
Forced Oscillation Technique in the Detection of Smoking-Induced Respiratory Changes

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem with high and increasing prevalence (Gold 2011). According to WHO estimates, 80 million people have moderate to severe COPD (WHO, 2012). There is general agreement in the literature that it is necessary to develop new accurate and noninvasive tests of lung function (Enright and Crapo, 2000; Kaminsky and Irvin, 2001; Polkey et al., 2004). In the particular case of COPD, the National Heart Lung and Blood Institute recently recommended that research on new technologies to improve the non-invasive testing of lung function in this disease should be a priority (Croxton et al., 2002).

The Forced Oscillation Technique (FOT) offers a simple and detailed approach to investigating the mechanical properties of the respiratory system. This method characterizes the respiratory impedance and its two components, respiratory system resistance (R_{rs}) and reactance (X_{rs}). These parameters are usually measured at various frequencies using small pressure oscillations superimposed at the mouth during spontaneous breathing. The method is simple and requires only passive co-operation and no forced expiratory maneuvers. Another important advantage, particularly in pathophysiological research, is that FOT can be used to provide information on the mechanical characteristics of the respiratory system that is complementary to the information provided by spiroometry (Navajas and Farré, 2001; Macleod and Birch, 2001; Oostveen et al., 2003; Bates et al., 2011; Kaczka and Dellacà 2011). This technique has the potential to greatly increase our knowledge regarding the pathophysiology of smoking, as well as to help in the clinical diagnosis of early smoking-induced respiratory alterations and COPD (Faria et al., 2009; Faria et al., 2010; Silva et al., 2011; Postma et al., 2012; Amaral et al., 2012).

This chapter discusses the history and current state of the art of FOT for detecting smoking-induced respiratory diseases. We focus on how FOT has emerged as a powerful method not

only to extract clinically relevant information but also to provide insight into the mechanisms responsible for smoking-induced respiratory diseases. The main topics covered by this review will be as follows:

- First, we present a short overview of COPD in section 2;
- Section 3 provides a brief description of FOT for basic clinical assessment. Here, we describe the interpretation of the FOT parameters and the potential and limitations of this technique;
- The main results presented in the literature concerning the diagnosis of the effects of smoking and COPD using multi-frequency and single-frequency FOT methods are described in section 4;
- Section 5 presents and discusses new results concerning the evaluation of diagnostic accuracy in patients classified by the GOLD (2011) stage;
- In section 6, we highlight important future directions for this research field. We discuss the high potential of FOT in telemedicine, the use of FOT to evaluate changes in the complexity of the respiratory system, and the use of FOT parameters in clinical decision support systems based on machine learning;

We conclude by examining the current use of FOT as a diagnostic tool in smoking-induced respiratory diseases and suggesting further studies needed to achieve its full potential in routine clinical use.

2. Short review of Chronic Obstructive Pulmonary Disease

COPD is a preventable and treatable disease, characterized by airflow limitation, which is partially reversible (GOLD, 2011).. The limitation is often progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, especially cigarette smoke (GOLD, 2011). COPD increases in prevalence and mortality worldwide each year, causing enormous socio-economic damage. Estimates by the World Health Organization (WHO) suggest that approximately 65 million people have moderate to severe COPD. Worldwide, more than 3 million people died of COPD in 2005, which corresponded to 5% of all deaths worldwide (WHO, 2012). In 2002, the disease was the fifth leading cause of death worldwide. The total deaths from COPD are projected to increase by 30% over the next 10 years unless urgent measures are taken to reduce the underlying risk factors, particularly tobacco use. Estimates indicate that by 2030, COPD may become the third leading cause of death worldwide (WHO, 2012).

The complex pathophysiological behavior of COPD is characterized by the presence of chronic bronchitis, obstructive bronchiolitis and emphysema (GOLD, 2011). The disease process is directly related to an amplified inflammatory response of the lungs, triggering the destruction of the lung parenchyma and the consequent disruption of defense mechanisms and normal repair. Such changes are responsible for airflow limitation and air trapping, observed in various stages of the disease (GOLD, 2011). Pathological changes occur in four different regions of the lung: larger caliber airway, peripheral airways, lung parenchyma and pulmonary vasculature (ATS/ERS, 2004, GOLD, 2011). In larger caliber airways, structural

changes occur in the goblet cells and submucosal glands, causing mucus hypersecretion and squamous metaplasia, as shown in Figure 1 (ATS/ERS, 2004, GOLD, 2011).

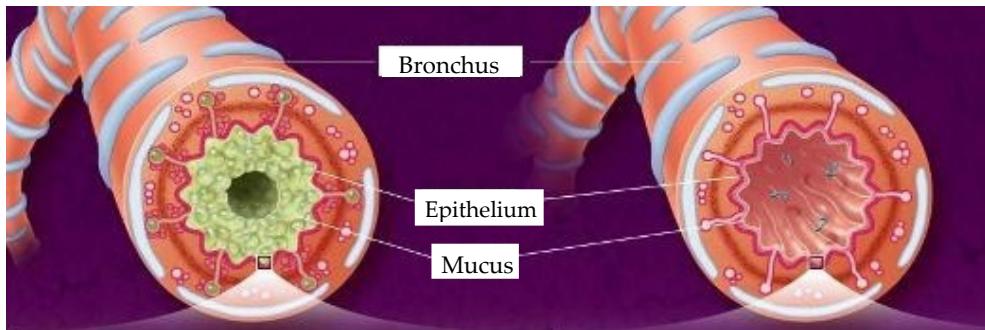


Figure 1. Normal bronchus (right). On the left, a bronchus depicting the inflammatory process due to COPD (Source: <http://www.nlm.nih.gov/images/ency/fullsize/19377.jpg>).

In peripheral airways (<2 mm diameter), we observed thickening of the airway wall, peribronchial fibrosis, exudate, narrowing of the airways (obstructive bronchiolitis) and increased inflammatory response. In the lung parenchyma, the structural changes involve the destruction of the alveolar wall, the apoptosis of epithelial cells and emphysema (Figure 2) (ATS/ERS, 2004, GOLD, 2011).

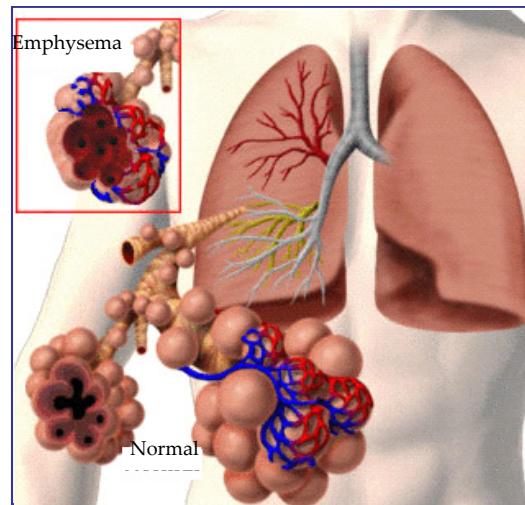


Figure 2. Illustration of an alveolar emphysema (highlighted). Destruction of lung parenchyma and vasculature. (Source: <http://www.nlm.nih.gov/images/ency/fullsize/19377.jpg>).

The main characteristic of COPD is airflow obstruction, which is not fully reversible. Spirometry is the gold standard technique used to assess this obstruction, and the parameters obtained for these analyses are derived from forced expiratory maneuvers

(ATS/ERS, 2005). However, the modifications to respiratory mechanics are not always detected by this test (Coe et al. 1989). Moreover, some patients are not able to reliably perform spirometry, as the methods require good subject co-operation and maximal effort (Crapo et al., 2003). Whole-body plethysmography features a more complex method in which the individual must remain isolated from the external environment, breathing spontaneously within a hermetically sealed box (ATS/ERS, 2005). The advantage of this method is the opportunity to obtain important variables related to lung mechanics, especially the residual volume and functional residual capacity (ATS/ERS, 2005). The main disadvantage is the maintenance of individuals in a closed environment, which can generate claustrophobic reactions. Recommendations for research in COPD (Croxton et al., 2002) include the need for improved noninvasive mechanical tests of lung function. In this context, FOT was suggested by Crapo et al. (2003) as an attractive alternative for diagnosing obstruction in COPD, as it requires little patient effort and cooperation. A brief description of this technique is provided in the next section.

3. Forced oscillation basics

Since the FOT methodology was introduced in the mid-1950s (DuBois et al., 1956), numerous variants of the FOT have been developed. This short review is focused on the use of FOT in the clinical diagnostic of COPD, addressing only the most basic concepts, and the reader is referred for more detailed information to other review and monograph articles (Peslin and Fredberg, 1986; Navajas and Farré, 2001; Macleod and Birch, 2001; Oostveen et al., 2003; Marchal and Hall, 2010; Bates et al., 2011; Kaczka and Dellacà 2011).

3.1. Measurement principle

Subjecting a physical system to forced oscillations is a very general approach to the investigation of its structure and other properties (Ljung, 1987). Its application to respiratory mechanics was first proposed by DuBois and co-workers (1956). This method consists of applying small sinusoidal pressure variations to stimulate the respiratory system at frequencies higher than the normal breathing frequency and measuring the flow response. The basic instrumentation used to evaluate respiratory impedance by FOT is described in Figure 3.

An electric signal is produced in the impedance analyzer and applied to a loudspeaker that converts it to a corresponding pressure waveform. Usually, this pressure signal presents an amplitude of approximately 2 cm H₂O (peak-to-peak). This signal is directed to the airway opening of the patient, which is connected *via* a mouthpiece to the set-up. The airflow (V') is measured using a pneumotacograph (PNT in Figure 1), and the pressure (P) is measured at the airway input of the patient. The resulting signals are amplified, filtered and digitized in the impedance analyzer. Then, the respiratory impedance (Z_{rs}) is calculated using the fast Fourier transform (FFT) of these signals (1):

$$Z_{rs}(f) = \frac{FFT(P)}{FFT(V')} \quad (1)$$

In practice, the sinusoidal pressure excitations are superimposed on the subject's spontaneous breathing. To enable spontaneous breathing by the patient, the system allows the individual to breathe comfortably during the experiment through a tube (Bias tube in the Figure 3) that operates predominantly as a pneumatic inertance element. This inertance provides a low-impedance path to the atmosphere for the low frequencies associated with the breathing process, while imposing high impedances to the high frequencies produced by the loudspeaker. A pneumatic resistor may also be used for this purpose. To renew the air breathed by the individual, the system also includes a bias flow (Figure 3) of approximately 0.2 l/s near the subject's mouth.

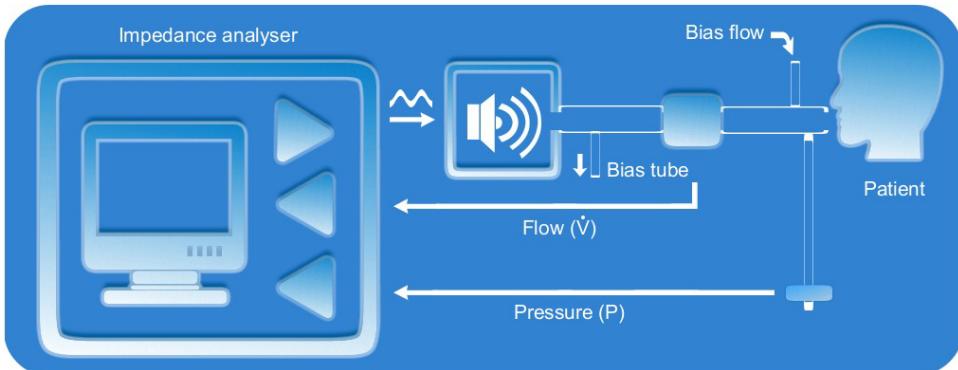


Figure 3. Basic schematic arrangement of forced oscillation respiratory impedance measurement.

To perform the FOT analysis, the volunteer remains seated, keeping the head in a normal position and breathing spontaneously through a mouthpiece. During the measurements, the subjects firmly support their cheeks and mouth floor using both hands, and a nose clip is worn. This method allows the evaluation of the "respiratory input impedance". Applying the oscillating pressure across the chest wall and measuring the oscillatory flow downstream at the mouth allows us to estimate the "transfer impedance". The respiratory input impedance is much more widely used clinically and is the focus of this work. The interested reader may find detailed information on "transfer impedance" in previous works (Mac Leod and Birch, 2001; Oostveen et al., 2003).

3.2. Devices

FOT analysis can use oscillations on a single (mono) frequency or more than one (multi) frequency test signals. Each implementation has its advantages and disadvantages. Analyses using a single frequency are suitable for instantaneous assessment of the total impedance, making it possible to identify the rapid changes in impedance associated with changes in airway caliber during the respiratory cycle.

However, tests using several frequencies are slower, with results that reflect the average behavior of the respiratory system over several cycles. Multifrequency instruments usually

include a frequency range of approximately 4–32 Hz. The advantage in this case lies in a much more detailed analysis that provides indices associated with the total resistance and reactance in several frequencies. The original multi-frequency FOT method focused on two forms of forcing: a forced white noise signal (Michaelson et al., 1975) and an impulse waveform applied at the mouth (Landser et al., 1976). We now know that an impulse is the least reliable and desirable excitation waveform to apply for system identification because of signal-to-noise limitations over the bandwidth of interest (La Prad et al., 2008; Pintelon and Schoukens, 2001). The highest possible signal-to-noise ratio is produced using pseudorandom noise (MacLeod and Birch, 2001; Oostveen et al., 2003; Bates et al., 2011), which is a periodic signal designed specifically to include only a designated set of desired frequency components, each represented by a precisely defined amplitude and phase.

FOT based on a pseudorandom noise signal has been validated over a period of more than three decades (Mac Leod and Birch, 2001). Importantly, FOT should not be confused with the more recently introduced technique of Impulse Oscillometry (IOS). IOS differs from classical FOT in the data processing and the parameters used to interpret the raw data (Mac Leod and Birch, 2001; Hellinckx et al., 2001). Several technical and clinical validation issues also remain to be assessed for IOS techniques (MacLeod and Birch, 2001; Hellinckx et al. 2001; Ritz et al., 2002). Although the signal used in IOS has the practical advantage of being relatively easy to generate, it has significant disadvantages in terms of energy distribution (Bates et al., 2011). From a system identification point of view, the impulse excitation signal used in IOS is a much worse excitation signal than the multisine used in FOT. This difference is associated with a worse crest factor in the impulse signal (La Prad et al., 2008; Pintelon and Schoukens, 2001). This characteristic introduces concerns associated mainly with the following points (Mac Leod and Birch, 2001): (a) whether energy transfer during impulse excitation is sufficient (especially ~ 5 Hz), (b) the tendency of impulses to induce non-linear flow effects, (c) the possibility of reflex responses to impulses and (d) possible shear effects occurring at the locus of the airway wall.

3.3. Limitations

As for other techniques of functional assessment, the limitations of FOT and its consequences must be recognized. An important source of errors is related to the process of spontaneous breathing of the patient, which introduces both random and systematic errors. These errors are reduced by using excitation frequencies at least 10 times higher than those present in the spontaneous ventilation process and with appropriate acceptance criteria (Mac Leod and Birch, 2001; Oostveen et al., 2003; Melo et al., 2000). The errors may be easily evaluated using the coherence function (γ^2) between the pressure and airflow signals. The coherence function is the equivalent in the frequency domain of a correlation coefficient in the time domain. A perfect coherence (1.00) describes no influence of the respiratory signal in the results and may be obtained performing the exams in apnea conditions. In practice, the patient ventilates during the exam. The respiratory influence increases with the amplitude and frequency of the ventilation (irregular breathing or acute hyperventilation), introducing proportional reductions in the coherence function. A minimal coherence value

of 0.9 is usually considered adequate (Mac Leod and Birch, 2001; Faria et al., 2010). Any time the coherence computed for any of the studied frequencies is smaller than this threshold, the maneuver may not be considered valid, and the examination needs to be repeated.

The compliance of the soft tissues of the upper airways, including the cheeks, comprises a mechanical impedance placed in parallel with the respiratory system. The resulting effect of this placement is to reduce the impedance measured in relation to its actual value. This effect is more pronounced in the presence of high impedances, as is the case for highly obstructive COPD patients. In practice, this drawback is minimized by asking the patient to firmly support their cheeks and mouth floor (Navajas and Farré 2001, Oostveen et al., 2003). Artifacts can also occur if the glottis is closed or if the seal around the mouthpiece is lost during testing. Swallowing or an improper seal with the nose clip during the measurement are reasons to discard the measurement. Most of these events can easily be detected in the flow signal.

3.4. Interpretation of the results

FOT characterizes the module of the respiratory impedance (Z_{rs}), which is associated with respiratory system resistance (R_{rs}) and reactance (X_{rs}) as described in equation (2):

$$Z_{rs} = \sqrt{R_{rs}^2 + X_{rs}^2} \quad (2)$$

The Z_{rs} is related to the total mechanical load provided by the respiratory system, including the resistive and reactive properties of the lung and chest wall. A convenient way to represent the behavior of the impedance tests employs the description of the resistive and reactive properties of the respiratory system, allowing a direct correlation with the mechanical properties involved.

3.4.1. Multi-frequency

Usually, the results obtained in multi-frequency systems are described for each studied frequency in the whole range evaluated, as demonstrated in Figure 4A. The R_{rs} measured by FOT describes the total resistance of the respiratory system, including both frictional losses during the airflow process (similar to airway resistance measurements in plethysmography) and the resistance related to lung and chest wall tissue. There is no consensus in the literature concerning the parameters used in the interpretation of these curves. Some groups use simple resistance values, describing the total resistance in the specified frequency, whereas other groups use an analysis of linear regression in the frequency range between 4 and 16 Hz (Figure 4A).

This analysis is used to obtain the intercept resistance (R_0) and the slope of the resistive component of the impedance (S). These parameters are associated with the total resistance of the respiratory system (Lorino et al., 1997) and with the respiratory system's non-homogeneity (Peslin et al., 1991; Pride, 1992), respectively. Using the same frequency range, the mean resistance (R_m), a parameter commonly related to airway caliber, is also calculated (Macleod D, Birch M, 2001).

The X_{rs} is directly related to the energy storage by the components of the respiratory system. These components are the dynamic compliance and the inertance. The dynamic compliance is composed of the thoracic gas compression, the lung and bronchial wall compliances, the compliance of the chest wall/abdomen compartment and the compliance of the soft tissues of the mouth, cheeks and pharynx (upper airway). On the other hand, the respiratory inertance includes the mass of the central airway gas and the tissue inertance. While the lower frequency portion of the X_{rs} curve is dominated by the effects of the dynamic compliance (negative values in Figure 2B), the higher frequencies are dominated by the effects of inertance (positive values in Figure 4B). In the case where the effects of compliance and inertance are equal, X_{rs} becomes zero, and resonance occurs (resonant frequency - f_r in Figure 4B).

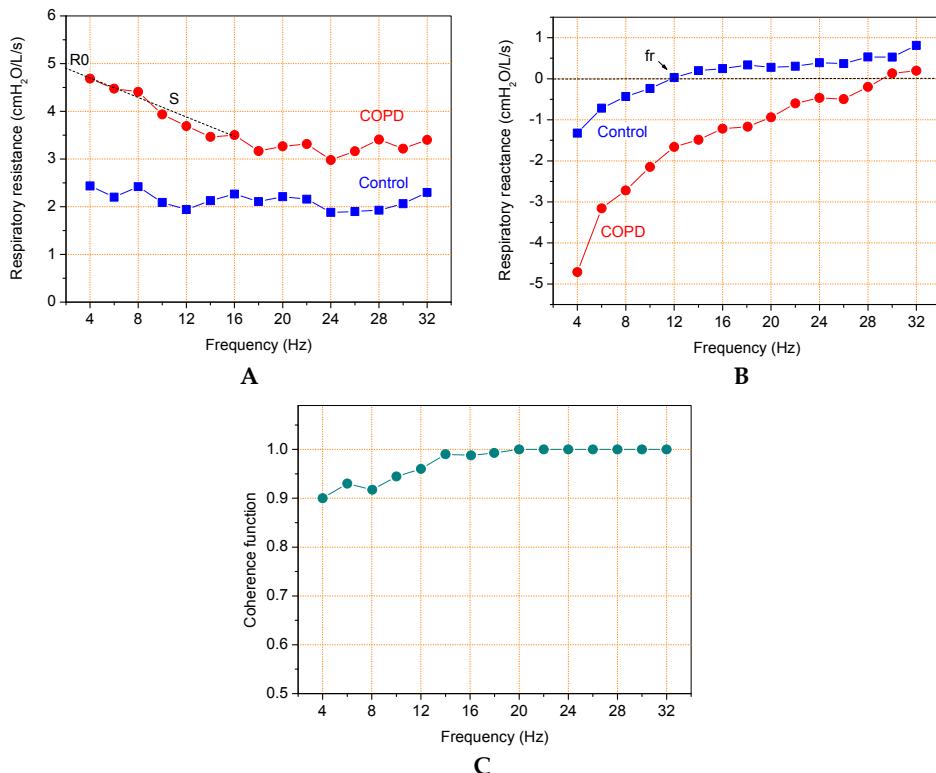


Figure 4. Examples of results for the resistance (A), reactance (B) and coherence function (C) obtained in normal subjects and in patients with COPD. The analysis used to obtain the intercept resistance (R_0) and the slope of the resistive component of the respiratory impedance (S) is described in the text.

There is a consensus in the literature concerning the behavior of respiratory input impedance in normal subjects and patients. In general, normal individuals show resistances with nearly constant values (Figure 4A). The reactance at low frequencies is negative due to

system compliance, displaying an increasing value up to a null at approximately 8 Hz (resonant frequency). From this point, the reactance becomes positive, dominated by the inertial properties of the system (Figure 4B). Patients generally exhibit higher levels of resistance, decreasing with increasing frequency (Figure 4A). The magnitude of the reactance at low frequencies is greater because of reduced compliance, and the resonant frequency is generally higher. Figure 4B illustrates the behavior described.

Figure 4C shows experimental results demonstrating the typical behavior of the coherence function. Note the decrease in the coherence function in the region of low frequencies, which is associated with interference due to the harmonics derived from the spontaneous breathing process.

3.4.2. Mono-frequency

The use of multi-frequency or mono-frequency FOT depends on the desired application. Multi-frequency is preferred in studies exploring the patterns or mechanisms of the frequency dependence of Zrs in health and disease. In contrast, single-frequency is used in the study of relatively rapid changes in Zrs, such as the changes observed during the respiratory cycle (Dellacà et al., 2004), deglutition apnea (Souza et al., 2008), deep inspiration (Slats et al. 2007), and the evaluation of airway patency in sleep apnea (Badia et al., 1998; Lemes et al., 2003). Figure 5 shows representative examples of the typical morphology of the airflow and impedance signals obtained in a control (A) and a COPD (B) individual. Notice the difference in the impedance scales.

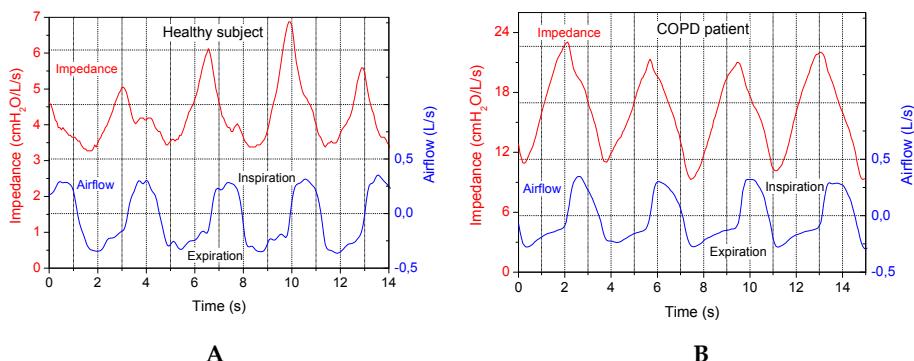


Figure 5. Typical airflow and respiratory impedance observed in normal subjects (A) and COPD individuals (B). Notice the difference in the impedance scales.

A characteristic feature of COPD is that Zrs is often very different between inspiration and expiration, in contrast to the situation in normal subjects (Dellacà et al., 2007; Bates et al., 2011). These characteristics may be observed in Figure 5. Note the smaller difference between inspiration and expiration in the normal subject (Figure 5A) and the higher values of expiratory impedance in the COPD patient (Figure 5B).

The parameters used to interpret raw single-frequency FOT data depend slightly on the research group (Dellacà et al. 2004; Johnson et al. 2005; Dellacà et al. 2010; Silva et al., 2011). In general, Zrs and its components (Rrs, Xrs) are considered as the mean values during inspiration (Zi, Ri, Xi) and expiration (Ze, Re, Xe), the difference between Xi and the mean Xe (Δ Xrs) has been used as an index of expiratory flow limitation (Dellacà et al. 2004). In previous studies from our group (Silva et al., 2011), the mechanical alterations during different phases of the respiratory cycle were characterized using the following parameters:

- The mean respiratory impedance (Zm), calculated for the complete exam;
- The mean impedance during the inspiration cycles (Zi);
- The mean impedance during the expiration cycles (Ze);
- The mean impedance at the beginning of inspiration (Zbi);
- The mean impedance at the beginning of expiration (Zbe);
- The mean peak-to-peak impedance (Zpp), the difference between Zbe and Zbi;
- The mean change in the impedance (Δ Zrs), the difference between Ze and Zi.

This analysis has been successfully applied in our laboratory in the diagnosis of respiratory changes in advanced COPD patients. These results, together with other studies aiming to diagnose the abnormal effects of smoking and COPD using multi and mono-frequency FOT, are described in the next section.

4. Main results presented in the literature concerning the diagnosis of the effects of smoking and Chronic Obstructive Pulmonary Disease

FOT has been applied by a number of investigators to obtain a detailed analysis of the respiratory mechanics in smokers compared with non-smokers and former smokers. COPD was also studied. This section focuses on a historically organized review of the main works dedicated to the diagnosis of abnormal changes in respiratory mechanics due to smoking. It is important to point out that FOT has also allowed other important advances in COPD, associated, for example, with the study of animal models (Bates et al., 2011), mechanical ventilation (Navajas and Farré, 2001) and pharmacological response (Woulers et al., 1992).

4.1. The first studies in the 1960s and 1970s

Grimby et al. (1968) investigated 15 patients with varying degrees of obstructive lung disease (11 COPD) using oscillations of 3, 5, 7 and 9 Hz. The authors observed frequency dependence of both resistance and compliance, which were interpreted as effects of the uneven distribution of the mechanical properties in the lungs. It was concluded that measurements of total respiratory resistance by the FOT appear to be as useful for assessing abnormalities in airway resistance as the plethysmographic or esophageal pressure techniques. In the 1970s, a random noise pressure wave was used in the classical work of Michaelson et al. (1975) to investigate 10 normal subjects, 5 smokers, and 5 patients with COPD. The authors observed small differences between normal subjects and smokers. These two groups behaved approximately like a second-order system. In COPD, however, the

phase angle was more negative at all frequencies, and the resonant frequency was between 15 and 29 Hz. In addition, the behavior of Zr deviated markedly from the second-order behavior observed in normal subjects. Kjeldgaard et al. (1976) studied a group of non-smokers ($n = 10$) and two groups of smokers, the first without respiratory symptoms ($n = 14$) and with an average of 20 pack-years and a second group of smokers with respiratory disease ($n = 6$) and with an average of 48 pack-years. A significant increase in the resistance values measured at 3 Hz and dependence of the resistance on frequency (S) was observed between the control group and the group of smokers without symptoms and between the control group and the group of smokers with the disease. Hayes et al. (1979) compared the respiratory function of 12 nonsmokers, 15 young smokers (mean age 29.9 years) and 8 patients with COPD. The authors observed a non-significant increase of resistance in the smokers compared with the control group and a significant increase in the group of patients. In the resistive curve, there was a rise in values in the COPD group compared with the control group throughout the frequency range. A greater dependence of the resistance values on the frequency was observed in COPD patients. The authors also reported a reduction of dynamic compliance between the control group and the group of smokers and between the control group and the group of patients with COPD. However, these changes were only statistically significant when comparing the control group with the group of patients. The increase in f_r was significant when comparing the control group and the smokers, as well as in the comparison of the control group with the patients. These changes were obtained in the reactance curve, in which the values were more negative in the curve of patients compared with the control group. The authors suggested that the difference is associated with lower compliance and a less homogeneous respiratory system.

4.2. Studies performed in the 1980s

The development of digital computers, methods of signal analysis based on the FFT and accurate sensors contributed to the development of sophisticated instrumentation (Delavault et al., 1980; Farré et al., 1986; Farré et al., 1989; Franken et al., 1985; Pelle et al., 1986), which allowed the expansion of this research area. In the early 1980s, Peslin et al. (1981) studied the impedance of smokers and former smokers compared with a control group. A non-significant increase of resistance was observed in ex-smokers and a significant increase was observed in smokers. Unlike the peak flows, the FOT indexes were not correlated with cigarette smoking expressed in pack-years, indicating that FOT would not be able to detect early changes in the airways caused by smoking. Landser et al. (1982) showed a small increase in the values of the resistance curve when comparing smokers with nonsmokers and concluded that FOT had little sensitivity in detecting the effects of smoking on lung function. Brochard et al. (1987) studied the effect of smoking on the lung function of workers in a gas industry. They observed no significant increases of R_0 and f_r when comparing the control group with the group of ex-smokers and smokers. Cauberghs and Woestjine (1989) analyzed the behavior of R_{rs} and X_{rs} in 16 subjects with obstructive diseases (asthma and COPD) and with different degrees of airway obstruction. The authors noted that R_{rs} showed higher values and more negative X_{rs} values with increasing

obstruction. A significant increase in fr was observed. Coe et al. (1989) evaluated the effects of smoking on lung function in young and older individuals. The authors observed increased resistance (of 6 Hz) and fr when comparing all non-smokers with all smokers. The subjects were subsequently classified into groups aged 32-44 years (24 pack-years) and between 45-64 years (24 pack-years). No significant changes were observed in the comparisons in the younger group. On the other hand, significant changes were observed in comparing resistance and fr in subjects over 45 years.

4.3. Studies performed in the 1990s

Initially, Van Noord et al. (1991) studied individuals with asthma, chronic bronchitis and emphysema, comparing the parameters of FOT, spirometry and plethysmography. The authors' conclusion was that the FOT parameters were more sensitive in classifying these individuals. Pasker et al. (1996) also assessed lung function in different groups of individuals with and without respiratory disorders using FOT and spirometry. In the group of patients with obstructive diseases (asthma, chronic bronchitis and emphysema), changes were found in the values of the resistance and reactance of the respiratory system. The authors emphasized that the data from the impedance measurements by FOT are complementary to that obtained from spirometry.

4.4. Studies in the 21st century

The developments in the twenty-first century begin with Yang and Yang (2002). These researchers evaluated the lung function of 180 non-smokers, 109 smokers with 18.8 mean pack-years and 82 ex-smokers with 20.3 mean pack-years. They found resistance significantly increased in the group of smokers compared with nonsmokers. No significant changes were found when comparing nonsmokers and former smokers. Janssens et al. (2001) observed that Obstructive Lung Disease (OLD) is highly prevalent in elderly subjects but markedly under-diagnosed, which may be associated with the fact that only 40-50% of hospitalized elderly patients are able to adequately perform spirometric tests. These authors evaluated the diagnostic value of the FOT for identifying OLD in an acute-care geriatric hospital. Significant correlations were found between spirometric and Zrs measurements. The Zrs parameters yielding the best sensitivity and specificity for detecting OLD were fr ($Se=76\%$; $Sp=78\%$) and R0 ($Se=76\%$; $Sp=74\%$). Seventy-six percent of the patients were correctly classified as having OLD or not. The authors concluded that FOT could contribute to the diagnosis of OLD in elderly hospitalized patients. In a later work assessing the high potential for FOT in this age range, Guo et al. (2005) investigated the diagnosis of obstructive lung disease in older patients. These authors studied 97 subjects, 48 normal subjects (control group) and 49 patients who were assessed by FOT, the interrupter technique (IT) and spirometry. The authors aimed to compare the performance of FOT and IT in the diagnosis of elderly patients with abnormal flow-volume curves and bronchodilator response. There was significant correlation between the FOT indices and FEV1 and FEV1/FVC. Furthermore, FOT precisely identified 81.4% of cases of obstruction, with Se of 78% and Sp of 85%. The fr and R0 were the parameters with better sensitivity (Se)

and specificity (Sp). The authors concluded that FOT presents better performance than IT in the evaluation of bronchial obstruction in elderly subjects (Guo et al. 2005). Di Mango et al. (2006) compared healthy subjects ($n = 21$) with a group of COPD classified according to the degree of airway obstruction (mild, $n=16$; moderate, $n=23$; and severe, $n=40$) to evaluate the clinical potential of FOT in detecting changes in the respiratory mechanics in these patients. The COPD Rrs curves were significantly higher than for the control group. The increased obstruction caused an increase in total resistance, especially at lower frequencies, resulting in a dependence of the resistance on frequency. The Xrs became more negative with obstruction, with the most marked changes in the lower frequencies. All resistance values showed significant changes with the degree of obstruction ($p<0.0001$). The mean values of R₀ and R_m increased significantly when the groups of normal and COPD patients with mild obstruction were compared. S decreased significantly, but there was no difference between the control and COPD with mild obstruction. All parameters showed significant changes in the reactive parameters ($p<0.006$). It was shown that by increasing the degree of obstruction, Rrs increased, and Xrs become more negative. Interestingly, the resistance showed significant changes in the initial condition of obstruction, whereas in the later stages, the reactive parameters were most sensitive. This behavior is consistent with the mixed pattern usually developed in the later stages of COPD. Dellacà et al. (2004) used FOT at 5 Hz to detect expiratory flow limitation (EFL) in 15 subjects with COPD. This work studied the Zrs parameters along the ventilation cycle and compared them with the gold standard method, esophageal balloon manometry. According to the authors, the parameter that best described the EFL was Δ Xrs (difference between mean inspiratory and expiratory Xrs), with Se=95% and Sp=98%. This work established that Δ Xrs values $\geq 2.8 \text{ cmH}_2\text{O}$ are characteristic of EFL. The authors also correlated higher values of Δ Xrs with a more advanced stage of the disease. In a later study from the same group, Dellacà et al. (2006) studied the EFL through monofrequency FOT (5 Hz) in patients with COPD and restrictive ventilatory disease. Nasal continuous positive airway pressure (CPAP) was used at different levels to evaluate the reduction of the EFL (0, 4, 8 and 12 cmH₂O). The Δ Xrs was able to correctly classify 94.8% of breaths as flow-limited or not, producing a 95% sensitivity and specificity of 98%. The authors suggested that the identification of EFL by FOT can modulate the level of CPAP titration to correct the EFL, eliminating unnecessary hemodynamic effects and inspiratory muscle overload due to increased lung volume (Dellacà et al. 2006). More recently, this group (Dellacà et al. 2007) compared FOT (5 Hz) with the technique of negative expiratory pressure (NEP) in the evaluation of the EFL. The authors found Δ Xrs sensitivity and specificity values of 93% and 91%, respectively. It was reported that both techniques are effective for detecting EFL, although they employ different methodologies. They pointed out that FOT has the advantage of allowing a quantitative measurement of the phenomenon of EFL. The study conducted by Johnson et al. (2007) examined the ability of single-frequency FOT (5 Hz) to detect longitudinal changes during an exacerbation of COPD compared with spirometry, gas exchange, symptoms and a quality of life questionnaire. Thirty-nine subjects with COPD were analyzed. FOT parameters were positively correlated with changes in symptoms and quality of life, representing objective measurements to document the exacerbation. Slats et al. (2007) analyzed by FOT at 8 Hz the effect of deep inspiration in Rrs of individuals with asthma and COPD compared with a control group. In asthmatic

patients, a direct relationship was found between the number of inflammatory cells and the bronchodilator effect of deep inspiration, resulting in reduced resistance of the respiratory system. In subjects with COPD, this relationship was not clearly observed, possibly due to the absolute loss of alveolar septa, leading to a reduction of the effect of parenchymal interdependence. This mechanism was probably related to fewer bronchodilations by deep breaths in COPD patients. The authors assume that this loss in ability to reduce respiratory resistance by deep inspiration is due to structural damage of the airways or lung parenchyma in COPD. These results indicated that, in both asthma and COPD, the mechanisms of bronchodilation by deep inspiration are changed. However, this change occurs by different pathophysiological mechanisms, most easily identified by monofrequency FOT in asthma (Slats et al. 2007). Faria et al. (2009) investigated if FOT would be able to detect the early effects of smoking. To this end, pulmonary function was assessed by FOT and spirometry in a group of smokers ($n=28$) and in a group of nonsmokers ($n=28$). A small, non-significant reduction was observed of the spirometric parameters, which were still at normal levels. In contrast, the FOT parameters (R_0 , fr and Zrs) increased, and more negative values in Xm and a more reduced $Cdyn$ were observed. The Rrs curves showed higher values in smokers than in nonsmokers. In the Xrs curves, the values for the smokers were more negative. The clinical potential of FOT was evaluated by calculating the area under the ROC curve (AUC) (Swets, 1988). This analysis showed that R_0 , $Cdyn$, and Zrs offered accuracies equal or greater than 75%, indicating that these parameters can be useful in identifying early changes due to smoking. Interestingly, comparing the AUCs obtained among oscillometric and spirometric parameters, it was observed that the accuracy was significantly higher for the FOT parameters (Figure 6, Table 1). These results suggested that FOT might be more sensitive than spirometry to detect early changes due to smoking. They also suggest that FOT could be a useful tool in screening smokers who will develop respiratory disease resulting from changes induced by smoking. If this hypothesis is confirmed in a wider number of subjects, FOT may offer the possibility of demonstrating abnormalities during a phase at which pathological changes are still potentially reversible, helping to prevent the development of COPD. Continuing this research, Faria et al. (2010) compared the diagnostic accuracy of the FOT and spirometric parameters in groups with different degrees of tobacco consumption. One hundred and seventy subjects were divided into five groups according to the number of pack-years smoked: four groups of smokers classified as <20, 20-39, 40-59, and >60 pack-years and a control group. The early adverse effects of smoking in the group with < 20 pack-years were adequately detected by FOT parameters.

In this group, the comparisons of the ROC curves showed significantly better diagnostic accuracy ($p<0.01$) for the FOT parameters. On the other hand, in the groups of 20-39, 40-59, and > 60 pack-years, the diagnostic performance of the FOT was similar to that observed with spirometry. This study provided additional evidence that the FOT parameters are able to detect early smoking-induced respiratory involvement when pathologic changes are still potentially reversible (<20 pack-years). These findings also suggest that FOT presents a similar sensitivity to that presented by spirometry in detecting more advanced changes (20-39, 40-59, and >60 pack-years). Ionescu et al. (2010) compared healthy and COPD groups by applying constant-phase models (Bates et al. 2011) to FOT data within the range 4-48 Hz.

Changes in respiratory mechanics from healthy COPD patients were observed with four- and five-parameter constant-phase models. Tissue damping ($p<<0.01$), tissue elastance ($p<0.02$) and tissue hysteresivity ($p<<0.01$) provided significant separation between healthy and COPD groups. The authors concluded that the identified model values are sensitive to variations between healthy and COPD lungs. In a recent work from our group, Silva et al. (2011) used the parameters described in section 3.4.2 to evaluate the diagnostic potential of mono-frequency FOT in patients with severe COPD. The respiratory impedances were always significantly higher in COPD patients than in the control group (Figure 7; Z_m , Z_{bi} , Z_i , Z_{be} and Z_e ; $p<0.001$). Similar comparisons revealed that Z_{pp} ($p<0.001$) and ΔZ_{rs} ($p<0.005$) were also significantly increased in patients with COPD. It was observed that the respiratory impedance did not change significantly during the respiratory cycle in the control group (Figure 7; ANOVA, $p=ns$). Conversely, considering the cycle from the beginning of the inspiratory phase to the end of the expiratory phase, the Z_{rs} values were significantly increased in the COPD group (ANOVA, $p<0.005$). COPD patients presented Z_e significantly higher than Z_i ($p<0.001$) and Z_{be} significantly higher than Z_{bi} ($p<0.001$).

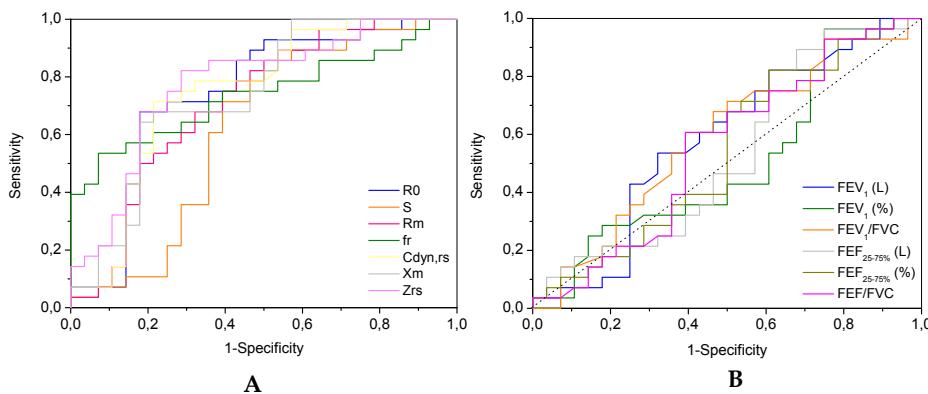


Figure 6. Receiver operating characteristic (ROC) curves for FOT (A) and spirometric parameters (B). The comparisons of these curves are described in Table 1.

According to the literature, ROC curves with AUCs between 0.50 and 0.70 indicate low diagnostic accuracy, AUCs between 0.70 and 0.90 indicate moderate diagnostic accuracy, and AUCs between 0.90 and 1.00 indicate high diagnostic accuracy (Swets et al. 2008; Golpe et al. 1999). An $AUC > 0.80$ is usually considered to be adequate for clinical use (Swets et al. 2008; Golpe et al. 1999). Taking these values into consideration, it was observed that Z_m , Z_i , Z_e , Z_{bi} , Z_{be} and Z_{pp} represented highly accurate measurements. However, ΔZ_{rs} values do not attain adequate values for clinical use. Z_e was the most suitable for correctly identifying the effects of COPD, with an AUC of 0.976, Se of 100% and a Sp of 90%. These promising results are consistent with the physiology involved (Silva et al. 2011) and suggest that the Z_{rs} observed in different phases of the respiratory cycle may be useful in the detection of COPD. It is important to point out that the description of sensitivity, specificity and

accuracy is dependent on the population studied and that the cited work was conducted in patients with severe airway obstruction. Studies in patients with mild and moderate airflow obstruction are still necessary to confirm this hypothesis. The role of FOT in the identification of "choke-points", where flow limitation occurs, was highlighted by Bates et al. (2011). Timmins et al. (2012) recently used single breath nitrogen washout and computerized tomography to study the relationship between airflow obstruction, emphysema extent and small-airways function in COPD. Single-frequency FOT (6 Hz) was also used to quantify EFL. The authors investigated 26 subjects with COPD and observed that the severity of COPD and of airflow obstruction are probably independently predicted by both small-airways disease and emphysema extent. Garcia et al. (2012) recently suggested that FOT is a promising solution for the problem of small-airways assessment and that FOT may represent a more sensitive test for early lung damage in smokers than the FEV₁.

	FEV ₁ (L)	FEV ₁ (%)	FEV ₁ /FVC (%)	FEF _{25-75%} (L)	FEF _{25-75%} (%)	FEF/FVC (%)
R0 (cmH ₂ O/L/s)	0.17±0.08*	0.25±0.10*	0.16±0.10	0.21±0.09*	0.21±0.10*	0.19±0.10
S (cmH ₂ O/L/s ²)	0.04±0.09	0.12±0.10	0.03±0.10	0.09±0.10	0.08±0.10	0.07±0.10
Rm (cmH ₂ O/L/s)	0.14±0.08	0.22±0.10*	0.13±0.10	0.18±0.09*	0.18±0.10	0.16±0.10
fr (Hz)	0.16±0.08*	0.24±0.09**	0.15±0.09	0.21±0.08*	0.20±0.09*	0.19±0.09*
Xm (cmH ₂ O/L/s)	0.16±0.09	0.24±0.09**	0.15±0.09	0.21±0.09*	0.20±0.09*	0.19±0.09*
Crs,dyn (L/cmH ₂ O)	0.17±0.07*	0.25±0.09**	0.16±0.09	0.21±0.08**	0.21±0.09*	0.19±0.10*
Z4Hz (cmH ₂ O/L/s)	0.21±0.08*	0.29±0.10**	0.20±0.10*	0.25±0.09**	0.25±0.10*	0.23±0.10*

Table 1. Differences and statistical significance in the diagnostic performances of FOT and spirometric parameters, calculated by the difference between AUCs. Positive values denote higher values of AUC in the FOT parameters. * p<0.05; ** p<0.01.

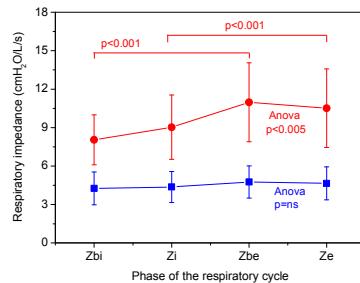


Figure 7. Mean Zrs values during the ventilatory cycle in COPD (red lines) and healthy subjects (blue lines). Adapted from Silva et al. 2011.

5. Diagnostic accuracy in patients classified by the GOLD

This section presents new results concerning the evaluation of the diagnostic accuracy of multi-frequency FOT in patients classified by the GOLD stage (GOLD, 2011). As far as we are aware, although it is a relevant technical and clinical question, there are no data in the literature concerning these evaluations.

5.1. Patients and methods

The study was performed in a control group formed by twenty healthy subjects and seventy-five outpatients with COPD, who were classified by spirometry according to the degree of airway obstruction as mild (n=20), moderate (n=20), severe (n=20), and very severe groups (n=15). According to GOLD orientation, these measurements were performed after the use of bronchodilator medication (GOLD, 2011). Bronchodilator administration was performed by means of the inhalation of four puffs of albuterol, each containing 100 µg, at 1-min intervals, using a spacer mouthpiece. The total dose administered was 400 µg. The exams were performed after 15 min of the bronchodilator administration. This study was approved by the Ethics Committee of the State University of Rio de Janeiro. Informed consent was obtained from all volunteers before inclusion in the study. The instrumentation and the measurement protocol used are described in section 3. The general characteristics of the evaluated subjects are given in Table 2. Volunteers in all five groups were comparable in age, weight and height, showing no statistically significant differences. In general, the spirometric parameters were highest in normal subjects and lowest in very severe patients, with the mild, moderate and severe subjects in between.

	control (n=20)	COPD				p value
		I (n=20)	II (n=20)	III (n=20)	IV (n=15)	
Age (year)	59.2 ± 14.4	64.8 ± 11.5	65.9 ± 9.6	66.0 ± 7.8	67.2 ± 8.9	ns
Height (cm)	159.5 ± 8.1	161.4 ± 7.3	165.0 ± 6.8	166.2 ± 9.0	159.9 ± 14.2	ns
Weight (kg)	63.0 ± 10.2	59.9 ± 8.9	59.4 ± 13.1	59.8 ± 12.5	57.7 ± 14.2	ns
FEV ₁ (L)	2.5 ± 0.7	2.2 ± 0.5	1.6 ± 0.4	1.1 ± 0.2	0.7 ± 0.2	<0.0001
FEF ₁ (%)	106.5 ± 19.8	89.1 ± 13.9	63.4 ± 8.3	41.6 ± 4.1	27.8 ± 6.9	<0.0001
VEF ₁ /FVC	85.8 ± 5.2	65.5 ± 5.5	51.9 ± 9.4	39.1 ± 8.2	35.8 ± 8.3	<0.0001

Table 2. Biometric and spirometric characteristics of the investigated subjects. Ns: non-significant.

5.2. Results

The mean Rrs and Xrs curves for the different COPD classifications are shown in Figure 8. The increment in airway obstruction caused an increase in total resistance, mainly at the lower frequencies (4-16 Hz) and not at the higher ones, and resulted in a frequency-dependent Rrs. The mean Xrs decreased in proportion to the degree of airway obstruction, becoming more marked at lower frequencies, which resulted in an increase in the resonant frequency.

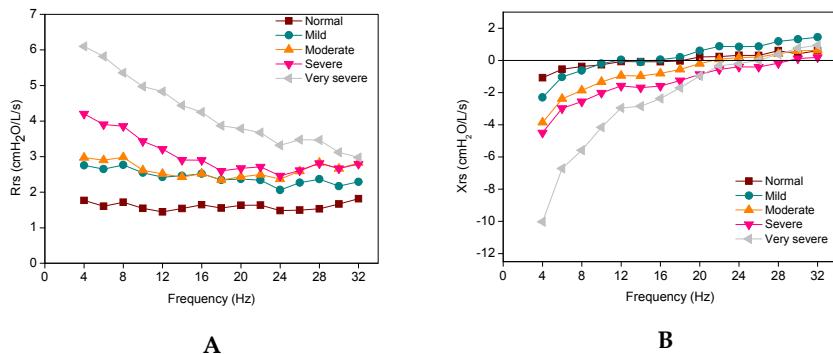


Figure 8. Mean values of resistance (A) and reactance (B) as a function of frequency in the control group and the different groups of COPD subjects.

Figure 9 shows the alterations of the resistive properties with advancing airway obstruction. All resistive and reactive parameters presented statistically significant differences ($p<0.0001$).

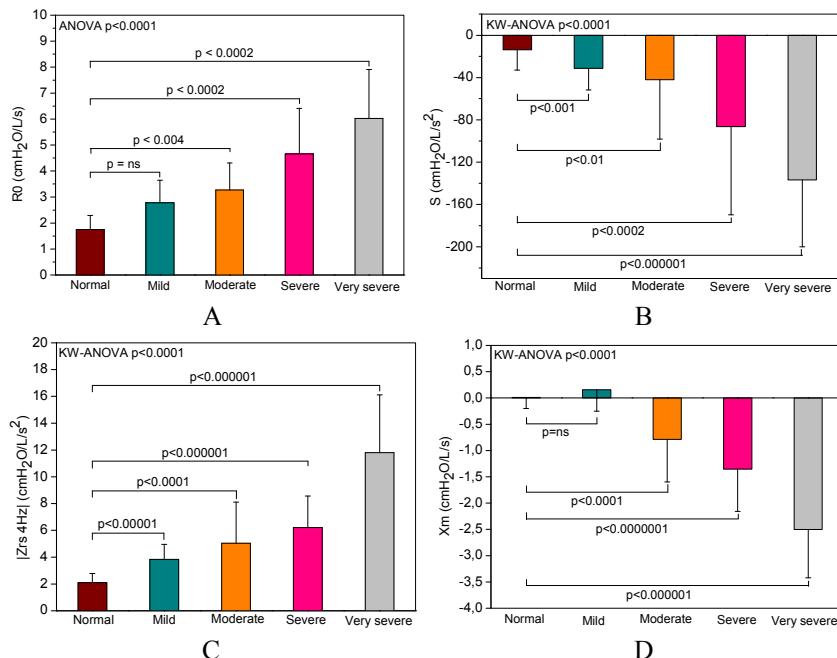


Figure 9. Changes in total respiratory resistance (R0; A), the slope of the resistive component of the respiratory impedance (S; B), mean respiratory reactance (Xm, C), and impedance modulus in 4 Hz ($|Z_{rs4Hz}|$; D) in control and COPD patients according to bronchial obstruction severity evaluated by the GOLD (2011) criteria.

The results of the evaluation of the clinical potential of the studied FOT indices are illustrated in the ROC curve presented in Figure 10. A complete description of the values of Se, Sp, area under the curve and the cut-off points is given in Table 3.

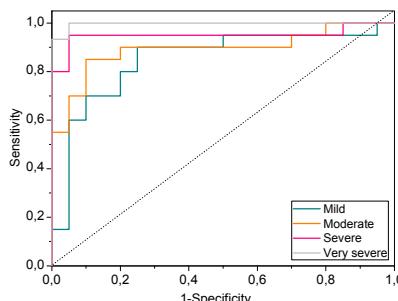


Figure 10. Receiver operating characteristic (ROC) curves for R0 obtained by comparing the control group and groups of COPD patients classified according to the GOLD (2011) criteria. Derived parameters are described in Table 3.

	AUC				Sensitivity (%)				Specificity (%)				Cut-off point			
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
R0 (cmH ₂ O/L/s)	0.85	0.89	0.95	1.00	90.0	85.0	95.0	100.0	75.0	90.0	95.0	95.0	1.91	2.14	2.53	2.53
S (cmH ₂ O/L/s ²)	0.81	0.74	0.85	0.99	75.0	65.0	80.0	100.0	90.0	95.0	95.0	95.0	-26.32	-37.52	-49.58	-41.18
Xm (cmH ₂ O/L/s)	0.61	0.89	1.00	1.00	50.0	75.0	95.0	100.0	85.0	95.0	100.0	100.0	0.16	0.28	0.47	1.52
Zrs4Hz (cmH ₂ O/L/s)	0.91	0.90	0.95	1.00	95.0	85.0	90.0	100.0	75.0	95.0	100.0	100.0	2.35	2.92	3.92	3.92

Table 3. Values of area under the curve (AUC), sensitivity (Se) and specificity (Sp) for the optimal cut-off points for the FOT indices in COPD patients presenting mild (A), moderate (B), severe (C) and very severe (D) airway obstruction. AUC: area under curve.

5.3. Respiratory impedance curves and derived parameters

Figure 8A shows that, in healthy subjects, the mean Rrs was approximately 2 cmH₂O/L/s in the frequency range of 4-32 Hz. The mean Rrs is greater in patients with COPD than in healthy subjects, due mainly to a reduction in the airway lumen, which results in increased resistance to flow. The increase in R0 clearly identified these changes (Figure 9A). There is also an increase in the dependence of Rrs on frequency, as illustrated in Figures 8A and 9B. Xrs tends to be more negative in COPD than in normal individuals at all frequencies (Figures 8B and 9D). The value |Zrs4Hz| is related to the total mechanical load of the respiratory system. Therefore, it may be associated with fatigue and breathlessness, which are important symptoms in predicting quality of life in COPD patients (GOLD, 2011). The changes in the resistive and elastic properties of COPD patients resulted in significant increases in |Zrs4Hz| (Figure 9C). The results described in Figures 8 and 9 are in agreement

with the previous results described in section 4, providing additional evidence that FOT provides parameters that are consistent with the pathophysiological fundamentals involved in COPD.

5.4. FOT as a diagnostic test: sensitivity and specificity of FOT indices

ROC curves were developed in the 1950s to evaluate radio signals contaminated by noise. It was later observed that these curves are very useful in medical decision-making. These curves describe the probability of true-negative (specificity) versus the probability of false-positive (1-sensitivity) for various decision criteria. In this context, the larger the area under the curve (AUC), the more valid is considered the diagnostic test in comparison with the gold standard. As noted previously, some authors suggest that an area under the ROC curve >0.70 is considered adequate (Goedhart et al., 2005), while others (Swets et al., 2008; Golpe et al., 1999) consider 0.8 to be a good cut-off value for a useful discriminator for clinical use. According to the literature, ROC curves with AUCs between 0.90 and 1.00 indicate high diagnostic accuracy (Swets, 1988; Golpe et al., 1999). In the present analysis, we considered 0.8 to be the minimum value of the AUC for adequate diagnostic accuracy. As expected, the AUC increased with increasing respiratory changes (Figures 8, 9 and 10, Table 2). The smallest diagnostic value of the FOT parameters is presented in patients with mild airway obstruction. It is interesting to note that, even in this adverse situation, R0 and S were able to obtain adequate values of AUC. On the other hand, Xm did not reach adequate values for clinical use. Among all the studied parameters, $|Zrs4Hz|$ was the best, showing a high diagnostic accuracy (AUC=0.91) with a Se of 95% and a Sp of 75% (Table 3). Adequate (R0, Xm) and highly accurate ($|Zrs4Hz|$) values of AUC were observed considering patients with moderate airway obstruction. The abnormal respiratory mechanics in COPD patients with severe airway obstruction were identified with high diagnostic accuracy by all of the studied FOT parameters (Table 3). Finally, all of the studied parameters provided an almost perfect diagnosis of patients in the group with very severe obstruction.

6. Some future directions

6.1. Clinical decision support systems based on machine learning algorithms to assist in the diagnosis of Chronic Obstructive Pulmonary Disease by forced oscillation

In the context of a diagnosis framework, the interpretation of resistance and reactance curves and of the derived parameters measured by the FOT require training and experience, and they represent a difficult task for the untrained pulmonologist. Methods based on machine learning (ML) have been widely used to develop classifiers. These systems can extract information from different classes of signals after having been trained to perform this specific task by learning from examples. This possibility raises the question of whether an ML-based approach to the analysis of FOT data can provide an efficient method to recognize COPD. In fact, only a few recent studies have addressed this question (Barruá et al., 2004; Barruá et al., 2005; Meratz et al., 2008). However, the cited studies used an Impulse

Oscillation System, which has differences from classical FOT, including data processing and the parameters used to interpret raw data (Mac Leod and Birch, 2001; Hellinkx et al., 2001; Ritz et al., 2002). Thus, to further elucidate this question, our group has investigated the development of a clinical decision support system based on ML algorithms to facilitate the diagnostic of COPD using FOT measurements. The first study was conducted using Artificial Neural Networks (ANN). The system was developed based on the results obtained in 15 normal subjects and 15 COPD patients (Amaral et al., 2010). Two training strategies and the performance of the resulting networks were evaluated by analyzing the diagnosis Se, Sp and accuracy. The proposed classifiers presented adequate performance (Se, Sp and accuracy > 0.9), both in the total FOT parameters analyzed and in the reduced sets of FOT parameters. This result indicates that the ANN-based classifiers can help to facilitate the diagnosis of COPD by FOT (Amaral et al., 2010). On the basis of these promising results in the continuation of this work (Amaral et al., 2011), the methods described below were also investigated:

- Neuro-fuzzy classification (CNF);
- Linear Bayes Normal Classifier (LBNC);
- K Nearest Neighbor (KNN);
- Decision Tree (DT);
- Support Vectors Machines (SVM).

This second study included the examinations of 25 normal subjects and 25 patients with COPD. The training strategies of the ANN used previously were reevaluated, and new strategies were investigated. The performances of the resulting six classification algorithms were also analyzed for the determination of Se, Sp and diagnostic accuracy. The classifiers based on ANN, KNN and SVM presented the best performance, reaching values that allow a very accurate clinical diagnosis ($Se \geq 87\%$, $Sp \geq 94\%$ and $AUC \geq 0.95$), both in the total FOT parameters and in reduced sets of FOT parameters. Among all of the studied classifiers, the best performance was presented by KNN-based analysis (Se, Sp and accuracy = 1.00). This result was obtained using all parameters. The high accuracy obtained proved the feasibility of developing a system to support clinical decisions based on machine learning algorithms to simplify the diagnosis of COPD by FOT. More specifically, it shows that the best classifiers for this task are those based on RNA, KNN and SVM (Amaral et al., 2011).

6.2. Forced oscillation in telemedicine

The high prevalence of chronic respiratory diseases has led to an increasing demand for assistance services in recent years. This increase has introduced a gradual rise in the admission of patients (Murray and Lopez, 1997), increasing the financial burden. In addition, several COPD patients have difficulty accessing traditional health services due to the severe limitations that are associated with the disease in its advanced stages. To minimize these problems, health services using home care and telemedicine have been developed (Guo and Moulder, 2000; Demiris, 2004). Recently, the European Commission on Telemedicine (Commission of the European Communities, 2008) highlighted the potential of telehealth in the management of COPD and the pressing need for quality research in this field.

The ability of the FOT to measure respiratory impedance during spontaneous breathing could be useful for unsupervised monitoring of airway obstruction, resulting in great benefits to patients with COPD. However, the implementation of telemedicine services using FOT depends on the development of a dedicated instrument and protocol. Rigau et al. (2002) were the first to describe a portable FOT system for home care applications. The system allowed the online computation of Rrs and Xrs and of reliability indices at 5 Hz. The device was compared with a conventional FOT system using signals from 14 patients with chronic respiratory disease, showing results that virtually coincided with the ones computed with the reference conventional FOT system.

More recently, Dellacà et al. (2010) developed a FOT device for the home monitoring of Zrs, which transmits the data through the Internet. Its accuracy, stability and reliability were evaluated in a pilot study measuring the Zrs in the unsupervised self-measurements of five healthy subjects and 36 consecutive daily home measurements in one healthy subject and one COPD patient. The results of this pilot study demonstrate that unsupervised home monitoring of Zrs using the FOT yields accurate and reproducible data.

Telemedicine services using FOT hold the promise of improving the understanding and management of COPD and its exacerbation. They would also allow online interaction between the patient at home and the health provider, optimizing the follow-up monitoring of the disease and adjusting the treatment accordingly. Another contribution of this research would be to allow a daily monitoring of the variability in airway obstruction in patients with COPD. This possibility may provide new insights into the dynamics of the COPD airway obstruction, as described in the next section.

6.3. Contribution of forced oscillation to systems medicine and complexity measurements

Reductionism has been the predominant paradigm in the science of clinical medicine since Descartes and the Renaissance (Ahn et al., 2006). Although reductionism has been responsible for tremendous successes in modern medicine, there are indications that the approach has limitations, mainly when applied to chronic, complex diseases, such as COPD. Complex biological systems cannot be predicted by the sum of their parts alone, and an alternative and complementary explanation must be sought. One alternative explanation that has received much recent attention in respiratory medicine is the systems perspective (Kaminsky et al. 2011; Suki et al., 2011; Suki and Bates 2011; Frey et al., 2011) Rather than dividing a complex problem into its component parts, the systems perspective investigates the composite characteristics of a problem and evaluates the problem using computational and mathematical tools. Given the lung's highly complex structure and function, a systems biology approach to understanding the lung has been suggested as an ideal application of the systems perspective (Kaminsky et al., 2011).

In the particular case of respiratory physiology, it is now well recognized that respiratory functions often show signs of complexity, including fractal (Glenny, 2011; Nelson et al., 1990; Thamrin et al., 2010) and emergent (Glenny, 2011; Kaczka et al., 2011; Suki and Bates,

2011; Suki et al., 2011; Macklem, 2005) behavior. Other important characteristics include long-range fractal correlations (Frey et al., 2005) and power law distributions of the time series (Frey et al., 1998; Suki, 2002). These characteristics can contain useful and clinically relevant information (Thamrin and Stern, 2010), because complexity appears to be lost in the presence of an illness. Goldberger (Goldberger, 1997; Goldberger et al., 2002) proposed that the increased regularity of signals represents a 'decomplexification' characteristic of illness. According to this hypothesis, health is characterized by 'organized variability,' and disease is defined by decomplexification, increased regularity and a reduction in variability. In a more recent work, Vaillancourt and Newell (2002) proposed that disease may manifest with abnormally increased or decreased complexity.

Therefore, interest in using fluctuation analysis to characterize respiratory patterns has become widespread over the past five years (Frey et al., 2011; Thamrin and Stern, 2010; Veiga et al., 2011). Using these methods, Frey and colleagues (2005) investigated the use of the day-to-day fluctuations in peak expiratory flow (PEF) over 6 months in patients with chronic asthma to determine whether the future risk of exacerbation could be predicted from fluctuations in PEF. In a later study, Thamrin et al. (2009) showed that long-range correlations in daily PEF measurements were useful in predicting long-term treatment response. A telemedicine system based on forced oscillation associated with fluctuation analysis has the potential to provide valuable risk predictors on an individual basis that could help in evaluating treatment efficacy or disease control in COPD.

Fluctuation analysis has also the potential to contribute to the classification of COPD patients. Muskulus et al. (2010) recently investigated the hypothesis that short-term variability in respiratory impedance during continuous tidal breathing may distinguish COPD and asthma. These authors observed that stochastic approaches were not able to provide a clear discrimination. On the other hand, they were able to reliably distinguish COPD patients based on the data coming from a deterministic nonlinear system and using nonlinear time series analysis. This result suggests that the dynamics of the respiratory impedance provide relevant clinical information that may contribute to the differential diagnosis between COPD and asthma.

There are clear indications that the combination of reductionism and complex systems methodologies constitutes a powerful integrative approach to scientific research and clinical medicine. The unique ability of FOT to provide easy, noninvasive and detailed respiratory function data may offer a central contribution by allowing easy daily monitoring and by obtaining the large databases necessary for robust analysis.

7. Conclusions

This chapter initially provided a brief overview of COPD, FOT and their data interpretation. This was followed by a historical review that described the maturation of this method over the past five decades as a useful complement to spirometry in the diagnosis of smoking-induced respiratory changes. In addition to these previous studies, new results were presented concerning the diagnosis of COPD patients with different degrees of airway

obstruction. These results, together with the results described in the historical review, provided clear evidence supporting the use of FOT as a versatile clinical tool, able to contribute to COPD prevention and diagnosis. However, routine clinical use of FOT has yet to gain full acceptance. Interest in the approach is growing and shows considerable promise, especially for detecting respiratory changes due to smoking in the initial stages and for implementing telemedicine services. However, realizing this promise remains a work in progress. It relies on the development of patient-friendly portable systems for screening smokers and for home-care, and on an appropriate mathematical description of lung mechanics. It is also necessary to overcome a number of challenging practical problems related to validation studies in a great number of subjects and developments in sophisticated mathematical methods for the interpretation of the dynamics of lung impedance time series. The future of FOT as a diagnostic tool for smoking-related respiratory abnormalities is thus highly linked to the interdisciplinary work of engineers, physicians, mathematicians and physiologists.

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