Oscillometry to Assess Respiratory Function in Adult Cystic Fibrosis

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Abstract

Oscillometry to Assess Respiratory Function in Adult Cystic Fibrosis

Background and Rationale: Cystic fibrosis (CF) is a life-limiting multi-system disorder in which respiratory dysfunction predominates. Although spirometry is the most commonly used test of pulmonary function, it has recognized limitations. Oscillometry is an alternative test of respiratory function which provides complementary information. Oscillometry also offers a number of practical and physiological advantages and is increasingly used in both clinical research and patient care. Surprisingly, little data exists using oscillometry to evaluate lung function in adults with CF. Accordingly, the aim of this study was to compare spirometry and oscillometry in a large adult CF cohort.

Methods: Spirometry and oscillometry (tremoFlo® C-100, Thorasys Thoracic Medical Systems Inc., Montreal, Canada) were performed according to published guidelines during a routine visit to the Montreal Chest Institute Adult CF Clinic, McGill University Health Centre in 92 adults with established CF in stable state (mean age = 33.0 ± SE 1.3 yrs, 51 men). Oscillometry parameters included respiratory resistance at 5 Hz (R5), the difference in respiratory resistance at 5 and 20 Hz (R5-20), respiratory reactance at 5 Hz (X5), respiratory reactance area (AX), and resonant frequency (Fres).

Results: Respiratory function was significantly reduced for the group (forced expiratory volume in one second, FEV_1 = 2.27 ± SE 0.1 L; Z score = -3.38 ± SE 0.23). There was generally a good to strong correlation between spirometry and oscillometry parameters, particularly between FEV_1 and both X5 and AX, and all relationships were highly significant ($P < 0.001$). Results were generally similar when expressed as absolute values or Z scores. Logistic regression and marginal

models estimated via general estimating equations analyses between spirometry and oscillometry parameters showed a significant association between oscillometry parameters (i.e., R5, R5-20, X5, and AX) and abnormal spirometry parameters.

Conclusions: Oscillometry appears to be a reliable measure of impaired respiratory function in stable adult CF. Further work is needed to assess its ability to reliably identify changes in function occurring either spontaneously or with therapeutic interventions, particularly in comparison with spirometry, patient reported outcomes, and other measures.

Résumé

L'oscillométrie pour évaluer la fonction respiratoire chez les adultes atteints de fibrose kystique

Contexte et justification: La fibrose kystique (FK) est une maladie multisystémique limitant la durée de vie dans laquelle le dysfonctionnement respiratoire prédomine. Bien que la spirométrie soit le test de la fonction pulmonaire le plus couramment utilisé, elle présente des limites reconnues. L'oscillométrie est un test alternatif de la fonction respiratoire qui fournit des informations complémentaires. L'oscillométrie offre également un certain nombre d'avantages pratiques et physiologiques. Elle est de plus en plus utilisée, à la fois en recherche clinique et pour les soins aux patients. Étonnamment, il existe peu de données sur l'utilisation de l'oscillométrie pour évaluer la fonction pulmonaire chez les adultes atteints de FK. Par conséquent, l'objectif de cette étude était de comparer la spirométrie et l'oscillométrie avec une grande cohorte d'adultes atteints de FK.

Méthodes : La spirométrie et l'oscillométrie (tremoFlo® C-100, Thorasys Thoracic Medical Systems Inc., Montréal, Canada) ont été réalisées conformément aux directives publiées lors d'une visite de routine à la clinique de FK pour adultes de l'Institut thoracique de Montréal, Centre universitaire de santé McGill, chez 92 adultes atteints de FK ayant un état stable (âge moyen = 33.0 ± ETM 1.3 ans, 51 hommes). Les paramètres oscillométriques comprenaient la résistance respiratoire à 5 Hz (R5), la différence de résistance respiratoire entre 5 et 20 Hz (R5-20), la réactance respiratoire à 5 Hz (X5) et la surface de réactance respiratoire (AX).

Résultats : La fonction respiratoire était significativement réduite dans le groupe [volume expiratoire forcé en une seconde, VEMS = 2.27 ± ETM 0.1 L (score Z = -3.38 ± ETM 0.23)]. Les corrélations étaient généralement de bonnes à fortes. Il y avait généralement une corrélation bonne à élevée entre les paramètres de spirométrie et d'oscillométrie, en particulier entre le VEMS et les paramètres X5 et AX, et toutes les relations étaient hautement significatives (P < 0.001). Les résultats étaient généralement similaires lorsqu'ils étaient exprimés en valeurs absolues ou en scores Z. La régression logistique et les modèles marginaux estimés par des analyses d'équations d'estimation générales entre les paramètres de spirométrie et d'oscillométrie ont montré une association significative entre les paramètres d'oscillométrie (c'est-à-dire R5, R5-20, X5 et AX; P < 0,001) et les paramètres de spirométrie anormaux.

Conclusions: L'oscillométrie semble être une mesure fiable de l'altération de la fonction respiratoire chez les adultes FK stables. D'autres travaux sont nécessaires pour évaluer sa capacité à identifier de manière fiable les changements de fonction survenant spontanément ou lors d'interventions thérapeutiques, notamment en comparant avec la spirométrie, les résultats rapportés par les patients et d'autres mesures.

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Contributions of Authors

The work described in this manuscript is original and performed by the author.

Arash Rad (candidate): Performed the data collection, literature review, and analytic calculations. The candidate wrote the manuscript.

Dr. Kevin Lachapelle (Supervisor): Provided scientific insight, guidance, and support.

Dr. Stewart Gottfried (Co-supervisor): Responsible for the candidate throughout the data collection and thesis preparation and contributed to interpreting the results. He provided scientific insight and guidance, workspace, and supervision throughout the study.

Dr. Hadil Al-Jallad and Dr. Derek Rosenzweig (advisors): Provided scientific input for the study.

Dr. Andrea Benedetti and Dr. Ramana-Kumar Agnihotram (biostatisticians): Provided statistical knowledge and assisted the candidate in analyzing the data.

List of Abbreviations

AX = Area under the reactance curve

BMI = Body mass index

CF = Cystic fibrosis

CFTR = Cystic fibrosis transmembrane conductance regulator

CT = Computed tomography

COH = Coherence

COV = Coefficient of variation

Ers = Respiratory system elastance

FDR = False Discovery Rate

$FEF_{25-75\%}$ = Forced expiratory flow between 25% and 75% of vital capacity

FEV_1 = Forced expiratory volume in one second

FVC = Forced vital capacity

FOT = Forced oscillation technique

Fres = Resonant frequency

GEE = Generalized estimating equations

Irs = Respiratory system inertance

IOS = Impulse oscillometry system

j = Imaginary number equal to $\sqrt{-1}$

LLN = Lower limit of normal

MRI = Magnetic resonance imaging

Rrs = Respiratory system resistance

R5 = Resistance at 5 Hz

R5-20 = Difference between resistance at 5 Hz and 20 Hz

SE = Standard error

ULN = Upper limit of normal

Xrs = Respiratory system reactance

X5 = Reactance at 5 Hz

Zrs = Respiratory system impedance

Chapter 1: Introduction.

1.1. Cystic Fibrosis.

Cystic fibrosis (CF) is a life-limiting multi-system recessive genetic disorder primarily affecting the respiratory system as well as the gastrointestinal tract, both exocrine and endocrine pancreatic function, and fertility in both men and women (1,2). In 1938 Dr. Dorothy Andersen, an American pathologist, first described CF as a distinct clinical entity in young children characterized by excessive mucus production in various organs, including the lung and the pancreas, and a six-month life expectancy (1,3). At first, the disease was assumed to be the result of abnormal exocrine gland function and was referred to as mucoviscidosis. However, the discovery of a sweat electrolyte defect (increased chloride) in the 1950s changed the perception of the disease to more than just a mucus disorder (2,3).

Geneticist Lap-Chee Tsui and his research team at the University of Toronto, along with U.S. collaborators, first identified the gene associated with cystic fibrosis in 1989 (4–8). Ultimately termed the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene because of its physiologic function, over 2000 variants have been identified to date (4–8). One mutation, however, ΔF508, is responsible for the great majority of cases (4–8). The CFTR defect has been categorized into six groups, as shown in Figure 1, to aid in understanding the consequences of these diverse mutations (9). The common end result is reduced chloride secretion, which leads to increased sodium absorption through epithelial sodium channels and the loss of water resulting in abnormally viscous secretions throughout the body (10).

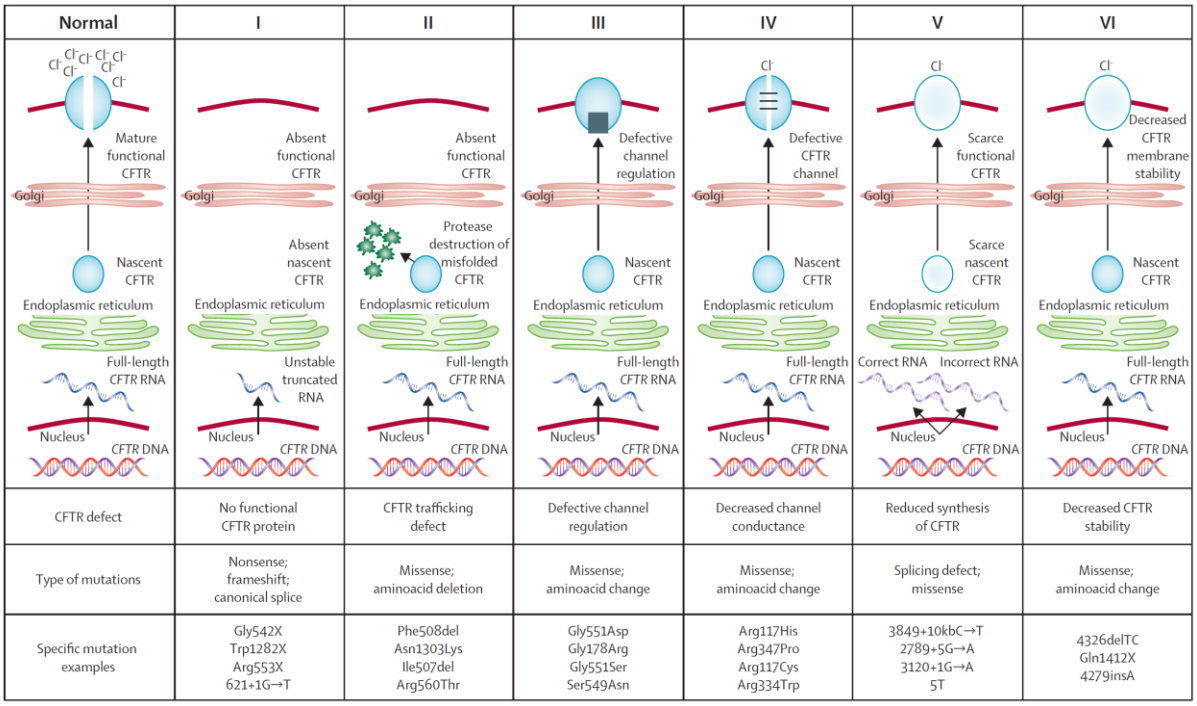

Figure 1. Classification of CFTR mutations. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) ultimately result in absent or reduced CFTR function and has been categorized into six classes according to the mechanism of the CFTR defect (9).

The loss of CFTR function in the respiratory system ultimately results in airway obstruction, associated infection, inflammation, and bronchiectasis with irreversible loss of lung function. Upper airway complications such as chronic sinusitis and nasal polyposis are common for similar reasons (8,11). In individuals with suspected CF, CFTR genotyping and sweat chloride testing are generally performed (12). The existence of two CFTR gene mutations and a sweat chloride concentration of more than 60 mmol/L helps establish the diagnosis (12).

Over 70,000 cases of CF are recognized worldwide, and approximately 4,400 affected individuals are living in Canada (13,14). It is estimated that one in every 25 Canadians is a carrier of a CFTR mutation (14). There is a 25% probability that a child born to two carriers will have CF (14).

According to Cystic Fibrosis Canada, CF is the most frequent life-limiting genetic disorder in the Caucasian population (14). CF has evolved from an acute pediatric disease into a chronic illness in adults, where in Canada the majority are young adults with a median age of 23.7 years (15–18). The estimated median age of survival for patients with CF in Canada has significantly improved from 33.2 years in 2001 to 52.1 years in 2019 (18). There are many reasons for this, primarily early diagnosis as well as considerable improvements in medical care. More accurate diagnosis of individuals with mild disease associated with uncommon CFTR mutations, as well as the availability and improved outcomes of lung transplantation, may also contribute. The recent advent of novel medications, singly or in combination, that can enhance CFTR production and/or function suggests that significant increases in longevity will continue (19–24).

1.2. Respiratory System Disease.

The organ system most significantly affected in CF patients is generally the respiratory system, with respiratory failure accounting for more than 62% of mortality (25). At the cellular level, mutations in the CFTR gene ultimately result in reduced or absent CFTR function which is associated with unregulated absorption of ions and water molecules across the airway epithelial cells, shrinkage of the periciliary layer, and dehydration of the overlying mucus (Figure 2) (10,26). Impaired ciliary activity leads to an increasingly adhesive mucus layer in contact with the airway epithelium (26). Accumulation of immobilized mucus results in airflow obstruction, colonization with pathogenic bacteria, and chronic inflammation (17). Staphylococcus aureus and pseudomonas aeruginosa in particular are pathogens that characteristically colonize the respiratory tract in CF (3,27). The combined effect of ongoing inflammation due to bacterial colonization and recurrent

infection leads to cumulative damage to the airways and lung parenchyma, ultimately resulting in progressive lung function impairment (28–30).

The etiology of an acute pulmonary exacerbation is often attributed to an intercurrent viral respiratory tract infection. Other pathogens, non-infectious causes, or other factors may also be responsible (31–36). Presenting features generally include some combination of respiratory and constitutional symptoms, altered respiratory function, and changes in chest radiography. The pathophysiology in this context will depend in part on the specific etiology and the response of the affected individual and resulting severity, but will likely be characterized by some amplification of the underlying features of CF (31–36). This includes worsened airway narrowing with inflammation, edema, excessive thickened mucus with inspissated secretions, mucoid impaction, and potentially bronchospasm (27,31–36). Coexistent parenchymal involvement with atelectasis, consolidation, and worsened ventilation heterogeneity is often present as well. The functional consequences are increases in measures of respiratory resistance, lung stiffness, and ventilation heterogeneity (see below) (36–41). Clinically this will be associated with varying degrees of hypoxemia and, with advanced impairment and/or complications, hypercapnia (17,31–36,42).

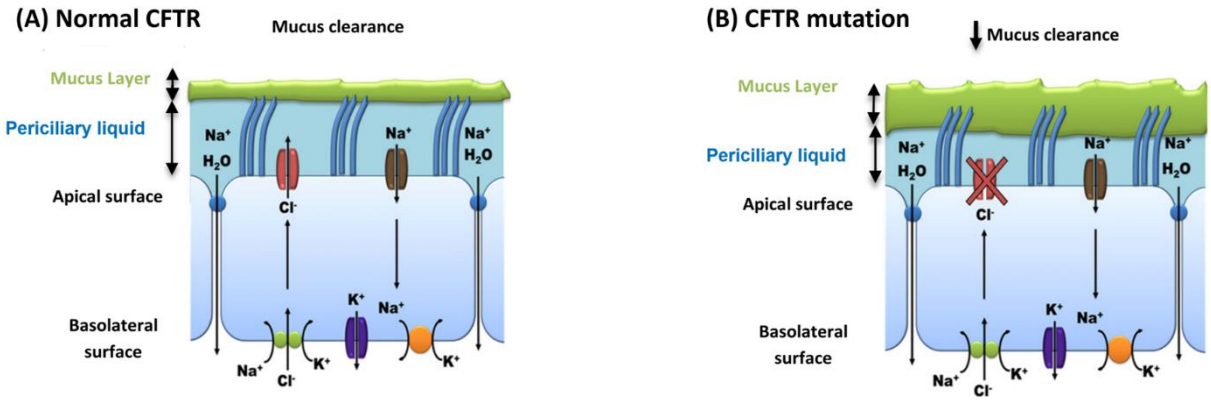

Figure 2. Airway epithelial ion and water transport, periciliary liquid and mucus layers, and mucus clearance in normal vs. cystic fibrosis individuals. (A) In the healthy airway, normal movement of Cl^- and water leads to proper hydration of the airway surface layer that is necessary for effective mucociliary clearance. (B) In the CF airway, impaired transport of Cl^- across the apical surface of the cell membrane and egress of water ultimately lead to reduced periciliary liquid with increased mucus and impaired airway mucociliary clearance. As a result, the ability to inhibit the growth of pathogens is impaired, putting CF airways at risk of inflammation and infection due to bacterial colonization (26).

1.3. Assessing Respiratory Function: Spirometry.

Spirometry is the most commonly performed test of lung function and is obtained on a regular basis in the outpatient setting to monitor lung health and manage the risk of pulmonary exacerbations in CF as is the case for other chronic respiratory disorders (40,43,44). The methodology for spirometry is well standardized and population-based reference values are readily available (44). For this, individuals are asked to reproducibly perform a maximal forced exhalation from total lung capacity down to residual volume (44).

The most frequently reported spirometry parameters are forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), the FEV_1/FVC ratio, and forced expiratory flow over 25% to 75% of the exhaled volume ($FEF_{25-75\%}$) (45). FEV_1 is generally the primary spirometry output parameter used to monitor CF patients in clinical settings and the key outcome measure in many CF clinical studies (46,47). While exceedingly useful, spirometry does have some well-recognized shortcomings. The test is highly effort dependent, and reproducibility is an important issue. It requires the active cooperation of the patient and coaching by a trained healthcare professional to help ensure that acceptable and reproducible results have been obtained (44,45). It is not applicable in children too young to follow the instructions (generally 6 years of age or younger) or those with significant weakness, frailty, difficulties in comprehension, or other relevant limitations. For example, satisfactory results could not be obtained in up to 20% of elderly patients despite proper supervision and the number of maneuvers performed (48). In addition, it has been argued that spirometry does not correlate well with patient reported outcomes and prognosis (49–55). For instance, traditional evaluation of COPD relies mainly on assessing lung function, particularly FEV_1. However, the evidence suggests that FEV_1 is a relatively weak correlate of symptoms such as dyspnea and the impact of COPD on daily life (56). Moreover, research on the pathophysiology of COPD has indicated that extensive small airway disease exists before it is identifiable with conventional spirometry parameters (57,58). Similarly, in asthma, parameters such as FEV_1 correlate weakly with the severity of symptoms and quality of life (59–61).

1.4. Assessing Respiratory Function: Oscillometry.

Oscillometry, also known as the forced oscillation technique (FOT), was first described in 1956 by Arthur DuBois et al. (62). Oscillometry evaluates the mechanical properties of the total

respiratory system (i.e., upper and intrathoracic airways, lung tissue, and chest wall) by generating small pressure or flow oscillations at the airway opening (63,64). The waveform generated in oscillometry may be a train of square wave signals at a set frequency (e.g., 5 Hz) and contains integer multiples of this fundamental frequency (e.g., 10, 15, 20, 25 Hz). This is the approach applied in impulse oscillatory systems (IOS). Alternatively, the pseudorandom approach utilizes a single composite signal containing sinusoidal waves at multiple discrete frequencies (Figure 3) (65–67). Sometimes referred to as multi-frequency or spectral oscillometry, many consider this the preferred approach (67–70).

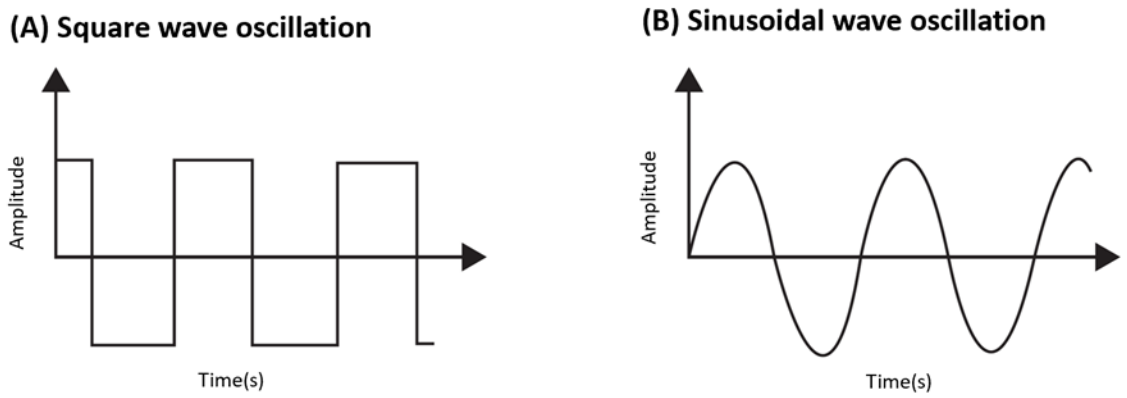

Figure 3. Schematic presentation of type of waveform applied in oscillometry. (A) Square wave generated in IOS devices. (B) Sinusoidal wave utilized in multi-frequency devices. In practice, a single composite signal containing multiple sine waves at specific discrete frequencies is utilized (67).

Measurements are conventionally obtained during brief periods of spontaneous tidal breathing (~20-30 s) without the need for repeated forced vital capacity maneuvers (63,64). As a result, oscillometry is essentially an effort independent test, and reliable results can generally be obtained in preschool children and the elderly as well as those unable to satisfactorily perform spirometry for various reasons as enumerated above (63,64,68,71). Furthermore, a deep inspiration, which

can differentially alter airway caliber in patients with normal lung function compared to those with bronchial hyper-responsiveness (a common finding in CF), is not required (72). Oscillometry also provides additional information with respect to the presence and severity of airway obstruction, small airway dysfunction, expiratory flow limitation, and altered respiratory compliance and/or ventilation heterogeneity (71,73–78). As a result, oscillometry is considered an important complement to spirometry and other standard tests of lung function (63).

Due to a number of recent technological advances, particularly in modern computing, oscillometry is now commercially available and is increasingly used for both research and clinical care (79,80). Standardized testing procedures, population-based reference values, and extensive use in pediatrics and more recently adults with a variety of disorders affirm oscillometry's ease of use and generalizability (64,71,80–82). As alluded to above, oscillometry addresses a number of recognized shortcomings of spirometry, which also apply to the evaluation and management of CF.

1.4.1. Basic Principles of Oscillometry.

In oscillometry, a pressure or flow stimulus is superimposed as a high frequency input signal onto the tidal breathing waveform as shown in Figure 4. Advanced signal processing is then used to filter out tidal breathing components from the recorded flow and pressure waveforms produced by the stimulus (64,83). The ratio between filtered oscillatory pressure and flow waveforms is used to measure input impedance and describe the overall mechanical properties of the respiratory system (64,83).

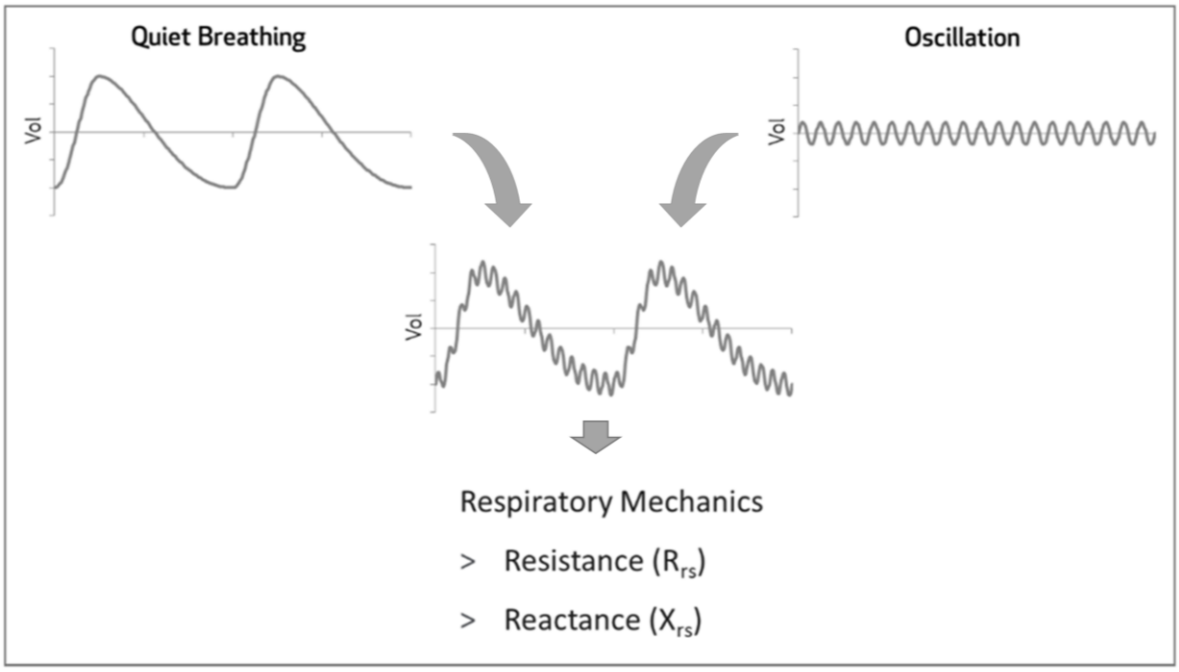

Figure 4. Illustration of the superimposed oscillatory signal on the tidal breathing waveform during oscillometry (83).

Input oscillations in the frequency range of approximately 4–40 Hz are used in most human studies and are produced by a loudspeaker in classical devices (63,64,79,84). Respiratory system impedance (Zrs) evaluates the relationship between the oscillatory components of pressure and flow changes superimposed on the breathing signals (64). Zrs consists of two key components, resistance (Rrs) and reactance (Xrs), as shown in the equation below, where "j" is an imaginary number equal to $\sqrt{-1}$:

$$Zrs = Rrs + jXrs$$

Rrs is calculated using the pressure component in phase with flow whereas Xrs describes the impedance component that is established between flow and the pressure component out of phase with flow. Because of the nature of its mathematical representation, which involves the imaginary number "j", Xrs has also been referred to as the "imaginary" component of impedance. In the clinical setting, the term "imaginary" is best avoided, since it might be misleading or confusing to one not familiar with oscillometry (64).

Although Rrs represents total respiratory resistance (i.e., including lung tissue and chest wall resistive properties), it is often referred to as a reflection of airway caliber. Resistance is higher in narrower and longer airways as a result of the higher frictional pressure loss as air travels through a tube. Rrs is further influenced by the heterogeneous distribution of resistance and reactance throughout the airway tree, with increased heterogeneity increasing the measured resistance at any given frequency (85). However, it is often overlooked, especially in clinical terminology, that Rrs comprises substantial components from extrapulmonary structures, such as the upper airway and chest wall – abdomen compartment (86).

Reactance is determined by two primary components: elastance (Ers) and inertance (Irs). Elastance is a measure of the stiffness of the entire respiratory system (due primarily to the pulmonary parenchyma and chest wall tissues). A more negative reactance represents a higher elastance or stiffness. At any given frequency, increasing heterogeneity causes a reduction in the reactance (i.e., a more negative value corresponding to an increase in apparent elastance or stiffness) (64,85,87,88). Inertance is an indicator of pressure loss in the central airways, which is mostly caused by gas column acceleration, and it becomes more noticeable at higher frequencies when

the bulk of the air and structures in the lungs oscillate at a faster rate. Moreover, inertance indicates the forces opposing acceleration, which operate in the opposite direction to elastance. As frequency increases from 4 Hz, the contribution of inertance increases. When the corresponding magnitudes of the elastic and inertive forces are identical (64), they cancel each other out (since they act in opposite directions) and reactance is zero (64). Accordingly, when Xrs = 0 then Zrs = Rrs (shown in Figure 5). This occurs at what is termed the resonant frequency (Fres) and corresponds to a frequency of 8 to 12 Hz in healthy adults (84). Xrs becomes positive at frequencies above Fres because it is dominated by the apparent inertia of the gas and tissues (64).

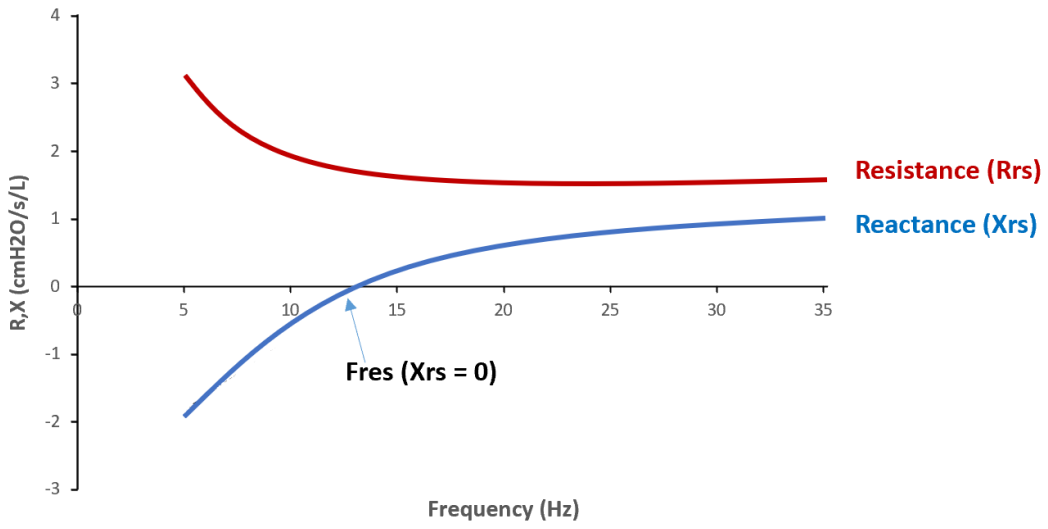

Figure 5. Simplified schematic representation of impedance-frequency relationships. The resonant frequency (Fres) is where the reactance-frequency relationship crosses the x-axis (i.e., where reactance is zero) (64).

1.4.2. Frequency Dependence of Resistance and Reactance.

Airway and subtending lung resistances, elastances, and inertances vary in magnitude and are distributed in a diverse manner, implying that the respiratory system has inherent heterogeneity. The uneven distribution of Rrs and Ers components explains a key mechanical feature of oscillometry which is frequency dependence (64). Respiratory resistance, as well as elastance and inertance, all change to some extent with frequency (Figure 5). The specific contribution of factors such as airway tree heterogeneity, tissue viscoelasticity, airway wall shunt, and pendelluft are often overlooked or not considered (64). As alluded to earlier and as might be expected, the frequency dependence of impedance parameters will also vary with the nature and magnitude of disease (64,71,89). With increasing frequency within the commonly used range of approximately 4 to 40 Hz, the contribution of the lung and chest wall tissues to Rrs decreases in healthy adults so that Rrs tends to be frequency independent and primarily influenced by airway properties. As previously stated, the magnitude of elastic reactance decreases with increasing frequency, and inertial reactance begins to dominate so that Xrs becomes less negative. This is referred to as positive frequency dependence (64).

1.4.3. The Oscillogram.

The oscillogram displayed in Figure 6 is a plot of both respiratory system resistance and reactance against the corresponding oscillatory frequency in an adult with CF (90–94).

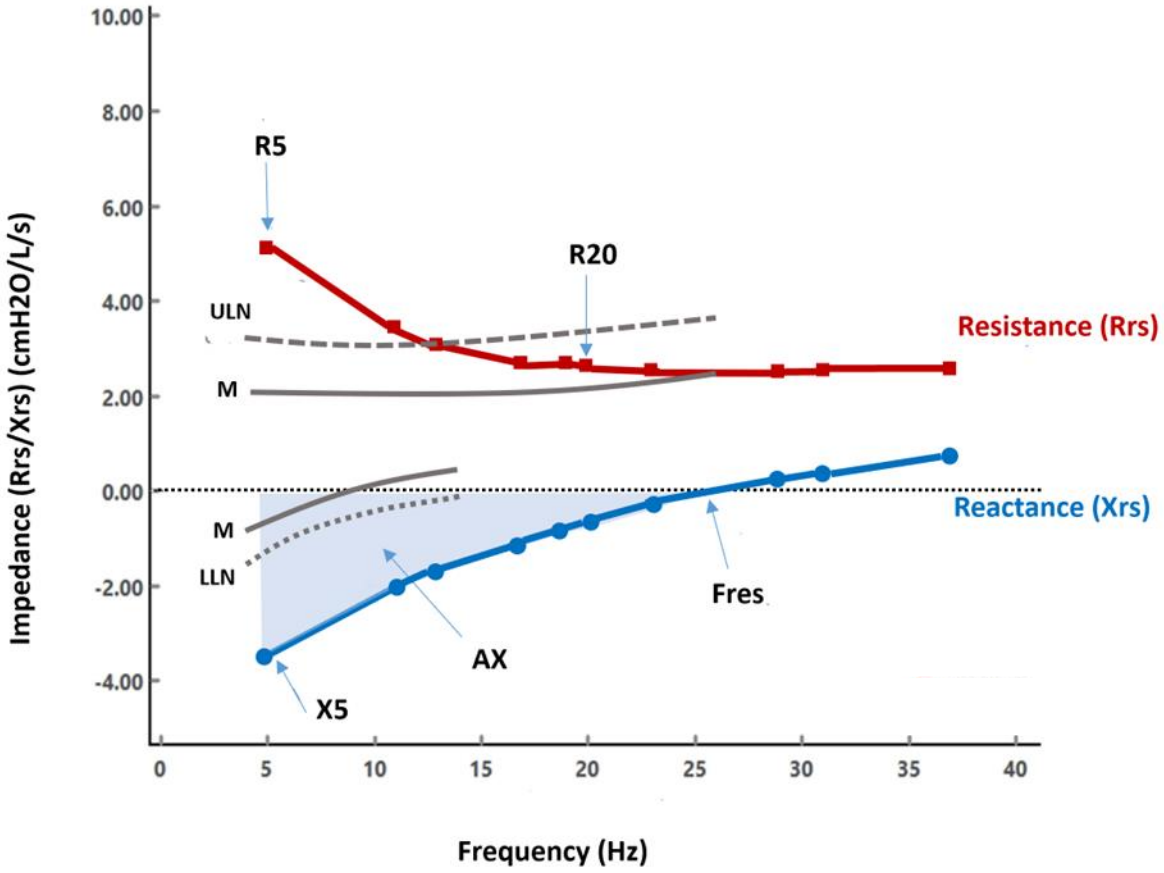

Figure 6. Oscillometry in an adult CF patient illustrating the impedance-frequency relationship for respiratory system resistance (Rrs) and reactance (Xrs). Standard parameters R5, R20, X5, AX, and Fres are specifically identified. Dashed and solid lines above indicate the upper limit of normal (ULN, Z score = 1.64) and mean reference value (M) of resistance, respectively, while below these indicate the lower limit of normal (LLN, Z score = -1.64) and mean reference value (M) of reactance, respectively, for this individual (84). See text for further explanation.

The definition of each standard oscillometry parameter derived from the oscillogram is provided as follows. R5 is the resistance at 5 Hz, representing total respiratory resistance, whereas R20 is the resistance at 20 Hz which is felt to reflect central airway resistance. The difference between

total and central resistance, R5-20[1], is considered a reflection of small airway function. This simplification overlooks the frequency dependence of resistance due to other considerations, in particular upper airway shunting. While tissue resistance is another potential factor, it is generally only an issue at frequencies < 5 Hz. An exception to this is in the setting of restrictive or chest wall abnormalities (e.g., morbid obesity) (63,95–100). The other parameter X5, reactance at 5 Hz, reflects primarily respiratory elastance or stiffness[2](71,101–103). The resonant frequency Fres, as discussed previously, is the frequency at which the reactance curve crosses zero on the impedance axis (71). The reactance area (AX) is measured as the area underlying the reactance vs. frequency relationship from 5 Hz to the Fres. AX has been shown to be a reasonable estimate of respiratory elastance and/or ventilation heterogeneity (71,104,105).

1.5. Clinical Applications of Oscillometry.

Oscillometry has been used in a variety of clinical settings, particularly in pediatric lung disease, where it may have had the greatest clinical utility to date due to the inability of young children to satisfactorily perform spirometry and other standard tests of lung function. As mentioned earlier, oscillometry may be satisfactorily obtained in adult patients unable to perform spirometry to acceptable standards (106). In a study comparing oscillometry and spirometry in 277 subjects of advanced age (65-96 years old) and various associated comorbidities, only 39.4% satisfied all quality control criteria for spirometry (45,107). In contrast, oscillometry was considered to be successfully performed in all 277 subjects (106). Oscillometry parameters provide information that

[1] R5-20 is generally determined with impulse oscillometry systems (IOS) and R19 with multi-frequency devices. The tremoFlo measures R19 directly but provides an interpolated R20 value in its report. To avoid confusion and for the sake of simplicity, some authors will describe results as R5-20 irrespective of the precise frequency at which results were obtained (i.e., 19 vs. 20 Hz).

[2] More negative values or worsening of Xrs will be referred to as lower values.

complements spirometry and other standard pulmonary function tests (64,71,81,82,108,109). It is suggested that oscillometry can help distinguish between different types of respiratory disease and improve diagnostic quality (71).

Currently, there are a variety of commercially available devices approved for clinical use, many of which have been improved with upgraded hardware, modified oscillatory signals, and/or new data processing techniques (69,110,111). Oscillatory systems designed specifically to address important clinical applications in particularly challenging settings, such as testing of newborn infants or mechanically ventilated patients in the critical care unit, are currently in development (69,108,110,111).

In the following 3 subsections (1.5.1 to 1.5.3), we will briefly review oscillometry studies in obstructive airway disease (i.e., asthma and COPD), as it is most relevant to what we would expect and have seen in CF. We will then discuss the available literature specifically examining oscillometry in children as well as adults with CF in more detail.

1.5.1. Oscillometry in Asthma.

Oscillometry has been extensively used to assess lung function in both children and adults with asthma (71,82,112). Lung function varies over time in asthma and is influenced by a variety of factors, including allergen exposure and exercise. In many situations, asthmatics are responsive to bronchodilators and anti-inflammatory medications, which may return lung function to normal in ideal circumstances (113). In asthma, impedance is typically characterized by elevated overall resistance (R5) as well as increased frequency dependence of resistance (R5-20), the latter

consistent with small airway bronchoconstriction and/or ventilation heterogeneity. X5 is typically reduced, and consequently, AX and Fres are increased. Changes in indices of reactance (i.e., X5, AX, and Fres) are consistent with increased elastance and/or ventilation heterogeneity (65,114).

Galant et al. recently reviewed the literature and concluded that oscillometry can complement conventional clinical and spirometric assessments, improving asthma treatment in both children and adults (112). In children, oscillometry performed better than spirometry in distinguishing between asthmatics and healthy subjects (115,116). Furthermore, it may identify airway obstruction earlier than spirometry (112,117). In adults, oscillometry provides complimentary information on peripheral airway impairment, suggesting oscillometry can be especially beneficial when the FEV_1 is normal or unchanged (112). In a study conducted by Sharshar et al. in 50 adults with asthma classified into two groups of either mild to moderate or severe disease, the results of oscillometry and spirometry were compared after three months of treatment according to the Global Initiative for Asthma (GINA) guidelines (118). They noted that there was a significant improvement in both spirometric and oscillometric parameters in those with mild to moderate asthmatic. However, only oscillometric parameters improved in the asthmatics with severe disease, (119).

In evaluating airway hyper-responsiveness in 18 adults with mild to moderate asthma (18 to 65 years old), oscillometry appeared to be more sensitive than spirometry, i.e., at standard methacholine provocation concentrations the magnitude of change in oscillometry parameters (particularly R5) was greater than in FEV_1 and the other spirometry indices (120). In a study of 30 patients with mild to moderate stable asthma (mean age of 34 years), Short et al. noted that both

bronchodilator (salbutamol) and bronchoconstrictor responses (oral propranolol) were greater with oscillometry in comparison to spirometry (121). These findings suggest that oscillometry, in general, is a simple, effective, and sensitive method for assessing asthma and monitoring treatment response. In children, oscillometry appears to be useful for early diagnosis and therapeutic intervention to control future disease progression. In adults, oscillometry can be used to complement spirometry, particularly when the latter is normal.

1.5.2. Oscillometry in COPD.

Detection of early-stage COPD can be challenging as spirometry can remain essentially normal despite identification of structural changes in the lung, particularly in peripheral or small airways (71,122,123). In a recent review on oscillometric findings in COPD, Lipworth et al. suggest that AX might be used to identify changes in lung function either as a screening tool in the early stages of COPD or to monitor long-term deterioration in more advanced disease (124). In the ECLIPSE cohort of 2054 COPD patients, Crim et al. found changes in AX and R5-20 correlated with disease severity as reflected by GOLD 1 through GOLD 4 stages of disease (123). In 215 COPD patients, Wei et al. demonstrated a good correlation between standard pulmonary function tests and oscillometry, particularly with reactance parameters (125). In a smaller study of 25 COPD patients, Mousa et al. reported a significant correlation between spirometry parameters and both R5 and X5 (126). Eddy et al. examined the association between oscillometry and ventilation defects identified by magnetic resonance imaging (MRI) utilizing hyperpolarized helium in a group of ex-smokers with COPD (104). They demonstrated a significant correlation between ventilation-defect-percent (VDP) and oscillometry parameters, including R5-19, X5, and AX (104).

In general, oscillometry in established COPD may have many of the same characteristics found in asthma, such as increased total resistance (R5), frequency dependence of resistance (increased R5-20), and elevated AX (71). In COPD, however, such changes should not be largely or totally reversible with bronchodilator administration (113,127). Early COPD may be characterized by an increase in R5-20 and AX while spirometry remains relatively well preserved (128). Oscillometry is also useful in distinguishing COPD from other disorders. For example, in some contrast, proximal (upper airway) obstruction (e.g., vocal cord paralysis or tracheal stenosis) leads to a constant or fixed increase in resistance across all oscillating frequencies with no impact on reactance (see Figure 7) (112,129). In restrictive lung disease, there is typically no effect on resistance but a significant increase in AX (101–103,129).

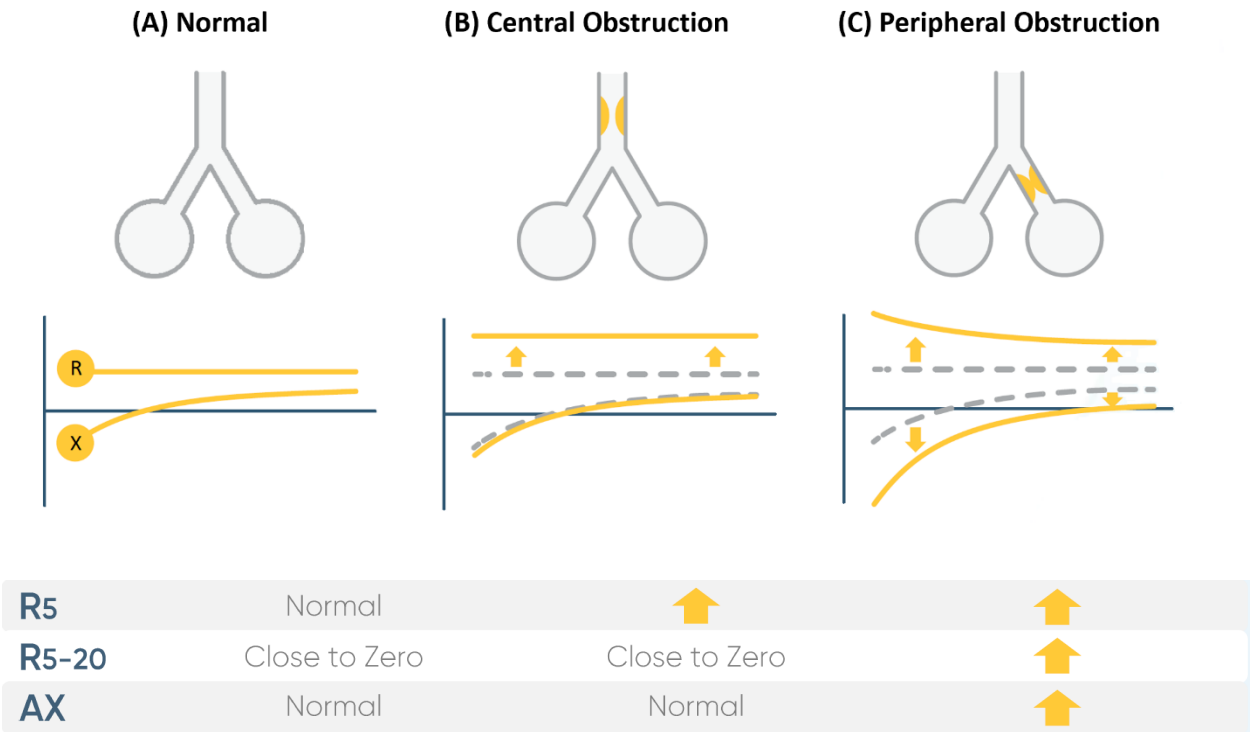

Figure 7. Stylized oscillometry patterns in (A) a normal subject vs. individuals with (B) central or (C) peripheral airway obstruction (112,129,130).

1.5.3. Oscillometry in CF.

Most oscillometry studies regarding CF have been done in children (17,131–137). To the best of our knowledge, and supported by observations of Siddiqui and Horsely (17), prior to 2015 there were no English language publications examining oscillometry in adults with CF. Several have appeared since, although technical and other factors limit the interpretation and utility of their results. In addition, pediatric data may not be strictly comparable to our study in adults, since in children different oscillating frequencies and/or reported values were used and changes in technology over time impedes interpretation of these older studies (131–137). Based on an English language literature search (PubMed and Google Scholar), there are 18 studies in children and four in adults. In this section, the most relevant and important oscillometry findings in children and adults will be reviewed.

Nielsen et al. performed oscillometry in a group of 30 children aged 2-8 years with CF (136). This was a 4-year prospective study where oscillometry was applied at only 5 Hz, while baseline results from 120 healthy subjects (2 to 7 years old) from their previous study were used as a reference group. Spirometry, on the other hand, was performed when children reached 6 years old. They reported the inability of oscillometry to detect abnormal lung function in CF children with abnormal spirometry and also found no correlation between oscillometry and spirometry (136).

Gangell and coworkers examined oscillometry (6-10 Hz) in 58 preschool children (aged 2-7 years old) classified into two groups - symptomatic and asymptomatic (135). Rather than using a concurrent control group, they used baseline results of their previous oscillometry study in 158 healthy young children aged 2–7 years as their reference values. They noted CF children had higher

Rrs and lower Xrs (more negative) in comparison with their healthy reference population. In addition, resistance was greater and reactance more negative in children with current symptoms in comparison with those who were asymptomatic. They concluded that oscillometry has the potential to enhance understanding of CF in its early stages, noting the fact that spirometry could not be obtained easily in this age range (135).

In another study, 184 preschool children (aged 3-6) were examined by Ramsey et al. on 422 occasions when children were felt to be clinically stable and removed from an acute exacerbation or change in clinical status (133). Oscillometry and chest computed tomography (CT) scanning were performed prior to bronchoscopic bronchoalveolar lavage, all at the time of an annual follow-up visit. They found a poor association between oscillometry parameters and indices of lung inflammation, infection, and structural lung abnormalities as well as progression of these variables over time. They concluded oscillometry has a lack of sensitivity in detecting underlying lung disease (133).

In contrast, Ren et al. performed oscillometry and spirometry on a group of 14 older school-age children with CF (8 to 18 years old) to examine changes in lung function before and after treatment of an acute exacerbation (which included intravenous antibiotics, chest physiotherapy, and nutritional support) (132). They noted spirometry was abnormal on admission and improved after two weeks of therapy. For oscillometry, R5 decreased and X5 became less negative during this period. There was also a significant correlation between changes in X5 and FEV_1. This study revealed that oscillometry could detect changes in respiratory function in older children with CF after receiving inpatient treatment for an acute respiratory exacerbation (132).

In a very recent study, *within-breath* changes in oscillometric impedance of the respiratory were examined by Zannin et al. (131). Oscillometry at 8 Hz during inspiration, expiration, and the whole breathing cycle was evaluated in 33 children (aged 6-17 years). Other lung function tests, including spirometry, body plethysmography, and multiple breath washout as well as MRI, were also obtained. They found a moderate negative correlation between FEV_1 and both expiratory resistance and differences between inspiratory and expiratory resistance. FEV_1 also showed a moderate positive correlation with expiratory reactance. There was a poor correlation between oscillometry and multiple breath washout parameters, while there was no correlation between oscillometry and the MRI derived morphological score in CF as described by Eichinger et al. (131,138).

Moreau et al. compared oscillometry to previously obtained spirometry in 30 CF children who were between 4 and 19 years of age (137). This ***retrospective*** study demonstrated a weak but significant correlation between spirometry and oscillometry parameters. Additionally, they examined the ability of oscillometry to categorize the severity of lung function impairment based on FEV_1 using receiver-operating characteristic curves (ROC). They concluded that oscillometry was unable to reliably identify and track lung function deterioration in CF children as determined by spirometry (137).

Sakarya et al. reported the results of oscillometry in 49 children (aged 3-18) when stable or at exacerbation as compared to a control group of 45 healthy children (134). Resistance values (R5, R10, R15, and R20) as well as Fres and AX were significantly higher in the children with CF

compared to the control group, while reactance (X5, X10, X15, and X20) in the CF children was lower (more negative). It was also noted that resistance increased during exacerbation and returned back toward baseline values after recovery. Reactance similarly worsened during exacerbation and improved after treatment. They concluded oscillometry can be used to evaluate pulmonary function in children with CF and help identify acute exacerbations in such patients (134).

As discussed above, the studies in children with CF reviewed above were contradictory and not uniformly consistent. Most reported an increase in Rrs and a reduction in Xrs, while others did not find the same changes (132,135–137). Moreover, oscillometry parameters were not found to be associated with CF symptoms (137) and correlated poorly with spirometry in one study (137), which conflicted with another. This may well be explained by the fact that oscillometry and spirometry were not performed systematically and concurrently (137). In addition, comparing oscillometry with spirometry was not comprehensively examined in all children on all occasions, as might be expected since spirometry in preschool children may be difficult or impossible to obtain. In general, data from older children showed oscillometry was able to assess lung function and it correlated with spirometry (131,132,134). Further work with attention to suitable study design and an adequate number of patients considering age group and disease condition is clearly needed. Applying quality control considerations for both oscillometry and spirometry is another important factor that should be considered (44,45,63,64,139,140).

The literature on adults is remarkably limited and also problematic in many respects (see Table 1 below).

Table 1. Oscillometry in CF adults: *Prior study characteristics*.

	Device	Parameters	Reference Values	CF (n)	Control (n)	Z score
Lima et al. (141)	Non-commercial Multi-frequency	R4 to R32 and X4 to X32 AX and Fres	Not used	27	23	N/A
Wallaert et al. (142)	Resmon Pro Multi-frequency	R5, R19, X5 (insp, exp, whole) AX, Fres not provided	Not used	30	11	N/A
Lacerda et al. (143)	Non-commercial Multi-frequency	R0, Rm, Fres, Xm R5, R5-20, X5, AX not provided	Not used	21	22	N/A
Blin et al. (144)	Jaeger IOS	X5, R5, R5-20, AX, and Fres	Oostveen et al. (63)	42	-	R5, X5 only
Rad (This thesis)*	tremoFlo Multi-frequency	R5, R5-20, X5, AX, and Fres	Oostveen et al. (84)	92	-	Available

N/A: not available; IOS: impulse oscillometry system; R0: zero-intercept resistance (extrapolated value of resistance at zero frequency); Rm: mean resistance; Xm: mean reactance; insp: inspiration; exp: expiration. *Original data and further information from this thesis will be presented in detail in subsequent sections.

Lima et al. evaluated oscillometry in 27 adults with CF using a non-commercial device (141). They observed an increase in total and peripheral resistance as well as a more negative reactance compared to a control group. They noted moderate correlations between resistive oscillometry parameters versus spirometry. Similar correlations were found for reactance parameters. It was concluded that oscillometry could identify the biomechanical changes related to CF and showed great potential in the clinical evaluation of respiratory mechanics in adults with CF (141).

In a study conducted by Lacerda et al., oscillometry (using a non-commercial device) as well as multidetector thoracic CT were performed in 21 CF adults (143). Interpreting and comparing these results with that of others was limited due to the failure to use conventional oscillometry parameters (143). Nonetheless, they reported that both resistive and reactance properties of the respiratory system were altered. Specifically, respiratory resistance and resonant frequency were

both elevated and reactance reduced (being more negative) in comparison with their healthy control group. In addition, the extent of hypoventilated lung regions identified by CT correlated with the resistive parameters obtained by oscillometry as well as a reduction in diffusing capacity of the lung obtained as part of standard pulmonary function testing (143).

The effect of a single session of autogenic drainage of respiratory secretions on respiratory function assessed by both oscillometry and spirometry in 31 CF adults was reported by Wallaert et al. (142). Resistance and reactance were separately assessed during inspiration, expiration, and the whole respiratory cycle (introducing another novel feature of oscillometry in the evaluation of respiratory function in adult CF). Regarding spirometry, only FEV_1 and FVC showed a small but statistically significant improvement after autogenic drainage. In terms of oscillometry, whole breath and inspiratory resistance were significantly decreased by autogenic drainage, whereas no significant effect on expiratory resistance was observed. It was suggested that reflex adduction of the glottis during expiration could account for this apparent discrepancy between inspiratory and expiratory resistance. There was a moderate correlation between changes in inspiratory resistance and the changes in spirometry parameters (i.e., FEV_1 and FVC). Inspiratory reactance also improved after autogenic drainage. The authors suggested that oscillometry can provide useful insight into the effects of chest physiotherapy on lung function in CF (142). Although this study compared oscillometry with spirometry, the omission of two standard parameters (i.e., AX and Fres) is problematic, considering the utility of AX in particular in evaluating airway obstruction in other disorders (142).

In contrast, Blin et al. examined 42 adults with CF when stable and during an acute exacerbation. They concluded that both oscillometry and spirometry have a limited ability to identify the development of an acute CF exacerbation (144). This was a *retrospective* study, however. Oscillometry and spirometry were *not* performed on the same occasion, which clearly limits the usefulness of these observations.

Overall, in reviewing the literature, interpretation of these recent studies in adults with CF is limited for various reasons, which include the use of a non-commercial device, omission of one or more standard oscillometry outcome parameters, inclusion of non-standard parameters, small sample size and/or absence of population-based reference values. Limited information concerning adherence to quality control and quality assurance recommendations and other technical considerations is an additional concern. Accordingly, the aforementioned issues indicate further comprehensive studies in adult CF are warranted.

1.5.4. Recent Applications of Oscillometry.

Cho et al. demonstrated that oscillometry can be useful in monitoring graft function following lung transplantation (145). Weekly oscillometry, spirometry, and scheduled surveillance transbronchial lung biopsies were obtained in 156 double lung transplant recipients during the first 3 months post-transplant. Oscillometry was able to detect physiological changes related to acute cellular rejection as well as the response to anti-rejection treatment, while spirometry was unchanged or even improved over this time period (145).

Another role for oscillometry was suggested during the COVID-19 pandemic. Routine use of spirometry and other standard pulmonary function tests was discontinued due to concerns of aerosol generation and the risk of nosocomial viral infection (146,147). This is related to the expected extent of aerosol generation during forced expiratory maneuvers and cough as well as close proximity between patient and technician, often in small or enclosed areas without sufficient ventilation to mitigate the risk of viral exposure (70,146). Lundblad et al. proposed oscillometry as a viable alternative to spirometry to assess lung function under these circumstances since repeated FVC maneuvers (often associated with cough) would not be required. In addition, the use of Bluetooth® or similar (infrared) wireless technology would enable oscillometry to be performed under direct supervision but with sufficient distancing between subject and technician (146,148). Preliminary case reports in COVID-19 positive patients without identified secondary nosocomial infection would support this proposal (149).

Advances in digital technologies have led to the development of dramatically smaller oscillometry devices equipped with internal data storage and internet access for remote data transfer suitable for self-administered home monitoring (150,151). Increased variability of airway function is a hallmark feature of asthma in general and particularly so at the onset of an acute exacerbation in some individuals (152–155). In a study of 10 nonsmoking patients with mild asthma, Gobbi et al. demonstrated that the variability of inspiratory resistance obtained by daily home oscillometry monitoring over 6 consecutive months facilitated the early detection of an asthma exacerbation (156). In principle, home oscillometry could also be used to assess the presence or absence of variability of respiratory function in patients with suspected but unconfirmed asthma who have not been fully evaluated (154,155). Increased variability in airway function heralding the onset of an

acute exacerbation has also been recognized in COPD (157). As reported by Zimmerman et al. in 15 COPD, patients utilizing home oscillatory monitoring over an 8-9 month period, day-to-day variability in inspiratory reactance was related to disease symptoms and early development of an exacerbation (157).

Chapter 2: Rationale, Hypotheses and Objectives.

2.1. Rationale.

Reliably recognizing early disease, identifying the risk for and actual development of an acute exacerbation in established disease, determining disease progression and ultimate prognosis all play important roles in the management of more common chronic obstructive airway disorders such as asthma and COPD. Similar considerations apply to CF. This highlights the necessity for a sensitive and reliable measure of lung function in adult patients with CF.

Spirometry is the most frequently applied test of respiratory function. However, it has well-recognized limitations with respect to the above considerations in general, and certainly for CF (49–55,102,158–161) The reasons for this are not fully understood and may simply represent unrealistic expectations. However, there are a number of factors that likely do contribute in this regard (159). For example, spirometry is highly effort dependent, requiring proper understanding and cooperation which may not always be possible (45,159,162). This is particularly true when acutely ill or with advanced disease as well as other circumstances (159,162,163). The impact of alterations in lung volume history associated with repeated maximal forced expiratory maneuvers on bronchomotor tone and airway caliber is well recognized, but is difficult to predict in an individual patient and may vary over time (164–166). Spirometry is considered a poor measure of small airway function (76). It remains normal until more than half of small peripheral airways are lost (76,167). This may preclude reliable diagnosis, monitoring of disease progression, determining prognosis, and establishing relationships to patient reported outcomes during the early phases of disease (76,159,168–170).

Oscillometry is considered a complementary test of lung function and may address some of the general limitations of spirometry noted above (55,68,71,108,109,159). For example, since oscillometry is performed during quiet tidal breathing, it is likely to be better tolerated in general, but particularly in circumstances where patient performance may be limited for various reasons. This also avoids the potential confounding influence of changes in lung volume history on bronchomotor tone and airway caliber (64,68). Oscillometry may also provide a better measure of small airway function, with R5-20 being a more reliable and sensitive indicator of small airway dysfunction in comparison to $FEF_{25-75\%}$ in most settings (75–77,124,171–173).

As discussed earlier, most studies examining oscillometry in CF have been performed in children. Surprisingly, there are only a few reports in adults with CF. Moreover, the utility of these data is limited because of the use of a non-commercial device, inclusion of non-standard parameters, omission of standard parameters, small patient numbers, and/or absence of population-based reference values. In addition, quality control methods were not clearly identified, suggesting that current quality control guidelines were likely not followed (141–144). With all this in mind, the need for a comprehensive study to reliably characterize oscillometry findings in adult CF remains. Due to recent advances in technology, oscillometry devices are now commercially available and equipped with published reference values and automated software allowing for prompt analysis and display in rapid or near real time (63,64,79,84). Some devices are portable, enabling point of care testing on the hospital inpatient ward, in the emergency room or during an outpatient clinic visit rather than being restricted to the PFT laboratory. This has the potential to allow for a broader application and more thorough understanding of the impact of CF on oscillometry and its potential

to improve clinical decision making and patient outcomes throughout the natural history of the disease.

2.2. Hypotheses.

We hypothesized that (i) oscillometry can be reliably and reproducibly obtained in adults with CF in an ambulatory clinic setting as another metric of lung function, (ii) there is a significant correlation between accepted oscillometry and spirometry parameters, and (iii) there is a significant association between oscillometry parameters and abnormal spirometry parameters

2.3. Objectives.

This thesis may be viewed as a preliminary study to comprehensively examine the ability of oscillometry to reliably and reproducibly characterize respiratory function in adult CF compared to spirometry, as well as to provide insight for future work. Accordingly, the main objective of the study is to assess oscillometric characteristics of respiratory function in a large cohort of adult CF patients during routine outpatient evaluation using an approved commercially available device with accepted parameters and to compare these to spirometry obtained on the same occasion.

Chapter 3: Materials and Methods.

3.1. Subjects.

Ninety-two patients previously enrolled in the Adult CF Clinic of the Montreal Chest Institute, McGill University Health Centre with a routine follow-up appointment were evaluated from September 2018 to March 2020. Those with any change in respiratory or general symptoms, medication usage, or an unscheduled healthcare interaction (outpatient clinic, emergency department or hospitalization) due to a change in clinical status during the preceding four weeks were excluded from an initial study evaluation at that time. Repeat testing was performed on one or more subsequent visits in some patients which may have included some change in their clinical status. This was based on the treating physician's evaluation and limited to a relevant change in medication regimen, which may have included the initiation of oral antibiotics and/or corticosteroids. Measurements were not obtained at that time in any patient requiring emergency department or hospital admission. The study protocol was approved by the institutional ethics review board and written informed consent was obtained.

3.2. Testing.

Patient characteristics including age, gender, height, and weight were recorded. Oscillometry and spirometry were then performed according to published guidelines and recommendations (45,63,64,84,139,140,174).

3.2.1. Oscillometry.

Oscillometry was administered in the outpatient clinic setting by a trained healthcare provider using a Health Canada approved commercially available device (tremoFlo® C100, Thorasys Thoracic Medical Systems, Inc., Montreal, Canada). For this, patients were asked to breathe quietly through a standard mouthpiece-filter interface attached to the device while seated with the head and neck in a neutral position and nose clips in place. The patients were asked to support their own cheeks and submental region to minimize upper airway distention and avoid artifacts during oscillation (63,64,139). Multi-frequency (5-37 Hz) airway oscillations (~1-2 cmH2O) were applied at the airway opening for several brief 20-30 second periods with rest intervals in between. Airway pressure, flow, and tidal volume were monitored during data acquisition, and conventional impedance versus frequency plots were reviewed immediately after each oscillation period (83). Trials with evidence of leak, glottic closure, coughing, swallowing, an irregular breathing pattern or other artifacts were rejected. A minimum of 3 acceptable trials with a coherence value (COH) > 0.08 (67,68,81,108,175) and a coefficient of variation for R5 (COV) < 15% was obtained in each subject (63,64,139). R5, R5-20, X5, and AX were recorded and results expressed as absolute values and Z scores (63,64,84). Absolute values for Fres were also noted.

3.2.2. Spirometry.

Spirometry was obtained by a respiratory therapist in the outpatient clinic setting (Spirobank® and Winspiro PRO®, MIR Medical International Research, Rome, Italy) and was performed after oscillometry in all cases. FEV_1, FVC, FEV_1/FVC ratio, and $FEF_{25-75\%}$ were determined. Results were expressed as absolute values, percent predicted, and Z scores based on National Health and Nutrition Examination Survey (NHANES) III reference equations (45,176).

3.3. Statistical Analysis.

The normality of distribution of spirometry and oscillometry parameters was assessed using the Shapiro-Wilk test. Distributions were found to be mixed, i.e., several were normal and others were non-normal. Spirometry and oscillometry results are provided as the mean ± standard error (SE) and the median and interquartile range (first quartile and third quartile) with this in mind as well as to facilitate comparison with previously reported results. Spirometric results are also expressed as percent predicted values for the latter reason (177,178).

Results obtained at the initial evaluation in all patients were utilized for cross-sectional analysis. In contrast, longitudinal data analysis used values determined from all evaluations performed in all patients studied. The relationship between spirometry and oscillometry parameters was evaluated by Spearman's correlation coefficient for cross-sectional data and mixed effects model for longitudinal results (179,180). The association between oscillometry parameters and *abnormal* spirometry was assessed using logistic regression analysis for cross-sectional values and marginal models estimated via generalized estimating equations (GEE) for longitudinal results (181–183). With respect to longitudinal data, both the mixed effects model and marginal models estimated via GEE are used to estimate regression models that take into account the correlation between observations in the same subject. These models are able to accommodate the inclusion of data from subjects with one or several observations and account for within-subject and between-subject variability. Abnormal was defined as a parameter having a value greater than the upper limit of normal (ULN, i.e., a Z score > 1.64) or less than the lower limit of normal (LLN, i.e., a Z score < -1.64) (84,177,178). To adjust for multiple comparisons, the False Discovery Rate proposed by Benjamini and Hochberg was utilized (184). P values < 0.05 were considered statistically

significant. Statistical analyses were performed using SPSS version 26, Python 3.6 with Jupyter notebook version 6.0.3, SAS version 9.4, and R studio version 4.1.0.

Chapter 4: Results.

Overall, 92 patients were initially evaluated on at least one occasion when clinically stable. Of these, 52 were studied on one or more subsequent occasions (range 1-5, 82 additional tests in total), which may have included some change in their clinical status, as noted above. Patient characteristics determined *only* at the time of the initial assessment are provided in Table 2. On average, patients were young, of expected stature (mean male and female height were 171.3 ± SE 1.0 cm and 159.3 ± SE 1.0 cm, respectively) and had a normal BMI.

Table 2. Patient characteristics.

Age (yrs)	33.0 ± 1.3	29.9 (23.6, 36.9)
Gender (M/F)	51/41	-
Height (cm)	166.0 ± 1.0	165.5 (159.3, 173.0)
Weight (kg)	63.2 ± 1.5	61.0 (54.0, 68.7)
BMI (kg/m^2)	22.8 ± 0.4	22.4 (20.2, 25.0)

Values are presented as the mean ± SE in the left column and the median (first and third quartile) in the right column. BMI: body mass index.

Results for spirometry at the initial assessment in all patients are shown in Table 3, where group mean values ± SE are displayed as absolute values, percent predicted, and Z scores. The median and corresponding first and third quartile values are also given. All parameters were appreciably reduced for the group. On average, patients exhibited a moderate obstructive defect characterized by a reduced FEV_1 and FEV_1/FVC ratio. The decreased FVC (Z score = -2.36 ± SE 0.20) was

likely attributable to the degree of obstructive impairment, although a co-existent restrictive defect could not be excluded since concurrent static lung volume measurements (i.e., total lung capacity) were not systematically obtained as part of the study protocol.

Table 3. Spirometry.

	Absolute	% Predicted	Z score
FEV_1 (L)	2.27 ± 0.10 *2.22 (1.56, 2.86)*	63.27 ± 2.49 *61.93 (44.07, 82.04)*	-3.38 ± 0.23 *-3.51 (-4.99, -1.74)*
FVC (L)	3.27 ± 0.12 *3.31 (2.44, 3.93)*	74.99 ± 2.10 *75.36 (61.66, 90.85)*	-2.36 ± 0.20 *-2.28 (-3.54, -0.88)*
FEV_1/FVC (%)	67.96 ± 1.35 *68.60 (60.33, 78.70)*	–	-2.43 ± 0.22 *-2.32 (-3.84, -0.81)*
$FEF_{25-75\%}$ (L/s)	1.74 ± 0.12 *1.52 (0.77, 2.53)*	45.2 ± 3.1 *37 (20, 65.25)*	-2.39 ± 0.15 *-2.59 (-3.48, -1.51)*

Values are presented as the mean ± SE above and the *median (first, third quartiles)* below. FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow over 25 to 75% of FVC.

Oscillometry results obtained at the initial assessment in all patients are summarized in Table 4. The group mean value for each parameter is provided as an absolute value-and Z score. The median and corresponding interquartile range are again shown as well. On average, all oscillometry parameters were significantly outside the normal range (i.e., Z scores either greater than 1.64 or more negative than -1.64). Not shown in the table, COH values averaged 0.90 ± SE 0.01. The coefficient of variation for R5 was 4.51 ± SE 0.22%.

Table 4. Oscillometry.

	Absolute	Z score
R5 (cmH2O/L/s)	5.17 ± 0.24 *4.42 (3.71, 6.03)*	1.98 ± 0.15 *1.65 (1.00, 2.93)*
R5-20 (cmH2O/L/s)	1.34 ± 0.14 *0.86 (0.47, 1.77)*	3.50 ± 0.37 *2.67 (1.10, 4.80)*
X5 (cmH2O/L/s)	-2.54 ± 0.19 *-2.00 (-3.09, -1.27)*	-2.85 ± 0.31 *-2.40 (-4.25, -0.70)*
AX (cmH2O/L)	24.17 ± 3.00 *13.13 (5.37, 29.46)*	2.47 ± 0.17 *2.4 (1.2, 3.80)*
Fres (Hz)	20.71± 1.00 *20.18 (13.57, 27.05)*	-

Values are presented as the mean ± SE (above) and *median (first, third quartiles)* (below) for each parameter. R5: respiratory resistance at 5 Hz; R5-20: difference in respiratory resistance at 5 and 20 Hz; X5: respiratory reactance at 5 Hz; AX; respiratory reactance area; Fres: resonant frequency.

Figure 8 depicts the mean oscillometry results compared to reference values. It illustrates the average respiratory impedance vs. frequency relationships in all 92 CF adults obtained at the initial visit. Resistance was higher than the reference value at all frequencies. It was extremely high at 5 Hz and relatively high for other frequencies above 5 Hz. On the other hand, reactance was substantially more negative than the reference value at 5 Hz and crossed the x-axis at a Fres (20.71 ± SE 1.00 Hz), which is higher than seen in healthy subjects (64).

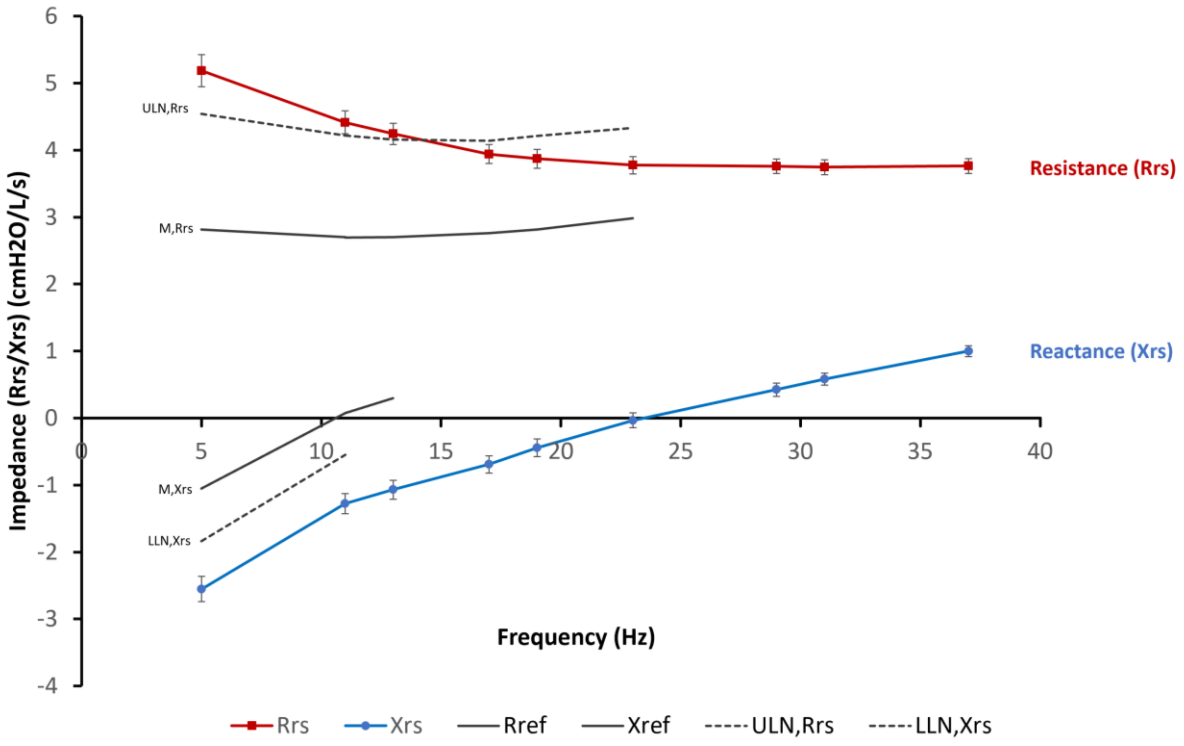

Figure 8. Group mean values ± SE of respiratory resistance and reactance as a function of frequency at the initial visit for all 92 CF patients are shown. Dashed and solid lines on top indicate the upper limit of normal (ULN, Z score = 1.64) and the mean (M, Z score = 0) for reference values of resistance, respectively, and below indicate the lower limit of normal (LLN, Z score = -1.64) and mean (Z score = 0) for reference values of reactance, respectively, for this group (84).
See text and Table 4 for definition of individual oscillometry parameters.

The correlation coefficients between spirometry and oscillometry parameters expressed as absolute values and Z scores are shown separately in Figure 9. Results are presented in the form of a heatmap with the color-coding indicating the magnitude and sign of the correlation coefficients. The correlation coefficients represent cross-sectional data, being determined from values obtained during the initial assessment in all patients. As can be seen, there was a good to strong correlation between spirometry and oscillometry parameters. The highest correlations were between FEV_1 and both X5 and AX expressed either as absolute values or as Z scores. It is clear

increasing resistance was associated with worsening spirometry and, hence, the negative correlation. On the other hand, the more negative value of X5 associated with worsened respiratory function was characterized by a positive correlation with spirometry.

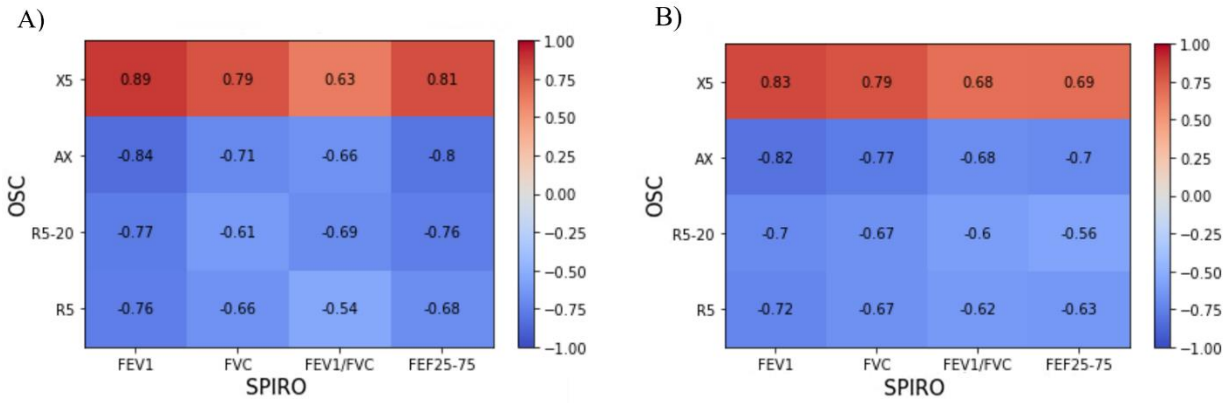

Figure 9. Correlation coefficients between spirometry and oscillometry parameters for cross-sectional data expressed as (A) absolute values and (B) Z scores. P values were < 0.001 for all comparisons. The heatmap color coding reflects the magnitude and sign of the correlation coefficients. For further explanation see text.

To further explore the relationship between spirometry and oscillometry on a longitudinal basis, i.e., using results obtained in all patients on all occasions, a mixed effects model was generated (179). Correlation coefficients analyzed separately for data expressed as absolute values and Z scores are given in Figure 10. Results are again depicted in a heatmap format as seen in Figure 9. The correlation coefficients were generally very similar to those observed using the initial cross-sectional data demonstrating good to strong relationships between spirometry and oscillometry parameters, particularly between FEV_1 and both X5 and AX.

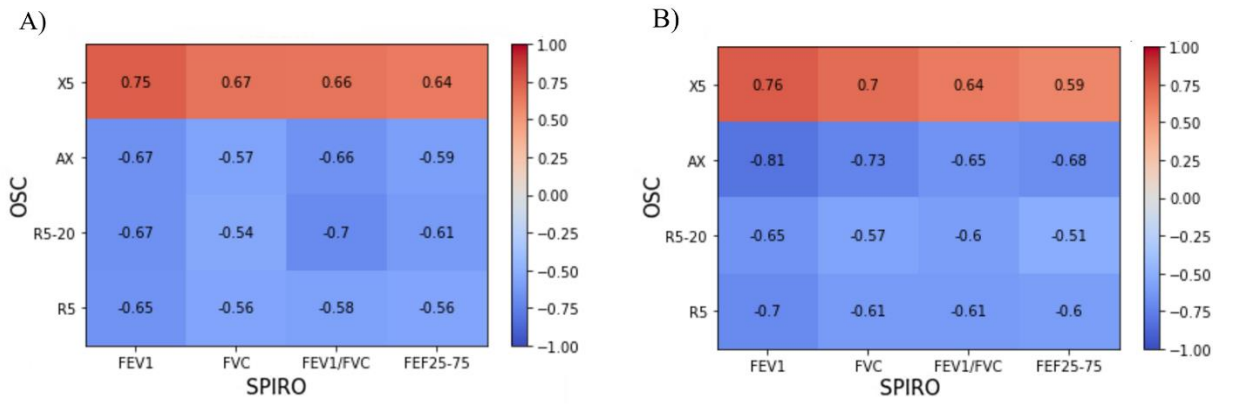

Figure 10. Correlation coefficients for spirometry vs. oscillometry parameters for longitudinal data expressed as (A) absolute values and (B) Z scores. P values were < 0.001 for all comparisons. As in Figure 9, the heatmap color coding indicates the magnitude and sign of the correlation coefficients. For further explanation see text.

In a somewhat different approach, the association between ***abnormal*** values for spirometry vs. oscillometry parameters was evaluated using logistic regression analysis for cross-sectional data and marginal models estimated via generalized estimating equations (GEE) for longitudinal data (181–183). Abnormal parameters were defined as having a Z score above 1.64 or more negative than -1.64. Tables 5 and 6 provide results for the logistic regression analysis and marginal models estimated via GEE, respectively, between oscillometry parameters and individual abnormal spirometry parameters. Results for univariable and multivariable analysis are shown separately. We focused on the multivariable findings as the univariable results were relatively similar. These data indicate that there is a significant association between oscillometry parameters and abnormal spirometry parameters by both logistic regression analysis and marginal models estimated via GEE. Moreover, in the multivariable logistic regression analysis, R5, R5-20, X5, and AX were all strongly associated with an abnormal FEV_1 (odds ratio 2.31 to 3.84, $P < 0.002$). Findings for marginal models estimated via GEE were similar (odds ratio 1.93 to 3.22, $P < 0.002$). This appeared most evident for both X5 and AX, with an odds ratio of 3.84 and 3.50, respectively, for

logistic regression analysis (cross-sectional data) and 3.22 and 3.19 for marginal models estimated via GEE (longitudinal data).

Table 5. Association between oscillometry parameters and abnormal spirometry parameters using logistic regression analysis for cross-sectional data.

		Univariable			Multivariable		
		Odds ratio	95% CI	FDR-adjusted P value	Odds Ratio	95% CI	FDR-adjusted P value
FEV_1	**R5**	3.15	1.81-6.36	0.0005	3.38	1.81-7.56	0.0011
	R5-20	1.92	1.36-2.99	0.0013	2.31	1.48-4.17	0.0016
	X5	3.07	1.90-5.81	0.0002	3.84	2.08-9.00	0.0008
	AX	3.24	1.96-6.26	0.0002	3.50	1.99-7.47	0.0008
FVC	**R5**	3.13	1.93-5.75	0.0002	2.68	1.63-4.99	0.0010
	R5-20	2.09	1.51-3.16	0.0041	1.87	1.36-2.84	0.0011
	X5	3.34	2.12-6.14	0.0002	3.07	1.93-5.71	0.0008
	AX	3.87	2.33-7.51	0.0002	3.46	2.06-6.77	0.0008
FEV_1 /FVC	**R5**	2.79	1.77-4.92	0.0002	2.65	1.63-4.82	0.0009
	R5-20	1.62	1.27-2.22	0.0010	1.59	1.23-2.21	0.0017
	X5	1.84	1.40-2.59	0.0002	1.85	1.38-2.69	0.0008
	AX	2.29	1.59-3.55	0.0002	2.25	1.52-3.59	0.0008
$FEF_{25-75\%}$	**R5**	2.51	1.59-4.41	0.0011	2.64	1.88-3.94	0.0011
	R5-20	1.86	1.47-2.46	0.0011	1.75	1.31-2.52	0.0011
	X5	2.69	0.73-2.90	0.0011	2.14	1.65-2.95	0.0011
	AX	2.57	1.71-4.30	0.0011	2.16	1.12-4.57	0.0011

Multivariable models are adjusted for age, gender, and BMI. To adjust for multiple comparisons, the False Discovery Rate (FDR) proposed by Benjamini and Hochberg was utilized.

Table 6. Association between oscillometry parameters and abnormal spirometry parameters using marginal models estimated via GEE for longitudinal data.

		Univariable			Multivariable		
		Odds ratio	95% CI	FDR-adjusted P value	Odds Ratio	95% CI	FDR-adjusted P value
FEV₁	**R5**	2.89	1.72-5.95	0.0001	2.83	1.68-6.56	0.0010
	R5-20	1.82	1.32-3.10	0.0001	1.93	1.05-4.07	0.0003
	X5	2.90	1.90-4.81	0.0001	3.22	2.18-4.98	0.0003
	AX	3.17	1.96-4.31	0.0001	3.19	2.10-4.86	0.0003
FVC	**R5**	3.11	1.99-5.30	0.0003	2.77	1.63-4.99	0.0011
	R5-20	1.93	1.55-3.27	0.0001	1.79	1.26-2.52	0.0003
	X5	3.34	2.12-6.14	0.0001	3.04	2.28-5.48	0.0005
	AX	5.05	3.93-6.51	0.0009	3.49	2.26-5.28	0.0130
FEV₁ /FVC	**R5**	2.94	1.77-4.92	0.0001	2.86	1.63-4.82	0.0003
	R5-20	1.75	1.27-2.22	0.0007	1.74	1.23-2.21	0.0005
	X5	1.72	1.40-2.59	0.0001	1.77	1.38-2.69	0.0005
	AX	2.55	1.59-3.55	0.0001	1.73	1.52-3.59	0.0005
FEF₂₅₋₇₅%	**R5**	2.63	1.57-3.40	0.0001	2.41	1.51-3.99	0.0011
	R5-20	1.82	1.29-2.51	0.0001	1.81	1.31-2.52	0.0011
	X5	1.47	0.76-2.17	0.0010	1.46	0.76-2.17	0.0011
	AX	2.69	1.71-4.26	0.0010	2.59	1.78-4.31	0.0011

Multivariable models are adjusted for age, gender, and BMI. To adjust for multiple comparisons, the False Discovery Rate (FDR) proposed by Benjamini and Hochberg was utilized.

In an alternative approach, we compared each abnormal oscillometry parameter with abnormal spirometry using two constructs: first, when there was at least one abnormal spirometry parameter and, second, when there were at least two abnormal spirometry parameters. Results for both logistic regression analysis and marginal models estimated via GEE between each oscillometry

parameter and abnormal spirometry (defined with at least one abnormal parameter) are summarized in Tables 7 and 8, respectively. A significant association between each oscillometry parameter and abnormal spirometry (≥ 1 abnormal parameter) was observed using logistic regression analysis for cross-sectional data (odds ratios between 2.13 and 3.99, $P < 0.003$) and marginal models estimated via GEE for longitudinal data (odds ratios between 1.81 and 2.98, $P < 0.008$).

Table 7. Association between oscillometry parameters and abnormal spirometry (≥ 1 parameter) using logistic regression analysis for cross-sectional data.

	Univariable			**Multivariable**		
	Odds ratio	95% CI	FDR-adjusted P value	Odds ratio	95% CI	FDR-adjusted P value
R5	3.94	1.92-10.15	0.0015	3.99	1.94-10.17	0.0013
R5-20	2.26	1.41-4.24	0.0035	2.41	1.48-4.85	0.0028
X5	2.12	1.52-3.22	0.0004	2.13	1.53-3.25	0.0004
AX	2.96	1.71-6.05	0.0012	3.02	1.74-6.19	0.0010

Multivariable models are adjusted for age, gender, and BMI. To adjust for multiple comparisons, the False Discovery Rate (FDR) proposed by Benjamini and Hochberg was utilized.

Table 8. Association between oscillometry parameters and abnormal spirometry (≥ 1 parameter) using marginal models estimated via GEE for longitudinal data.

	Univariable			Multivariable		
	Odds ratio	95% CI	FDR-adjusted P value	Odds ratio	95% CI	FDR-adjusted P value
R5	3.15	1.72-4.58	0.0001	2.82	1.78-4.11	0.0053
R5-20	1.87	1.12-3.01	0.0011	1.81	0.80-2.40	0.0073
X5	2.79	1.78-3.63	0.0001	2.63	1.71-3.31	0.0036
AX	2.63	1.52-3.69	0.0001	2.98	1.84-4.09	0.0036

Multivariable models are adjusted for age, gender, and BMI. To adjust for multiple comparisons, the False Discovery Rate (FDR) proposed by Benjamini and Hochberg was utilized.

Tables 9 and 10 show results for logistic regression analysis and marginal models estimated via GEE between each oscillometry parameter and abnormal spirometry (defined by at least two abnormal parameters), respectively. A significant association between each oscillometry parameter and abnormal spirometry (≥ 2 abnormal parameters) was observed using logistic regression analysis for cross-sectional data (odds ratios between 1.83 and 2.85, $P < 0.005$). Relatively similar results were obtained by marginal models estimated via GEE for longitudinal data (odds ratios between 1.56 and 2.98, $P < 0.005$).

Table 9. Association between oscillometry parameters and abnormal spirometry (≥ 2 abnormal parameters) using logistic regression analysis for cross-sectional data.

	Univariable			Multivariable		
	Odds ratio	95% CI	FDR-adjusted P value	Odds ratio	95% CI	FDR-adjusted P value
R5	2.79	1.65-5.39	0.0008	2.85	1.67-5.54	0.0007
R5-20	1.72	1.26-2.58	0.0031	1.83	1.31-2.81	0.0018
X5	2.31	1.56-3.85	0.0004	2.38	1.59-4.04	0.0004
AX	2.50	1.62-4.30	0.0004	2.58	1.66-4.51	0.0004

Multivariable models are adjusted for age, gender, and BMI. To adjust for multiple comparisons, the False Discovery Rate (FDR) proposed by Benjamini and Hochberg was utilized.

Table 10. Association between oscillometry parameters and abnormal spirometry (≥ 2 abnormal parameters) using marginal models estimated via GEE for longitudinal data.

	Univariable			Multivariable		
	Odds ratio	95% CI	FDR-adjusted P value	Odds ratio	95% CI	FDR-adjusted P value
R5	2.82	1.66-4.46	0.0001	2.98	1.29-4.99	0.0001
R5-20	1.73	0.75-2.53	0.0001	1.56	0.80-2.40	0.0012
X5	2.49	1.55-3.27	0.0001	2.32	1.21-3.56	0.0001
AX	2.62	1.39-3.61	0.0001	2.57	1.59-4.16	0.0001

Multivariable models are adjusted for age, gender, and BMI. To adjust for multiple comparisons, the False Discovery Rate (FDR) proposed by Benjamini and Hochberg was utilized.

Chapter 5: Discussion and Conclusions.

Evaluating lung function in CF is a fundamental aspect of patient care, and spirometry remains the pulmonary function test most commonly used for this purpose. While extremely useful, there are well-recognized limitations as noted earlier (49–55,102,158,160,161). Oscillometry has been utilized in research for many years and is now being used more frequently in clinical settings such as asthma and COPD. It is generally considered complementary to spirometry in the assessment of lung function and has specific advantages in certain situations (80,146). Although promising, the added contribution of oscillometry to the management of the adult with CF has not been critically examined.

As a first step in this direction, the main objectives of the present study were twofold. First, we sought to comprehensively characterize oscillometric findings in a large group of adults with established CF when clinically stable using an approved commercially available device, standard measurement parameters, and published reference values. Second, we wished to systematically compare accepted oscillometry parameters to those obtained with spirometry on the same occasion. The main findings from cross-sectional and longitudinal data were relatively similar and may be summarized as follows: (i) a significant increase in both total (R5) and peripheral resistance (R5-20), (ii) an increase in the absolute magnitude of respiratory reactance (X5) as well as reactance area (AX) and resonant frequency (Fres), and (iii) a good to strong correlation between spirometry and oscillometry parameters, particularly between FEV_1 and both X5 and AX, (iv) a significant association between oscillometry parameters (i.e., R5, R5-20, X5, and AX) and abnormal spirometry parameters as determined by logistic regression analysis and marginal models estimated via GEE.

Spirometry parameters were all significantly reduced in our adult CF cohort, consistent with moderate obstructive impairment and in keeping with the Canadian Cystic Fibrosis Registry 2019 Annual Data Report as well as the United Kingdom Cystic Fibrosis Registry Annual Data Report 2019 (18,185). The average FEV_1 in our study was 63% predicted, which was also very similar to reported values in 3 of the recent publications that examined oscillometry in adult CF (141,143,144).

With respect to oscillometry, both resistance and reactance parameters were abnormal compared to population-based reference values (84). The average R5 and R5-20 values were generally comparable to those recently obtained in adults with CF by other investigators where these parameters were in fact measured (see Table 11) (141–144). The average X5 was close to that reported by Lima et al. (141) and Wallaert et al. (142), while the average AX and Fres were very similar to that observed by Lima et al. (141). Of note, Fres was significantly increased but expressed only as absolute values since we could not find adequate reference data providing Z scores across the full age range of the 92 patients studied (64,84). In general, the similarity with previous studies provides indirect validation and further confidence in our findings.

Table 11. Oscillometry in CF adults: *Prior study results*.

	R5	R5-20	X5	AX	Fres
Lima et al. (141)	~ 4.4*	~ 1.0*	~ -3.5*	~ 24.0*	~ 21.0*
Wallaert et al. (142)	5.58	R5-19 = 1.56	-2.65	-	-
Lacerda et al. (143)	R0, Rm (No R5)	-	Xm (No X5)	-	14.2
Blin et al. (144)	4.69 (Z = 1.90)	1.22 (No Z score)	-1.63 (Z = -1.72)	12.44 (No Z score)	16.14
Rad (Thesis)	5.17 (Z = 1.98)	1.34 (Z = 3.5)	-2.54 (Z = -2.85)	24.17 (Z = 2.47)	20.71**

* Data acquired by extrapolation from Figure 2 of Lima et al. (141). ** Z scores for Fres not provided in any of the studies cited. R0: zero-intercept resistance (extrapolated value of resistance at zero frequency); Rm: mean resistance; Xm: mean reactance. See text for further information.

The major strengths of our study are the large population of CF adults with concurrent oscillometry and spirometry measurements and, in particular, use of an officially approved portable commercial device with accepted standard oscillometry parameters and reported population-based reference values (84). In addition, we employed strict quality control criteria (64,139,140). As noted earlier, we ensured that a minimum of 3 acceptable maneuvers were obtained based in part on COH values and the coefficient of variation for R5. Both indices were provided in near real time by the oscillometer software so that acceptability could be promptly assessed (83). COH and COV have been employed as measures of data reliability and reproducibility, respectively, in the oscillometry literature (63,64,68,71,81,108,139). Prior studies in adult CF referred to the original 2003 ERS Task Force Report for quality control recommendations and other considerations, but specific details were generally not provided and actual values for COH and COV were not reported (63,141–144).

Although the precise criteria for COH acceptability have varied considerably for a number of reasons (see below), values greater than a threshold of approximately 0.80 have been most commonly utilized (67,68,81,108,175). As one might expect, COH is adversely affected by factors such as poor signal to noise ratio, leaks, glottis closure, swallowing, breathing pattern irregularities, and other artifacts (64,68,81,109,129). Low COH values may also reflect the severity of respiratory dysfunction, particularly severe airway obstruction with expiratory flow limitation, rather than poor quality data per se (64,68,81,109,129). In the absence of such findings, a low COH value in our hands was also used to help recognize any artifacts or breathing pattern irregularities that may have been missed by the oscillometer's automated software algorithms (64,68,81,109,129). The mean value of 0.90 ± SE 0.01 observed here in adult CF patients with moderate obstructive impairment would support the reliability of the data obtained. It is important to note, however, that COH is influenced by patient independent technical factors related to data acquisition and signal processing considerations (64,68,129,186). In addition, the computation of COH is not standardized and will vary across devices (64,81,109,186). Because of such considerations, the most recent 2020 ERS Task Force Report no longer recommended using COH to assess test reliability (64). It did recommend that the COV of the lowest frequency Rrs value (e.g., 5 Hz) continue to be used to assess data reproducibility (64). The threshold for COV acceptability was reduced from 15% to 10% in adults in this latest report (64). This was intended to exercise more rigor in the data collection rather than being based on theoretical or empirical information. It is interesting to note that the coefficient of variation for R5 obtained here in adult CF (4.51 ± SE 0.22%) is very similar to that reported for FEV_1 in stable COPD (187).

An important consideration of this study is the manner in which normal versus abnormal results were determined. While representing individual pulmonary function test parameters as a percentage of the predicted reference value may provide a convenient bedside method for the preliminary assessment of results, it is important to recognize that defining a normal range as 100 ± 20% predicted is not based on valid statistical principles (188,189). Accordingly, clinical pulmonary function test results are now generally provided with accompanying Z score values in order to facilitate proper interpretation (188,189). Spirometry results in our patients were provided as percent predicted in order to allow comparison with prior studies that used this approach. However, percent predicted values were not provided for oscillometry parameters and Z scores were used to compare oscillometry and spirometry. This is in keeping with the 2020 ERS Task Force Report on Technical Standards for Respiratory Oscillometry and other publications (64,71,190–192).

Our results showed some similarities with previous reports. As noted earlier and given in Tables 1 and 11, however, interpretation of the studies by Lima et al. (141) and Lacerda et al. (143) is limited in that oscillometry was performed on a small number of patients with a similarly small control group (rather than published reference values) using a non-commercial device and non-standard parameters (63,64). Accordingly, these results may not be generalizable. Omission of some standard parameters (despite using a commercial device) in addition to having a small group of patients and controls also hinders interpretation of the data provided by Wallaert et al. (142). Blin et al. retrospectively compared oscillometry and spirometry obtained on *separate* occasions, a major concern (144). Acute exacerbations were also identified retrospectively based on physician judgment and use of antibiotic therapy without strictly applied predetermined criteria (144).

Our own study, however, was not without limitations. Initial data was collected when patients were stable. Although subsequent additional measurements were done with some modest variation in clinical status in some patients, repeat testing was not performed during a recognized acute exacerbation (at least as defined by the need for intravenous medications, emergency department or hospital admission). Prior work in both asthma and COPD does indicate that oscillometry may be more sensitive than spirometry in recognizing the risk for or early development of an acute exacerbation (124,151,154–157). Although definitive evidence is lacking, one may hypothesize that this may be the case for those affected by CF as well (108). In addition, evidence in both children and adults with CF supports the notion that oscillometry parameters worsen during an acute exacerbation and return toward or to baseline following effective treatment (132,134,144). Although the impact of an acute exacerbation on oscillometry and spirometry was not directly examined here, appropriately designed studies in this area are clearly needed.

Oscillometry was obtained by a single operator in this study. The operator was trained according to current guidelines (63,64,139) and supervised during the period of initial patient testing (63,64,83). As a result, we were not able to able examine inter-operator variability and effects of operator training on the quality of oscillometry test results. To the best of our knowledge, there is only one recent publication examining data variability according to operator training or experience (140). These investigators demonstrated that a training program utilizing a standard protocol and adherence to quality control/quality assurance guidelines led to high-quality oscillometry measurements as reflected by an increase in the number of acceptable and reproducible tests (140). Although using more than a single operator for oscillometry could introduce increased variability

in results, conceivably, this would be offset with proper implementation of a standardized quality control/quality assurance program as reported by Wu et al. and Chang et al. (139,140). With this in mind, we believe that similarly high quality oscillometry data in adult CF patients can be obtained by others.

We were not able to explore the results of oscillatory in relationship to obstructive versus restrictive impairment. This is because complete pulmonary function testing, specifically plethysmographic determination of total lung capacity, was not systematically obtained in the Adult CF clinic. Full PFTs were performed intermittently for clinical indications in a subset of patients and in no temporal relationship to the oscillometry testing obtained for this study. It would be important to address this properly in future work.

Oscillometry in general does have certain limitations. First, breathing on the device for 20-30 s may not always be tolerated. This was not an issue here but may be problematic in individuals with more severe disease or experiencing an acute exacerbation. This challenge has been addressed in part by some manufacturers with improved specifications of the device itself as well as the mouthpiece-filter interface (i.e., reducing equipment impedance and dead space) (64,69). Second, a recent report by Dandurand et al. compared oscillometry using standardized test loads in 6 devices (5 of which were commercially available) (69). Important quantitative differences between some of the oscillometers were identified, particularly as impedance test loads increased into the range associated with moderate to severe obstructive disease (69). This was not the case for the device used in this study. Resolving the issue of standardization against an approved range of test loads is currently in progress (193). It is expected that this will be addressed in published guidelines

in the near future, as has been done for many years in the ATS/ERS guidelines for the assessment of spirometers (44,45,69,194–196). Third, although reference values for oscillometry exist, they are becoming dated, need to be expanded in many respects, and take additional factors into account (64,71,84,197). As previously noted and now well accepted for spirometry and conventional PFTs in general, reference values for oscillometry also need to be better standardized, taking into consideration potential ethnic influences, a wider age range and sample size, as well as current technical and quality control/quality assurance recommendations (64,139,140,196,197). The Global Lung Initiative (GLI) has been systematically addressing such issues for standard tests of pulmonary function including spirometry, plethysmographic measurement of lung volumes, and diffusing capacity (194,196,198,199). A similar approach has more recently been initiated for oscillometry (200). It should be recognized that it is likely that experience acquired over an extended time frame will be required to improve oscillometry reference values, similar to the improvement process that has occurred for the development of reference values for spirometry and other standard tests of pulmonary function (69,189,196,197). Hopefully, however, the time frame to reach these goals moving forward will be considerably shorter.

There are distinct advantages to the use of oscillometry. It is applied during spontaneous tidal breathing and maximal forced expiratory maneuvers are not needed. It requires minimal cooperation, i.e., the ability to breathe comfortably through the oscillometer for 20-30 s in a stable position with a satisfactory seal around the mouthpiece. In addition to the obvious benefits in terms of improved patient comfort and performance, potential confounding effects of deep inspiration and lung volume history on bronchomotor tone and resulting airway caliber are avoided (164–166). Applying oscillometry may be even more critical during episodes of clinical deterioration

when the ability to cooperate or the quality of the results obtained from spirometry may be adversely affected. Oscillometry might provide a better estimate of changes in lung function during such circumstances. Spirometry is not a particularly reliable or sensitive index of small airway function. Oscillometry may be preferable in this respect as it appears to be a better measure of small airway function than spirometric parameters such as $FEF_{25-75\%}$ (75–77,124,171–173).

One of the other possible ways to improve the clinical impact and accuracy of oscillometry is *intra-breath* analysis (201–203). Multi-frequency or spectral oscillometry is not able to properly identify dynamic changes in resistance and reactance that may occur throughout the breathing cycle (202–204). However, intra-breath measurement of respiratory mechanics has been proven to help identify such phenomena as airway obstruction, expiratory flow limitation, and mechanical heterogeneity in both children and adults (111,201–204). In addition, improved ability of *intra-breath* oscillometry to detect changes in airway tone in children compared to classic oscillometry as well as to predict the risk of respiratory infection in early life has been shown in previous studies (110,205,206). At the time the study was instituted, preliminary intra-breath analysis was performed. Unfortunately the magnitude of the work involved was well beyond the scope of this thesis (201,207). This work is currently ongoing and is expected to be reported as a separate project some time in the future.

It is clear that oscillometry does detect abnormalities in respiratory function in adult CF patients, and there is a close relationship between spirometry and oscillometry parameters. However, to define superiority and efficacy, more detailed studies would be needed. Oscillometry is able to assess lung function in adults and can be combined with spirometry as a complementary test (in

addition to more complete standard pulmonary function tests), but how well oscillometry may enhance the ability to detect early disease, recognize the risk for or development of an acute exacerbation, reliably identify treatment response or failure, and other patient-related outcomes including long term prognosis remains to be determined. Ideally, oscillometry should be obtained in combination with other "emerging" tests of respiratory function such as multiple breath washout (208) and functional MRI (50) in addition to microbiology, inflammatory markers, patient reported outcomes, clinical phenotypes, exercise performance, and other parameters to address such questions (209–216). Clearly well-designed prospective multicenter studies to validate the use of oscillometry in the ongoing management of CF in real-world practice are needed. Moreover, recent developments in molecular biology and CF modulator therapies suggest that taking such features into consideration would also be important.

It is well recognized that disease manifestations and outcomes differ substantially across individuals with identical CF mutations, even within affected family members (217). This suggests that unidentified genetic, environmental, or other factors are also important. It is likely that novel approaches in addition to that mentioned above would be needed to help address this and other challenges. For example, machine learning and related artificial intelligence methodologies have been informative in identifying disease phenotypes in other more common obstructive airway disorders, particularly in COPD (218–222). This has been possible as the result of several large prospective disease cohorts with the addition of advanced imaging and analytical molecular techniques to the more accepted biochemical, physiological, radiographic and patient reported outcome tools that have been used to date. In applying similar efforts to CF, it is likely that

including both conventional spectral and intra-breath oscillometry would be of significant additional benefit.

To summarize, this was a comprehensive study to reliably examine the relationship of oscillometry to spirometry in adult patients with CF in stable state. In some contrast to the available literature on adult CF, this study was undertaken in a large number of patients using a strict quality control protocol, a portable commercial device with automated software and accepted parameters, and population-based reference values. The results confirm that oscillometry can be applied as a reliable measure of impaired respiratory function in stable adult CF and correlates well with spirometry. Certainly many gaps in our knowledge remain. Further work is needed to evaluate the ability of oscillometry to help identify important changes in lung function occurring either spontaneously or with therapeutic interventions, particularly in comparison with and in addition to spirometry, patient reported outcomes, and other measures as noted above, to have a better understanding of the pathophysiologic changes in CF and how they can be best monitored in order to optimize patient care and clinical outcomes.

Chapter 6: References.

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