Applications of oscillometry in clinical research and practice

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ABSTRACT
Oscillometry is gaining in clinical use and while there is an increased interest in the technique, there is paucity in the understanding of its possibilities and limitations. Oscillometry has seen extensive use in research over several decades, but only recently is the technique being adopted in clinical practice; hence, there is a need to educate the novel users. The goal of the mini symposium arranged in San Diego in 2018 was to discuss the principles of oscillometry, showcase some of the recent ongoing research using this technique and to demonstrate how oscillometry may be used in clinical practice. It was concluded that oscillometry has several advantages over spirometry, most notably, with novel data being shown, its sensitivity allowing early detection of small airways disease not possible with spirometry and it can be used in subjects who have difficulties performing forced maneuvers such as preschool children, the elderly and subjects with handicaps. The site of respiratory pathology can be reflected by the various parameters generated by oscillometry and thus help with both disease diagnosis and localization. While the interpretation of oscillometry parameters and translating them into meaningful pathological correlates is still evolving, it is likely that oscillometry will soon be at the forefront of both pulmonary clinical practice and research.

RéSUMÉ
L’oscillométrie est de plus en plus utilisée en contexte clinique, mais malgré l’intérêt accru pour cette technique, la compréhension de ses possibilités et de ses limites est encore insuffisante. Pendant plusieurs décennies, l’oscillométrie a largement été utilisée dans la recherche, mais l’adoption de cette technique dans la pratique clinique est encore récente, de sorte qu’il est nécessaire de former les nouveaux utilisateurs. Le but de ce mini symposium qui s’est tenu à San Diego en 2018 était de discuter des principes de l’oscillométrie, de présenter les plus récentes études utilisant cette technique et de démontrer comment elle peut être utilisée dans la pratique clinique. Il a été déterminé que l’oscillométrie présentait plusieurs avantages par rapport à la spirométrie notamment, comme le démontrent de nouvelles données, sa sensibilité qui permet la détection précoce de la maladie des petites voies aériennes, ce que la spirométrie ne peut pas faire, ainsi que le fait qu’elle puisse être utilisée auprès de sujets qui éprouvent de la difficulté à effectuer des manœuvres forcées comme les enfants d’âge préscolaire, les personnes âgées et les personnes atteintes d’un handicap. L’emplacement de la pathologie respiratoire peut se refléter dans les divers paramètres produits par la spirométrie, ce qui peut contribuer à diagnostiquer la maladie et à la localiser. Bien que l’interprétation des paramètres de l’oscillométrie et leur traduction dans des corrélats pathologiques significatifs continue d’évoluer, l’oscillométrie sera vraisemblablement à l’avant-plan de la pratique clinique et de la recherche pulmonaire bientôt.

Introduction
The importance of small airways in the development of respiratory diseases is increasingly recognized. Several lung diseases are driven by inhalation of small particles whether from smoke, environmental pollution, allergens or infectious agents. As the awareness of the role of the small airways in lung diseases has increased, so has the demand increased for techniques quantifying the function of the small airways, aka the quiet zone. Measuring lung function in patients not only helps establishing a correct diagnosis but also monitors patient lung-health over time. In either case, one assumes that the measurement renders a correct assessment of the
respiratory system and that measurements are reproducible with minimal variation between repeat measurements yet sensitive enough to detect changes in lung status over time and be predictive of meaningful outcomes. Furthermore, the technique should be feasible to use in a wide range of patient populations including preschool children, the elderly and people with disabilities. The measurements should also provide the clinician with a clear understanding of what part of the respiratory system is affected. Dr. Siddiqui discussed the interpretation of oscillometry data and pointed out that oscillometry can separate lung function into peripheral and central airways and Dr. Dandurand gave an example from his clinic of a patient who put on a small particle treatment to target the small airways, did remarkably better. Similarly, this was also shown in a study where small particle inhalers were compared with standard inhalers; by using oscillometry the authors were able to demonstrate that the primary effect of the small particle was located in the small airways, something that spirometry did not register. Similar observations have been made in clinical studies where drugs with different particle size distributions were used and the smaller particle formulation was more effective and tied to effects in smaller airways as evidenced by effects on oscillometry parameters. Suffice to say, any respiratory measurement technique would benefit from being easy and quick to use with minimal effort on the patient’s part.

The aforementioned poses the question of how today’s standard, spirometry, lives up to these prerequisites. Obviously, spirometry is difficult, if at all possible, to perform by certain individuals such as preschool children, people with certain handicaps and also many elderly patients. In an editorial in Age and Ageing, alternatives to spirometry were warranted. In addition to the aforementioned limitations, the utility of spirometry is also limited because of its insensitivity to small airway pathology and can be hard to perform repeatedly. Oscillometry could, on one hand, be seen as an alternative technique to spirometry; however, probably better, on the other hand, it should be seen as an adjunct to spirometry providing information not detected by spirometry, thereby expanding the possibilities for correct diagnosis and better quality monitoring. Dr. Siddiqui gave several examples where oscillometry has been used in clinical research suggesting that oscillometry might be more sensitive than spirometry detecting treatment effects.

Oscillometry has been suggested to be useful not only in problematic patients but might offer insights into pathology not afforded by spirometry. It might even be an alternative to spirometry in some cases. While this might seem to be a tall order, the presentations at the Oscillometry Mini Symposium in San Diego May 21, 2018 illustrated that oscillometry is useful in most contexts of lung disease and, combined with spirometry, will add significant knowledge about the condition of the lung. Several cases were presented where the oscillometry detected changes in lung pathology that had gone undetected with spirometry alone. Data supporting the unique sensitivity of oscillometry to changes in the smaller airways were also presented.

Since its inception in the 1956, various types of oscillometry devices have been used primarily in research settings and have produced valuable insights into the details of lung diseases. Over the past 20 years, the use of oscillometry has become the gold standard in laboratory animal research and has contributed to a better understanding of how pathologies can affect the lung function at different levels with clear links between structure and function. Because of the advantages of oscillometry, it was speculated that it might become the new standard by which lung function is assessed and, at the same time, increase our understanding of respiratory diseases in a way similar to how it revolutionized animal research. Oscillometry is also an example where the same physiological measurements can be made in animal models as in human patients. Respiratory oscillometry has become the de facto standard technique used in the animal laboratory and the heterogeneity seen in allergic mouse lungs is similar to what is seen in human lungs as exemplified in Dr. Dandurand’s section in this article. Indeed, there is a great correlation between measures of lung volume and elastance in mouse lungs that corresponds to similar findings in human lungs with ventilation defects, as imaged with MRI and measures of the reactance-area (A_X), defined later in the paper. The phenomenon of heterogeneous ventilation of the inflamed human lung has been described previously but the novelty discussed at this symposium was that measures of respiratory impedance can correlate with patient reported outcomes.

While oscillometry has, thus far, mostly been used in preclinical and clinical research, it is now gaining ground in clinical practice too, with the promise to improve early diagnosis and disease monitoring. The goal of the symposium was not only to provide the audience with a better understanding of the potentials afforded by using oscillometry in research studies, but also to demonstrate how oscillometry could help clinical diagnosis and patient monitoring in adjunct to spirometry.

To address the possibilities and challenges using oscillometry in both the research as well as in the clinical setting, two speakers were invited to give their views on the utility of oscillometry. The mini symposium in 2018 on oscillometry addressed these topics in 2 talks; first “Applications of Oscillometry in Clinical Research” presented by Professor Salman Siddiqui, University of Leicester UK, where he works as a Clinical Professor of Airways Disease at the Severe Asthma and Phenomics Center. Professor Siddiqui introduced the subject by giving a background of oscillometry, explaining how the technique works, then moved on to discuss translational applications and, finally, pointed to future directions where oscillometry might play an important role in research.

The second presentation “Oscillometry Experiences and Case Studies from Community Practice: Reading the Oscillogram” was given by Dr. Ronald Dandurand, Montreal, Canada. Dr. Dandurand is a clinician at a community practice in Montréal and an Assistant Professor of Medicine at McGill University where he conducts clinical research at the Meakins-Christie Labs, and the Oscillometry...
Unit of the Center for Innovative Medicine. He collaborates with Dr. Ynuk Bossé, a physiology researcher at the Institut Universitaire de Cardiologie et de Pneumologie de Québec, University of Laval. Dr. Dandurand provided the audience with tools, which in his experience, will help the clinician understand and interpret the oscillogram in terms of quality, pattern recognition to support a diagnosis and how oscillometry together with spirometry has a tremendous potential to facilitate the clinician’s job.

Applications of oscillometry in clinical research

Introduction

The standard technique used to assess lung physiology is spirometry, which requires the patient having to perform a forced exhalation from total lung capacity down to residual volume. This is a very familiar technique that has been in use for many decades and is well standardized with normative data available. While useful in most cases, it does have some significant shortcomings. The test is effort dependent and the patient needs to be coached by an experienced technician to guarantee an acceptable maneuver; however, up to 20% of patients cannot perform an acceptable measurement. Furthermore, spirometry takes a relatively long time to perform, up to 20 minutes, and is not suitable for all patients (e.g., preschool children, elderly, very obese or people with certain handicaps). Spirometry is not sensitive to alterations in the small airways. Oscillometry, however, is effort independent because only quiet breathing is necessary, a test in triplicate is quickly performed within a couple of minutes, works well in preschool children and the elderly, as well as other patient groups who have difficulties performing traditional spirometry. Unlike spirometry, oscillometry is sensitive to changes in the small airway pathology, which makes it an excellent adjunct to spirometry. While oscillometry has been around for about 60 years, it has not been standardized to the same degree as spirometry; hence, there is a paucity of normative data with which to make comparisons. Indeed, thus far, oscillometry has primarily been used in clinical research and, while this is a limitation, it has also afforded the scientific community with a better and deeper understanding of lung disease than could have been achieved with spirometry alone.

Background of oscillometry

As previously mentioned, the effort from the patient is minimal because the signal used to measure the patient’s lung mechanics is generated by a device that delivers different frequencies of pressure oscillations to the respiratory system, spanning a frequency range typically between 5 Hz to about 40 Hz, and, ideally, these frequencies should be non-harmonic prime frequencies to avoid harmonic interference. The volume oscillations generate flow and pressure with the same frequency content and following signal processing the pressure divided by flow generates the impedance. The impedance can be broken down into its two key components, the Resistance (R) and Reactance (X), both plotted as a function of frequency, as graphed in Figure 1.

Figure 1. Representation of oscillometry measured on a phantom model of the respiratory system using a tremoflo C-100. From the resistance curve: $R_5$ represents the resistance of the whole respiratory system, $R_{20}$ primarily reflects the resistance of the proximal airways, and $R_{5-20}$ is the resistance of the small airways and reflecting ventilation inhomogeneities. From the reactance curve: $X_5$ is a measure of lung stiffness and heterogeneous ventilation and $F_{res}$ the resonant frequency where the whole impedance is explained by resistance. $A_X$ is the area under the reactance curve limited by y-value = 0, $X_5$ and $F_{res}$ reflecting the elastic properties of the respiratory system and airway obstruction.

The Resistance is the part of impedance that measures the in-phase component of pressure and flow and Reactance is a measure out of phase component of pressure and flow. This means that Resistance primarily reflects events occurring within the airways where there is flow. Reactance, however, is the sum of two forces: one primarily related to the stiffness of the lung (elastance), which in turn is closely related to lung volume; and the other, invariance arising from acceleration of air and tissue in the respiratory system. The lower frequencies pertain to the whole lung, whereas the higher frequencies tend to measure central airway properties. The difference between $R_5$ and $R_{20}$ is the heterogeneous component of $R_{res}$, and the heterogeneity can arise from central or peripheral airways. However, since in most cases of asthma and chronic obstructive pulmonary disease (COPD), these manifest more in the small airways, at least once obstruction is sufficient to increase $R_{res}$ and small airway heterogeneity is more commonly the source of $R_{5-20}$. As a result, the difference between Resistance at 5 Hz ($R_5$) and Resistance at 20 Hz ($R_{20}$) can pertain to the resistance of the smaller airways. While there has been some debate regarding the interpretations of $R_{5-20}$ in the past, the accumulated evidence is now supportive of interpreting $R_{5-20}$ as reflecting changes in the smaller airways. In a recent publication, using computational modeling and patient data, we show that $R_{5-20}$ is a direct measure of airway narrowing and that this correlated with asthma control and quality of life when patients were treated. Results from the recently published ATLANTIS study also lends strong support to the correlation between $R_{5-20}$ and $A_X$ and small airways disease in asthma. Oscillometry and spirometry results, which were used to assess dysfunction of small-sized to mid-sized airways, contributed most to the clinical small airways disease score and differed between small airways disease groups. Classifying small airways disease was considered meaningful, because it associates with disease severity, asthma control, quality of life and exacerbations.

### References

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13,15,23,26. The lower frequencies pertain to the whole lung, whereas the higher frequencies tend to measure central airway properties. The difference between $R_5$ and $R_{20}$ is the heterogeneous component of $R_{res}$, and the heterogeneity can arise from central or peripheral airways. However, since in most cases of asthma and chronic obstructive pulmonary disease (COPD), these manifest more in the small airways, at least once obstruction is sufficient to increase $R_{res}$ and small airway heterogeneity is more commonly the source of $R_{5-20}$. As a result, the difference between Resistance at 5 Hz ($R_5$) and Resistance at 20 Hz ($R_{20}$) can pertain to the resistance of the smaller airways. While there has been some debate regarding the interpretations of $R_{5-20}$ in the past, the accumulated evidence is now supportive of interpreting $R_{5-20}$ as reflecting changes in the smaller airways. In a recent publication, using computational modeling and patient data, we show that $R_{5-20}$ is a direct measure of airway narrowing and that this correlated with asthma control and quality of life when patients were treated. Results from the recently published ATLANTIS study also lends strong support to the correlation between $R_{5-20}$ and $A_X$ and small airways disease in asthma. Oscillometry and spirometry results, which were used to assess dysfunction of small-sized to mid-sized airways, contributed most to the clinical small airways disease score and differed between small airways disease groups. Classifying small airways disease was considered meaningful, because it associates with disease severity, asthma control, quality of life and exacerbations.
In a healthy individual, the Reactance curve starts off slightly negative at 5 Hz and then crosses the x-axis at what is known as the resonant frequency (\(F_{res}\)), where the entire impedance is explained by the Resistance. Above the \(F_{res}\), the reactance is dominated by inertive properties of the air being oscillated. The Reactance curve can be interpreted such that more negative values indicate lower capacitance with increased lung stiffness or loss of elastic recoil. Where the lung periphery is stiffer or does not see the pressure oscillations due, eg, to heterogeneous airway closure and consequently patchy ventilation, the lung will appear smaller and stiffer; hence, the \(X_5\) will become more negative. This is a pattern that underpins many lung diseases and will be reflected by elastance. The area under the Reactance curve (\(AX\)) was first developed by Michael Goldman\(^{27}\) and is a measure of loss of elastic recoil or increased stiffness of the lung. The area under the curve is a measure of the stiffness of the lung; indeed, it has the same units as elastance cmH\(20\)l.

As a result of the aforementioned processes, oscillometry generates patterns that may discriminate between peripheral lung diseases, eg, pulmonary fibrotic diseases, early COPD and asthma.\(^{23,29}\) The oscillogram (the plot of resistance and reactance) can display some characteristic patterns for various disease types such as early COPD, where \(R_{5-20}\) and \(AX\) are increased, while in some cases, spirometry is relatively well preserved. If there is a proximal (upper airways) obstruction, this will lead to a uniform elevation of Resistance with no effect on Reactance. In restrictive lung diseases, there is typically no effect on the Resistance but a significant increase in \(AX\).\(^{30,32}\) Hence, oscillometry could help discriminate between various types of lung disease and add to the quality of diagnosis.

**Repeatability of oscillometry**

Oscillometry data is extremely variable within a breath (intra-breath variability), which is likely due to the patient’s own breathing dynamically changing the lung volume. However, the average impedance is repeatable whether this is baseline repeatability, two-week repeatability or three-month repeatability in adults with moderate to severe asthma with correlations at least as good as with spirometry.\(^{33,34}\) In the pediatric population, spirometry presents an obstacle and most diagnosis is obtained without any objective physiological measurement.\(^{35}\) In children, interpretations of parameters derived from oscillometry were demonstrated to be predictable for loss of asthma control\(^{36}\) and in children with eosinophilic bronchitis, reversibility with oscillometry was demonstrated for both resistance and reactance, which suggests it is similar to asthma.\(^{37}\)

**Reference values**

One area that could be problematic in the field of oscillometry is that reference values are not present for all devices. Historically many different devices have been used, but as of today, there are no uniform reference data sets available. It is, however, possible to understand how oscillometry is influenced by different patient unique factors. In a study from 2013, Schulz et al. demonstrated by using quantile regression that oscillometry data depends on various anthropometric data such as sex, age, weight and height in subjects aged between 45 and 91 years; but, the study was ethnically homogenous as Caucasians were the only subjects studied.\(^{38}\) In a recent study of reference data, 34 studies were reviewed, dating from 1977 to 2016.\(^{39}\) During this time span, the oscillometry has developed from homebuilt devices to commercially engineered instruments. Alas, this review study spans a variety of different approaches. Most studies included relatively small cohorts and the authors concluded that there were marked variability in technique and performance of the impedance measurements. It appears that height and sex are the major determinants to predict impedance; however, in the obese, weight is also a significant contributor. The role of age was not found to be clear and, in general, elderly subjects were underrepresented in most studies.\(^{39}\) Because of the large variability in study approach and design, oscillometry technique, inclusion–exclusion criteria, the historical use of small cohorts, and differences between devices there is a need for large population-based studies that are based on standardized methodology.

**Modeling case studies in asthma**

A previous European union funded FP7 program, AirPROM (Airways Disease Predicting Outcomes Using Patient Specific Computational Models), identified important insights into the anatomical basis of oscillometry measurements by using forced oscillation (FOT) physics-based modeling on patient specific airway tree models. Current data suggest that reported measures of small airways dysfunction such as \(R_{5-20}\) are primarily promoted by narrowing within the small airways (more so than by central airways disease) and that heterogeneity is also an important determinant of the measures.\(^{8,40}\) Furthermore, a quantitative imaging biomarker study suggests that reversal of the normal ventilation gradient in the lung is an important determinant of \(R_{5-20}\).\(^{41}\) Heterogeneous ventilation of the lung correlates with parameters of oscillometry, in particular with the frequency dependence of resistance and the area under the reactance curve (\(AX\)) and, interestingly, also demonstrates some correlation with patient reported outcomes.\(^{18,19}\) In a recent abstract, it was reported that lung density also appears to be closely correlated to \(AX\),\(^{42}\) thus lending further support to the notion that heterogeneity, lung density and self-perceived lung health are somehow linked. It would thus appear that regionalization of lung diseases and both the degree and heterogeneity of narrowing in the small airways may be captured using the oscillometry approaches.

**Using oscillometry in studies of asthma**

Powering clinical studies is vitally important for their relevance to disease treatment and for regulatory approval. Employing data from several studies that use impulse
oscillometry demonstrates that in order to show a significant effect of anti-inflammatory drug treatment, with an α of 0.05 at a power of 80% would call for 44 subjects per arm, whereas an α of 0.05 at a power of 90% calls for 58 subjects per arm.43–45 Interestingly, oscillometry appears to be more sensitive than spirometry in airways hyper-responsiveness (AHR) testing situations, suggesting that lower doses of medicine (e.g., methacholine) might be needed to assess AHR if measured by oscillometry.46 In this context, oscillometry fills a significant void and has been demonstrated to be a more sensitive response outcome than spirometry, with respect to bronchoconstriction to oral propranolol and bronchodilation after salbutamol in adult patients with mild to moderate asthma.47 Furthermore, it was suggested that the magnitude of change seen with oscillometry outcomes, including peripheral airway resistance, area under the reactance curve and resonant frequency, was greater with oscillometry compared with spirometry.46 Hence, it is possible that oscillometry could be more sensitive than spirometry for assessing AHR.

Using oscillometry in studies of COPD

Detecting early stage COPD can be difficult because spirometry can stay essentially normal despite a sub-acute process in the lung periphery. Therefore, the question is whether oscillometry would offer any advantages over traditional pulmonary function tests (PFT). A recent review argues that oscillometry would improve early detection and diagnosis of COPD. It is suggested that measuring peripheral lung compliance as A_X might be useful for detecting subtle changes in lung function in COPD, perhaps as a screening tool in early stages of the disease or to monitor long term decline.22 Data from the ECLIPSE study revealed that R_5,20 and A_X both tracked with GOLD staging of COPD but also that smokers without COPD had an elevated A_X despite normal CT-scan densitometry. While their FEV_1 was within the normal range, it was lower than in non-smoking control subjects. This suggests that oscillometry might be more sensitive than PFT in early stage detection of COPD.48

Future directions

There are ongoing studies in birth cohorts of differing levels of maturity, which should shed light on the development of asthma from an early age into adulthood and help elucidate how the disease progresses in the lung. In these studies, oscillometry is deployed to understand the relationships between the various parameters obtained with oscillometry and with spirometry.

Other areas where oscillometry will be important include, eg, preschool wheeze, where there are no approved methods to distinguish this condition from true asthma. In this group, oscillometry has the potential to establish both baseline lung mechanics as well as airway reactivity, which will facilitate asthma diagnosis and disease management.49

Another area of importance would be bronchiolitis obliterans post transplantation, which is frequently diagnosed at a late stage; as a result, oscillometry might be more sensitive and specific than spirometry and identify those that need additional and potentially invasive tests such as CT imaging and transbronchial biopsy sampling.50,51

There are several groups who have difficulties performing classic spirometry, including elderly and frail patients, but also people with mental or physical handicaps might find spirometry hard or impossible to perform. Preschool children are another category where no objective lung function technique is available as of today. Deploying easy to use oscillometry to geriatric wards and pediatric clinics could be important to diagnose and track disease development with subsequent adjustments of therapy.9

Finally, idiopathic pulmonary fibrosis is an area that has not been explored in great detail with oscillometry but where the benefits of a non-radiation assessment to monitor disease progression in the lungs would be very beneficial.31 While spirometry remains a useful clinical tool, it is insensitive to early changes, and it could be assumed that oscillometry would be more sensitive to early stages of fibrosis in the smaller airways in analogy with its sensitivity in asthma and COPD.52 Indeed, systemic sclerosis patients can have elevated peripheral resistance as demonstrated by increased R_5,20 and A_X values, which correlated with HRCT.53 Additionally, oscillometry has been demonstrated to be useful in evaluating children with cystic fibrosis, in particular because young children have difficulties performing spirometry.54

The aforementioned examples from the literature concerning asthma and COPD are, of course, not an exhaustive list. It is important to note that oscillometry alone is not always enough to discriminate between diseases but is a tool that will help the physician arriving at a diagnosis. It provides an easy to use tool that provides reproducible and sensitive measures of respiratory mechanics, making it useful for monitoring an individual patient.

In summary, the use of oscillometry has a long history in pulmonary research and has obviously contributed to our understanding of respiratory diseases. Additionally, with new areas being explored, it is anticipated that the use of oscillometry will continue to expand in research. The advent of new easier to use and portable devices, in addition to the accumulated understanding of how to interpret oscillometry parameters, will likely make this technique more accepted and useful for daily clinical use.

Oscillometry experiences and case studies from community practice: Reading the oscillogram

Introduction

This section of the proceedings will focus on the practical aspects of deploying oscillometry in routine clinical practice. Reading and quality assessment of the oscillogram will be demonstrated in a manner similar to the interpretation of the spirogram. After illustrative cases have been presented, patterns of pulmonary pathology will become evident that
may prove useful, if validated by others. Finally, a case for simplifying the reading of the oscillogram to a single parameter analogous to the FEV1 of spirometry will be discussed.

Global estimates of obstructive lung disease now approach 1 billion people and a fast, accurate, objective measure of lung function will be critical to deliver effective respiratory care on such a large scale. While spirometry has a 72-year history as the cornerstone of asthma and COPD diagnosis and management, its shortcomings and potential problems are increasingly reported. Deployment outside of the academic setting is sparse and, when used, is usually of sufficiently poor quality to be of questionable value. The maneuver itself changes the respiratory mechanics of many subjects. Furthermore, given the biologic variation in airway size to lung volume, termed dysapnia, spirometry has the potential to misclassify some pathology-free individuals as having obstructive lung disease. Finally, spirometry is increasingly recognized as insensitive to early disease. Clearly, from a clinical perspective, a faster, easier, more sensitive and more specific form of lung function metric is needed to tackle the juggernaut of obstructive lung disease that will have to be diagnosed and managed in the coming decades.

**Reading the oscillogram**

As illustrated in Figure 1, the oscillogram is a plot of 2 curves as a function of the frequency of the air pressure oscillation, or acoustic waves, applied at the mouth by the oscillometer. The details of how the plot is derived are well described elsewhere and we will concern ourselves here only with parameter meanings and oscillogram plot patterns in health and disease. The following oscilometry parameter definitions are all that is required for the practitioner to effectively use oscilometry in the clinic;

1. The R\(S\) is the resistance of the total respiratory system from mouth to body surface.
2. The frequency dependence of resistance (R\(S\)–19 or R\(S\)–20) is a measure of heterogeneity amongst the airway impedances due to time constant inequalities. However, for clinicians, it may be more simply thought of as a sensitive measure of small airways disease. Occasionally, it may but can be confounded by upper airway and large airway shunting, and more often by morbid obesity.
3. The X\(S\) is the largely the elastic, or stiffness, properties of the respiratory system and worsens in obstructive lung disease.
4. The F\(res\) is where the reactance curve crosses the 0-impedance line. This is where the capacitive and inertive forces cancel out and the impedance is due to resistance alone.
5. The reactance area or Goldman’s triangle (AX) (Figure 1, blue shaded area) is the area bounded by the reactance curve starting at X\(S\), F\(res\) and the y-axis 0 line and has recently been shown to be a reasonable estimate of ventilatory inhomogeneity.

**Stimulation terminology**

There is much confusion surrounding the terminology used when describing oscillometry and the reader will come across the terms FOT for “forced oscillation technique” and IOS or iOS, for “impulse oscillometry,” often used interchangeably. While both are oscillation mechanics methodologies, they use different stimulations to achieve the same end, vibrating an air column from mouth to alveolus and the tissue beyond to evaluate the mechanical properties of the respiratory system, namely, the impedance, and its three components: resistance, elastance and inerstance. The “forced” of FOT refers the forcing properties of sine waves upon the respiratory system. They control the approximately 10 cc volume oscillations assuming a healthy subject, during both the upward and downward phases of the volume change. Unlike the FEV1, the term “forced” has nothing to do with the maneuver performed by the subject who only needs to quietly breathe for typically 16–30 seconds.

The IOS on the other hand, uses an impulse or square wave to vibrate the air column from mouth to alveolus. Some devices deliver sine waves only, others impulse only, and still others have the capability of using either. For this reason, the author prefers the use of the term “oscilometry” or “OSC,” which is the only term that correctly applies to all devices and modes of stimulation and avoids the term “forced” that may be confusing to some.

**Reasons why ventilatory inhomogeneity stiffens the lung**

Both obstructive and fibrotic lung disease downwardly depress the reactance curve signaling an increase in respiratory system elastance. While a stiffening of the respiratory system by fibrotic lung disease is easy to comprehend, it is less intuitive why this is so with obstructive lung disease. However, this is what sets oscillometry apart from other forms of lung function measurement. The R\(S\)–20 or R\(S\)–19 and the AX are good estimates of ventilatory inhomogeneity or the unevenness of ventilation as it is a direct measure of the mechanical/ventilatory heterogeneity of the respiratory system. At the oscillation rates, or frequencies, applied by oscilometry at the mouth, the small volume of air that is pushed and pulled into and out of the lungs by the oscillometer will distribute according to airway patency. In a normal and evenly ventilated lung, the approximately 10 cc of air will cause only small volume changes in the lung given its wide or even distribution and hence, small regional pressure changes. As increasing regions of the lung become partially obstructed by small airways disease, they will decrease and then, cease accepting their part of the oscillating air volume and the same 10 cc of air is now distributed to a diminishing volume of lung. Hence, these remaining communicating lung units experience greater volume changes resulting in larger pressure swings in response to the oscillating air. These larger pressure swings are responsible for making the lungs seem less compliant, or stiffer (more elastic). Hence, the reactance curve is displaced downwards and both the
magnitudes of $X_5$ and $A_X$ increase with increasing small airways disease.\textsuperscript{18,21,26,77}

**Understanding the oscillogram**

As is the case with spirometry, reading the oscillogram is a combination of pattern recognition and understanding measured or calculated parameters. Different diseases can generate distinct patterns that will be reflected by the parameters and help the physician detect pathology. It is, however, important to understand the limitations of oscillometry and to recognize that there can be overlap in patterns between different diseases, underlining the importance to consider more than only oscillometry to make a diagnosis. The following sections show a few examples collected at the author’s (RJD) community respirology practice located west of Montréal, QC, Canada. Some of these have been published in abstract form.\textsuperscript{31,42,78–86}

**Normal healthy subjects**

The oscillogram and oscillometry parameters from a healthy adult subject are typically characterized by an almost flat resistance curve. While age and height dependent, the values for $R_5$ should be $\leq 2.0$ to $3.0$ cmH$_2$O.s.L$^{-1}$. There is no, or very, minimal frequency dependence; hence, the $R_{5-20}$ is close to 0, which indicates the absence of small airway disease. The $X_5$ of the reactance curve is typically $\geq -2.0$ and the $F_{res}$ between 8 and 15 Hz. The normal $A_X$ is $<10$ cmH$_2$O.L$^{-1}$.

**Asthma**

The lung function in asthma is variable over time and is affected by several factors, eg, allergen exposure and exercise. Most cases of asthma are sensitive to interventions with bronchodilators and anti-inflammatory treatment that, in many cases, can return the patient to normal lung function.\textsuperscript{87} The impedance is frequently characterized by increased overall resistance but also increased frequency dependence, suggesting heterogeneous ventilation, at the same time the reactance and inertance are reduced suggesting airway obstruction.\textsuperscript{21} When treated appropriately these parameters can return toward normal, as exemplified in Figure 2.

Figure 2 shows the spiromograms (above) and oscillograms (below) of an asthma subject with fluctuating symptoms over a period of 10 months. At the first visit (1), the patient is well controlled with budesonide/formoterol but then deteriorated in panel 2, was non-compliant in panel 3, and, finally, started taking the prescribed medication (budesonide/formoterol + ciclesonide) and was found to be symptom free in panel 4. See text for details.

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**Figure 2.** A year of unstable asthma oscillometry. An example of a subject with asthma tested with oscillometry every 3 months as illustrated in panels 1–4. In panel 1, the subject was well controlled with budesonide/formoterol but then deteriorated in panel 2, was non-compliant in panel 3, and, finally, started taking the prescribed medication (budesonide/formoterol + ciclesonide) and was found to be symptom free in panel 4. See text for details.

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**Table 1.**

| Index | Base | %Pred |
|-------|------|-------|
| FEV$\_1$ | 1.801 | 63% |
| FVC | 2.401 | 64% |
| FEV$_1$/FVC | 75% | |
| FEF$\text{25-75}$ | 1.20 L/s | 44% |
The subject is given the same instructions, returns one month later (4), this time having complied, is now asymptomatic and free of ventilatory inhomogeneity as estimated by an $A_X$ of 5 cmH$_2$O L$^{-1}$. Of note, the $R_{5\text{-}20}$, the metric of small airways disease, tracks the $A_X$.

**Reversibility testing**

A core element of diagnosing lung disease is establishing the presence or absence of reversibility of bronchoconstriction. This is typically done comparing lung mechanics measurement before and after bronchodilation with an inhaled drug such as albuterol or terbutaline. The reversibility of lung function is a characteristic of asthma frequently determined with spirometry as a change of FEV$_1$ of 12% following inhalation of a bronchodilator. In a paper by Oostveen et al. the positive response in asthmatic patients as the 95th percentile of the bronchodilator response in healthy adults was established. The 95th percentiles for the absolute and relative changes in $R_{rs}$ and $X_{rs}$ at low frequencies due to bronchodila-

Patients with emphysema frequently demonstrate greater changes in the reactance than the resistance. This is due to loss of lung structure leading to obstruction resulting in wide spread airway closure. In the example in Figure 4, the oscil-

**COPD with emphysema**

Patients with emphysema frequently demonstrate greater changes in the reactance than the resistance. This is due to loss of lung structure leading to obstruction resulting in wide spread airway closure. In the example in Figure 4, the oscil-

**COPD without emphysema**

The oscillogram of chronic obstructive pulmonary disease (COPD) can share many of the same features with asthma, i.e., elevated resistance, frequency dependence (increased $R_{5\text{-}20}$), and increased $A_X$. However, patients with COPD are typically not fully reversible with bronchodilators and some patients likely have both asthma and COPD. COPD can present with or without emphysema and depending on the phenotype, and this will affect the appearance of the oscillogram and the resulting parameters. Figure 3 shows an oscillogram and oscillometry parameters of a subject with symptomatic GOLD Stage I, Grade A COPD, with mild airflow limitation and without emphysema as measured by quantitative CT scanning. Oscillometry is always performed before spirometry as spirometry alters the mechanics of the respiratory system. Three measurements were obtained and were then averaged. The coefficient of variance of $R_5$ was 6%, thus below the 15% threshold used to judge oscillo-

**$R_{5\text{-}20}$ and $A_X$ as markers of peripheral lung pathology**

As previously noted, oscillometry can be quantified with several parameters, each of which can have their own interpretation with respect to location within the respiratory system or pathology. The notion is that impedance acquired over a range of frequencies to determine the frequency dependence is related to changes in the lung periphery. Knowledge about the functionality of the lung periphery is considered important determinants of lung function and will add information about lung health not available with other techniques. In particular, two parameters calculated from
total lung impedance are considered capturing peripheral events in the lung; $R_{5-20}$ and $AX$. On the one hand, $AX$ has been suggested as a useful tool for early disease screening and monitoring in COPD, and may be more sensitive to therapy response than the frequency dependence of resistance. On the other hand, the frequency dependence of resistance ($R_{5-20}$) has been shown to represent the degree of heterogeneity of the airways and as such could be understood in terms of a distribution of time constants throughout the airways tree and be more sensitive than spirometry. On the other hand, the changes in resistance appears to be more useful than reactance for children. Obviously both parameters are based on the same impedance measurement; hence, it would not be surprising if they do covariate; nonetheless $R_{5-20}$ and $AX$ appear to reflect different properties of the airways.
In order to interpret impedance measurements, we need to be able to correlate the parameters with tangible and quantifiable properties of the respiratory system. This has been performed extensively in animal models \textsuperscript{16,103,104} and now, more recently, in humans with lung disease. Using positron emission tomography (PET), it was demonstrated that patients with obstructive lung disease have distorted ventilation patterns that are distinctly different from that of a healthy lung, which can lead to cluster formation that eventually can lead to catastrophic shifts in lung function.\textsuperscript{20}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{Index} & \textbf{Base} & \textbf{%Pred} \\
\hline
FEV\textsubscript{1} & 0.54 l & 26\% \\
FVC & 1.61 l & 65\% \\
FEV\textsubscript{1}/FVC & 33\% & \\
FEF\textsubscript{25-75} & 0.20 l/s & 8\% \\
\hline
\end{tabular}
\caption{Spirometry results for a subject diagnosed with GOLD2017 Stage IV, Grade D COPD with heterogeneously distributed emphysema as determined by CT.}
\end{table}

Figure 4. A subject diagnosed with GOLD2017 Stage IV, Grade D COPD with heterogeneously distributed emphysema as determined by CT. Coronal and sagittal CT images are shown as well as the spirometry time-volume and flow-volume curves, and the oscillometry results. Oscillometry obtained with a tremoflo C-100. See text for details.
Combining oscillometry and hyperpolarized magnetic resonance imaging (3He-MRI) quantifying ventilation distribution defects, it has recently been demonstrated that there are significant relationships between oscillometry parameters and ventilation heterogeneity in patients with either asthma or COPD. A common issue in clinical trials is the lack of a robust correlation between objective measures of lung function with patient reported outcomes. It is therefore of interest to note that oscillometry, as measured as $A_X$ or frequency dependence of resistance, appears to have a correlation with Asthma Control Questionnaire (ACQ) scores.

We recently explored how measures of oscillometry correlates with the ventilation pattern and as shown in Figure 5 where $A_X$ increases with increasing ventilation maldistribution. Four example cases of asthma, COPD, never-smoker and ex-smoker are shown in Figure 5. The upper blue...
images are produced by the subject inhaling 1 L of hyper-polarized helium gas from functional residual capacity (FRC) and undergoing static breath-hold magnetic resonance imaging (MRI). The derived metric of the volume of the poorly filled regions (shown as the absence of gas or black thoracic cavity) spatially identifies where gas does not distribute as ventilation defect percent (VDP). Below each image is the oscillogram for the same subjects 30 minutes prior to the ³He-MRI. Moderately strong correlations were observed between the AX and the VDP.¹⁹

Hence, it appears that parameters derived from resistance or reactance can be correlated to different compartments of the respiratory system such that X₅ and AX may reflect parenchymal stiffness and lung de-recruitment, whereas increased frequency dependence of resistance can be indicative of heterogeneous airways narrowing. Further interpretation of these parameters suggests that oscillometry might be able to identify COPD patients with and without emphysema. The ventilation defects seen in emphysematous lungs were reflected by changes in X₅ and AX. However, in patients without emphysema the ventilation defects were related to the frequency dependence of resistance and AX.¹⁹,¹⁰⁶ While AX is sensitive to airflow obstruction it is nonspecific to the type of obstruction, the frequency dependence of resistance has been shown to reflect obstruction in the peripheral airways.¹⁰⁶ Based on the aforementioned observations, I propose the following cutoffs for grading severity of COPD as illustrated in Figure 6. Using cutoff points that start at 10 cmH₂O L⁻¹ as a disease defining threshold²² and then doubling from 10 would result in a tentative staging of ventilatory inhomogeneity as estimated by the AX of; normal, ≤10; mild, >10 ≤20; moderate, >20 ≤40; severe, >40 ≤80 and very severe, >80 cmH₂O L⁻¹. The usefulness of this scale would, of course, have to be confirmed in future independent studies.

In summary, oscillometry is more easily and quickly performed in the office setting than spirometry. The oscillogram, like the spirogram, can be quickly read by pattern recognition, memorizing a few key parameters. The AX is linked to patient reported outcomes, the FEV₁ and the distribution of air within the lungs as measured by functional imaging.¹⁸,¹⁹,¹⁰⁷ Oscillometry is an easy, efficient and sensitive means by which to evaluate both asthma and COPD subjects as well as to monitor their response to treatment. Finally, the aim of these symposium proceedings is to convince others to adopt oscillometry into both practice and clinical trials and report their findings. Such independent validation and linking oscillometry parameters to important longitudinal patient outcomes is, of course, essential before advocating the replacement of spirometry by oscillometry for the diagnosis and management of obstructive lung disease in some, if not most, instances.

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