Respiratory Medicine 136 (2018) 37–47

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Review article

Forty years of reference values for respiratory system impedance in adults: 1977–2017

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ARTICLE INFO

Keywords:
Forced oscillation technique
Impulse oscillometry
Pulmonary function testing
Reference values
Prediction equations

ABSTRACT

Objective: To provide an evidence-based review of published data regarding normal range reference values and prediction equations for measurements of respiratory impedance using forced oscillation technique (FOT) and impulse oscillometry (IOs) in adults.

Methods: A non-language-restricted search was performed using *forced oscillation technique* and *impulse oscillometry* as primary terms. Original research studies reporting respiratory system impedance reference values or prediction equations based on cohorts of ≥100 healthy adults were included. Publications cited in identified studies were also considered for inclusion.

Results: Of 882 publications identified, 34 studies were included: 14 studies of FOT, 19 studies of IOs, and one study of both techniques. Nineteen studies provided prediction equations. Most reports were from Europe (n = 20) and Asia (n = 12) and included relatively small cohorts (median = 264 subjects). Across publications, there was marked variability in performance and technique of impedance measurements. Height and sex emerged as major contributors to available prediction equations. The contribution of weight was more pronounced at the obese end of the weight spectrum. The contribution of age was less clear, and elderly were largely under-represented. Ethnicity likely plays a role, but was under-reported in currently available literature. Inclusion of current and former smokers in some studies further confound the results.

Conclusions: Currently available literature providing reference values and prediction equations for respiratory impedance measurements in adults is limited. Until larger-scale standardized studies are available, the choice of prediction equations should be based on datasets that best represent the target patient population and modality in use within each pulmonary physiology laboratory.

1. Introduction

Although described by DuBois as early as 1956 [1], the measurement of lung impedance using pressure sound waves, termed forced oscillation technique (FOT) and its younger derivative, impulse oscillometry (IOs), have yet attained an established position in the arsenal of lung function testing tools that are routinely employed in the adult pulmonary function laboratory. Indeed, in 2003 the American Thoracic Society (ATS) officially adopted FOT as a modality only with respect to pulmonary evaluation of children under six years of age without providing clear guidance concerning technical aspects of study performance and quality control [2]. The same year, an European Respiratory Society (ERS)-designated Task Force acknowledged the need for further standardization of FOT in children and adults [3]. No similar statements regarding the use of IOs have been published by prominent pulmonary medicine societies to date.

The lack of guidance recommendations regarding standardization of performance and quality control of impedance testing parallels other gaps. First, guidance on appropriate use and clinical application of impedance testing in the adult population is somewhat limited [4,5]. Second, large-scale adult population-based datasets of normal values are also limited, culminating in lack of well-agreed upon prediction equations that will allow appropriate in-context interpretation of these measurements. Among more conventional testing such as spirometry, guidance from the ATS and ERS suggests that clinicians should select reference values for testing that are most similar in demographic and anthropometric characteristics to the clinical population being tested [6]. Similar strategies would be appropriate for selection of reference values in studies of respiratory impedance.

In this review, we summarize major studies published to date reporting normal reference values or prediction equations for both FOT and IOs in adults. The purpose of this review is to present options for

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https://doi.org/10.1016/j.rmed.2018.01.015
Received 25 October 2017; Received in revised form 22 January 2018; Accepted 27 January 2018
Available online 31 January 2018
0954-6111/

List of abbreviations

ATS	American Thoracic Society
Ax	reactance area
CO	coherence
ERS	European Respiratory Society
FOT	forced oscillometry technique
Fres	resonant frequency
IOs	impulse oscillometry
NHANES	National Health and Nutrition Examinations Survery
Rrs	resistance of the respiratory system
Xrs	reactance of the respiratory system

selection of reference values in performance of respiratory impedance measurements in adult clinical practice. In this regard, we elaborate on descriptive characteristics of the various studies' populations of healthy adult volunteers as well as the specific modalities and settings used to derive reference values and prediction equations.

2. Background

2.1. Forced oscillation technique and impulse oscillometry

Unlike spirometry, both FOT and IOs measurements are effort-independent and superimposed on tidal breathing, requiring only a good mouth seal and application of pressure on the cheeks and the floor of the mouth in order to reduce the upper airway shunt effect [7]. These features explain their natural appeal to the pediatric pulmonologist [8], but may also provide a rationale for their more routine use in adults with both physical and cognitive limitations, institutionalized patients, and the elderly [9]. The use of this modality gained much of its support based on the finding that the application of a range of forced oscillation frequencies to the airways by means of a loudspeaker allows to distinguish between the amount of resistance to flow contributed by the large and the small airways. Low oscillations in the range of 5–15 Hz transmit more distally in the airways, thus representing more of the whole respiratory system, while higher oscillations of ≥20 Hz tend to travel as far as the intermediate size airways, thus representing the respiratory system resistance from the mouth and up to that point [10]. This prospect was utilized for characterization of abnormalities localized to the more peripheral airways, for which spirometry was shown to be is less reliable [11].

FOT was originally based on multiple single-frequencies of sinusoidal oscillations in the range of 2–30 Hz, providing excellent temporal resolution. The incorporation of the fast Fourier transform of pseudorandom noise allowed the breakdown of different wave frequencies into unique single-frequency sine waves, later derived by spectral analysis, thus greatly simplifying the process of performing measurements over a range of frequencies [12]. Over the years, laboratories worldwide employed different FOT apparati, different standards of measurement, and different processing software, at least in part explaining the variations in results between major contributors to the bulk of the FOT literature. This problem was at least partially resolved following the publication of the ERS Task Force recommendations for standardization, quality control measures, and implementation guidelines in 2003 [3]. First generation FOT systems were considered time-consuming and required more expertise and specific training on part of the technician [13], however, currently available commercial FOT systems, such as Resmon Pro Diary® (Restech srl, Milan, Italy), termoFlo C-100® (Thorasys Medical Systems, Montreal, Canada), and MostGraph-01® (CHEST M.I., Tokyo, Japan), have largely overcome this limitation [14,15].

In 1998, the Jaeger IOs system (Erich Jaeger, Viasys GmbH, Hoechberg, Germany) commercially emerged as the “user-friendly” version of FOT [16]. IOs uses short impulses of fixed frequency-rectangular pressure waves from which all other frequencies can be derived using spectral analysis. This technique, which somewhat compromises the temporal resolution of the measurements, greatly simplifies study performance, allowing it to be more easily implemented in the laboratory [17].

2.2. Measurements of respiratory impedance

Analogous to an electric circuit in series, measurements of the mechanical properties of the airways, lungs, and chest wall obtained by FOT and IOs are described as a function of series-resistive elements. When a wave of airflow is superimposed on tidal breathing and applied to the air column in the respiratory system, the resultant transthoracic pressure, flow amplitude, and phase differences, as obtained by flow and pressure transducers, reflect the total impedance of the respiratory system (*Zrs*). This information can be broken down to provide the following measurements:

Resistance of the respiratory system (*R*rs): derived from analyzing the pressure oscillations that are the real part of impedance and in-phase with the pressure-flow relationship across the range of oscillation frequencies. Resistance measures reflect the sum of three respiratory system resistance components in series: the extrathoracic and central airways, the peripheral small airways, and the chest wall. Since low frequency oscillations transit more distally than high frequency oscillations, resistance measures at low and high frequencies allow differential characterization of the *frequency dependence* ($R_{low} - R_{high}$) of the respiratory system, providing information which is more inclusive of the smaller airways [17].

Reactance of the respiratory system (*X*rs): the reflection of the imaginary part of impedance or the out-of-phase component of the pressure-flow relationship, and attributable to two opposing mechanical factors: *capacitance* and *inertance*. Small airways, lung parenchyma, and chest capacitative pressure loss is dominant at low frequencies while the large airway inertive pressure loss is dominant at high frequencies. The *resonant frequency (Fres)* is the frequency at which the relative contribution of both vectors is roughly equal providing an Xrs value of zero. Integration of the low frequency reactance between 5 Hz (*X5*) and Fres provides *reactance area (AX)*, which describes the reactant properties of the more peripheral airways [17].

Coherence (CO) describes the temporal variability of the data sample at different frequencies, usually reported at 5, 10, and 20 Hz. CO is decreased by improper technique such as irregular breathing or flow obstruction by the tongue, resulting in its use as a technical quality measure, but it is also asserted that abnormal CO, representing the non-uniformity of respiratory mechanics, may be a property of obstructive lung disease such as chronic obstructive lung disease [17].

In general, repeatability of measures is reported within the acceptable range of 5–15% [3]. It appears that Rrs measurements are more reproducible than Xrs measurements [13,18,19]. There are reports to support that for FOT as well as IOs, both within-day [18,20–22] and between-day [18,20] reproducibility can be satisfactory. These findings are also in agreement with reports from pediatric studies [23].

2.3. Clinical applications in adults

Current literature provides sufficient evidence for a role of impedance measurements as complimentary to history, physical examination, spirometry, and imaging in the evaluation of patients with large and small airways disease as well as parenchymal lung diseases. Indeed, several studies have demonstrated the additive value of FOT in disease states characterized by respiratory abnormalities not yet reflected by spirometry [24,25] and in demonstration of favorable responses to therapy where spirometry did not provide such evidence