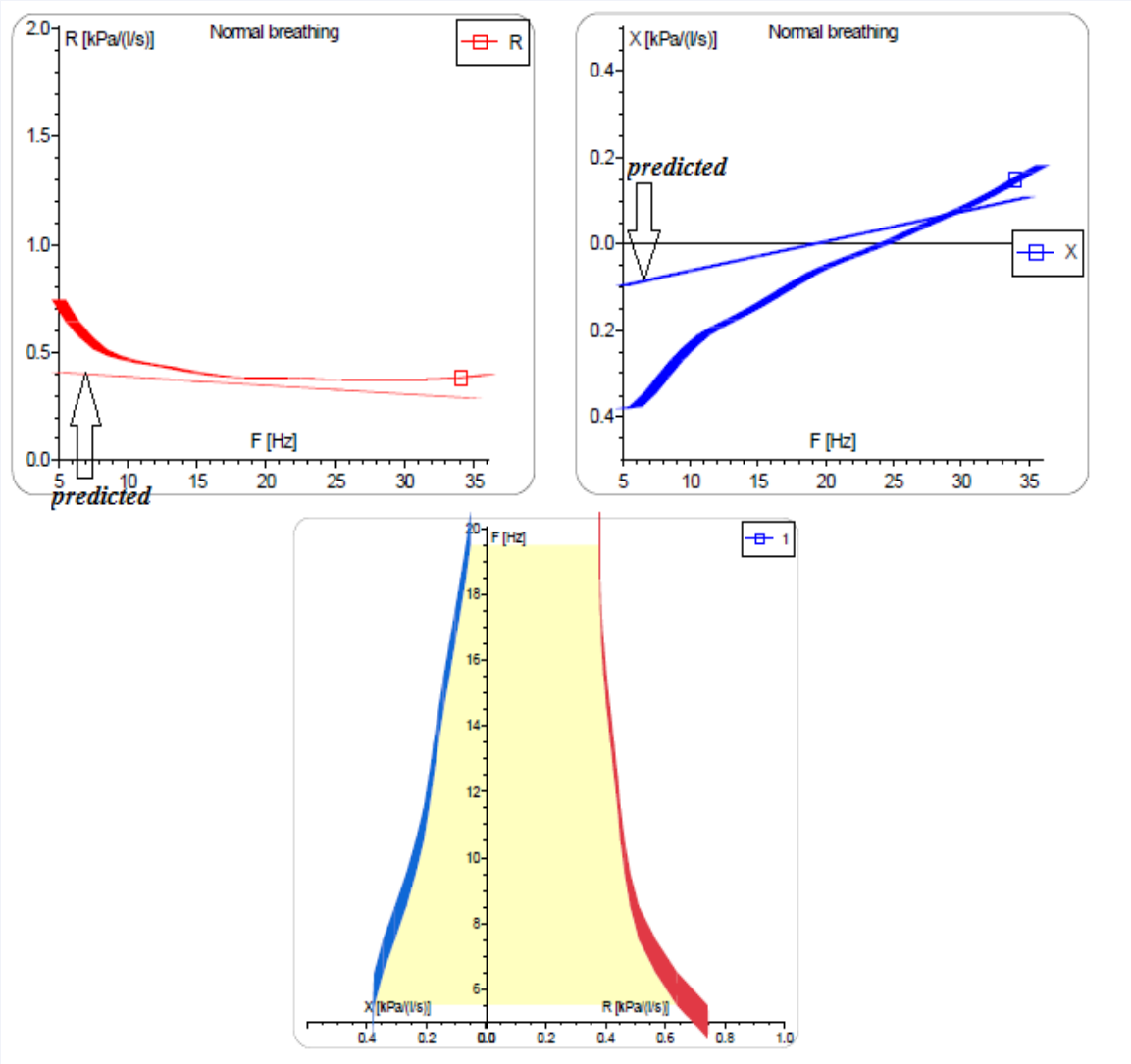

Figure 5 $R_{rs}(f)$ and $X_{rs}(f)$ curves of a 52 year-old patient with Idiopathic Pulmonary Fibrosis (IPF-UIP, TLC=44%) are depicted. Graphs come from the archives of the Centre for Smoking and Lung Cancer Research of the Hellenic Cancer Society, where the CareFusion(Master screen – IOS) machine is used. Significant increase of $R_{rs}5$=0.74 kPa/(L/s) can be observed, whereas high frequency resistance values remain within normal limits [$R_{rs}20$=0.38 kPa/(L/s)]. Thus, there is significant fdr=95%. Impressive increase of Xrs5= -0.38 kPa/(L/s) f_{res}=24 Hz and AX= 3.15 kPa/L can be observed in the same time. As a result, $X_{rs}(f)$ curve shifts to more negative values and significantly differs from its normal morphology. Additionally, high frequency X_{rs} values are also abnormal: Xrs20 = - 0.05 kPa/(L/s) = - 1022% of the predicted value.

while at the same time their sensitivity, specificity and diagnostic values allow safe clinical use and they obviously surpass the ones of the corresponding spirometric indices [110,111].

In any case, it is obvious that impedance indices modifications are of no specificity for restrictive syndrome, and vary significantly in respiratory system diseases with restrictive and mixed pathophysiology. However, it can be formulated that in most studies, reactance indices seem more reliable to evaluate the "strictly" restrictive pattern, while resistance indices variations probably suggest obstruction and mechanic non-homogeneity co existence, which are either restrictive syndrome aftereffects or of a different cause.

DISCUSSION AND CONCLUSION

Oscillometry (FOT and IOS) is a non invasive method to assess respiratory mechanics, and it is quit complete, concerning the amount of parameters evaluated. It is also quit easy to apply, as it demands only quiet, tidal breathing of the subject. However, it is must be pointed out that the main sources of existing data concern chronic obstructive pulmonary disease and bronchial asthma and that there is total lack of IOS data to evaluate many diseases with restrictive and mixed pathophysiology pattern. In addition to that, the total number of studies conducted using both techniques is also relatively restricted. Respectively, important issues such as bronchial hyper-reactivity indexes determination (challenge and dilatation tests), but also detection of specific patterns of impedance parameters modifications for obstructive

and restrictive syndromes, remain open.

Moreover, the use of different methodologies (single-frequency FOT, multi-frequency FOT, IOS), contribute to a variety of parameters existence, which very often describe the same disorder. On one hand, this increases complexity and possibly complicates clinical application of oscillometry, but on the other hand, many of these indices show different sensitivity and specificity values, and may describe different pathophysiological components of the disorders they are expected to evaluate.

Based on the above, oscillometry proves to be more of a significantly sensitive follow-up tool for respiratory system diseases progress and response to treatment, than a first class technique for diagnosis.

Within this reasoning, and according to the studies presented reasoning, we chose to present the current data in the present review, categorized on a basis of disease entity and not pathophysiological mechanisms and anatomy correlations, as often done in bibliography. At the same time, we attempted an analytical report on the pathophysiological substratum of each impedance component modification.

As far as one can tell, it is clear that impedance indices, as evaluated by FOT and IOS, express different and perhaps finer pathophysiological processes than conventional lung function tests, such as spirometry and body-plythesmography. This fact can probably be attributed to the inherent capacity of the method to evaluate quiet breathing. At the same time, no significant deviation is observed from conventional laboratory evaluation of respiratory diseases, a fact that is imprinted by moderate correlations among oscillometry and spirometry and/or body-plythesmography parameters, in most of the studies quoted.

Additionally, significant correlation of oscillometric indices with all daily symptoms of patients with respiratory diseases is detected, even for normal spirometric findings, which is exceptionally important in clinical practice. Thus, great sensitivity is achieved in detecting underlying pathology, and a different perspective is offered in approaching therapeutic interventions, as far as individualized care is concerned for patients' relief and improvement of their quality of life. Of great importance is also the fact that oscillometry is proved much friendlier to the subject than the conventional lung function tests, as it is a much simpler, more obvious, shorter method, requiring significantly less effort. Now, if we take under consideration that with simple quiet breathing of the subject-even one who cannot carry out correctly other conventional tests-almost all respiratory system mechanical properties can be evaluated satisfactorily, the choice of oscillometry as an evaluation tool for respiratory function seems ideal.

Summarizing, despite the significant sensitivity, easy appliance and significant correlation of the method's findings with the clinical manifestations of patients with respiratory disease, there are important issues under study. Furthermore, respective specificity doesn't seem to be achieved, as in many cases the results of oscillometry form a common denominator of heterogeneous pathophysiological entities, like for example emphysema and restrictive syndromes. In any case, deeper comprehension of pathophysiology of impedance parameters modifications is demanded, so that oscillometry results get deeper, clearer interpretation that can reinforce, to an even greater extend, the contribution of lung function testing to the quality of life improvement of the patients.

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