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Forced oscillation, integer and fractional-order modeling in asthma

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ABSTRACT

The purpose of this study was to evaluate the use of fractional-order (FrOr) modeling in asthma. To this end, three FrOr models were compared with traditional parameters and an integer-order model (InOr). We investigated which model would best fit the data, the correlation with traditional lung function tests and the contribution to the diagnostic of airway obstruction. The data consisted of forced oscillation (FO) measurements obtained from healthy ($n = 22$) and asthmatic volunteers with mild ($n = 22$), moderate ($n = 19$) and severe ($n = 19$) obstructions. The first part of this study showed that a FrOr was the model that best fit the data (relative distance: FrOr = 4.3 ± 2.4; InOr = 5.1 ± 2.6%). The correlation analysis resulted in reasonable ($R = 0.36$) to very good ($R = 0.77$) associations between FrOr parameters and spirometry. The closest associations were observed between parameters related to peripheral airway obstruction, showing a clear relationship between the FrOr models and lung mechanics. Receiver–operator analysis showed that FrOr parameters presented a high potential to contribute to the detection of the mild obstruction in a clinical setting. The accuracy [area under the Receiver Operating Characteristic curve (*AUC*)] observed in these parameters (*AUC* = 0.954) was higher than that observed in traditional FO parameters (*AUC* = 0.732) and that obtained from the InOr model (*AUC* = 0.861). Patients with moderate and severe obstruction were identified with high accuracy (*AUC* = 0.972 and 0.977, respectively). In conclusion, the results obtained are in close agreement with asthma pathology, and provide evidence that FO measurement associated with FrOr models is a non-invasive, simple and radiation-free method for the detection of biomechanical abnormalities in asthma.

1. Introduction

Asthma is a global health problem affecting 1–18% of the population in different countries. Given the increasing prevalence of this disease [1], it is necessary to focus on the investigation and routine evaluation of pulmonary function. The respiratory effects of asthma are usually evaluated with spirometry and body plethysmography. These tests, however, require a high degree of collaboration and maximal effort on the part of the subject. In addition, forced inspiratory and expiratory

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maneuvers may change the bronchial tone and modify the airway patency, rendering the indices obtained hardly physiologic.

The Forced Oscillation Technique (FOT) allows for the assessment of airway mechanics, examining subjects of any age with minimal cooperation and without any invasiveness [2]. It consists of applying small sinusoidal pressure variations (*P*) to stimulate the respiratory system at frequencies higher than that of normal breathing and measuring the flow response (V'). This method is currently the state-of-the-art for the assessment of lung function [3], allowing for the measurement of respiratory system impedance ($Zrs = P/V'$). Recent studies used this technique in the diagnostic of airway obstruction in adult asthmatics [4–8]. This method may help to simplify the routine evaluation of asthmatic patients [5] and the understanding of the pathophysiology of asthma [9].

FOT yields frequency-dependent curves of respiratory impedance that may be visually analyzed to recognize changes in shape and magnitude of the curves and distinguish healthy respiratory function from its diseased state. In addition, simple parameters, such as *Rrs* and *Xrs* data measured at a given frequency, may be obtained. To complement this basic analysis, inverse modeling is employed as an alternative approach to obtain detailed mechanical information about the respiratory system [3,10,11]. In these models, electrical components analogous to mechanical resistance, compliance, and inertance inherent in the respiratory system are used [12,13], allowing us to gain additional insight into the anatomical or pathophysiological changes that occur in respiratory diseases. In addition to being useful in furthering our understanding of respiratory biomechanical function, these model parameters could improve the detection, diagnosis, and treatment of different respiratory diseases.

Fractional-order (FrOr) modeling is increasingly used in biological systems [14–16]. The tools of fractional calculus support mathematical models that in many cases describe more accurately the dynamic response of living systems. In fact, many traditional areas of physical science and engineering (e.g., electromagnetics, electrochemistry, viscoelasticity, transport phenomena) currently have advocates of the fractional approach [15]. Of particular interest in respiratory physiology is the ability of fractional calculus to effectively describe (qualitatively and quantitatively) fractional power laws, hysteresis, and system memory. In this context, there is agreement in the literature that FrOr models have the potential to improve pulmonary clinical science and practice [3,10,11]. They would help us obtain new insight into the lung periphery mechanism of the disease and could be used to help classify patients. These models were previously used in asthmatic adults [17], in a mouse model of asthma [18], and with induced bronchoconstriction in humans [19]. Recently, new FrOr models were introduced [10,20–23] and have been found to be especially useful for the analysis of patients with COPD [20,21] and children with asthma [22] and cystic fibrosis [23]. Although promising, FrOr models are far from mature in clinical practice due to their difficult interpretation and high number of parameters to be related to lung pathology [20]. Recently, Ionescu et al. [21] emphasized that studies in groups of patients with various degrees of airway obstruction and lung abnormalities may also offer interesting information on the sensitivity of the fractional-order parameters and its possible use in a classification strategy.

The changes associated with asthma pathophysiology include inflammatory and structural changes in the small airways and in lung parenchyma [24]. Thus, FrOr models may provide a significant contribution to the particular case of asthma. However, to the best of our knowledge, these new FrOr models have never been used in the evaluation of groups of adult asthmatics with different degrees of airway obstruction and lung abnormalities.

In the present study, our first objective was to investigate whether the new FrOr model parameters are sensitive to asthma pathophysiology, and if so, which model would best fit the data. Another objective was to evaluate the correlations between the model parameters and lung function tests, contributing to elucidate an important debate in the literature concerning the relationship of these parameters and lung pathology. We also evaluated the contribution of these models in the diagnostic of airway obstruction in asthma.

2. Methods

2.1. Study population and pulmonary function

Sixty asthmatic patients were evaluated and classified into four categories based on their degree of airway obstruction [25], including those with mild ($n = 22$), moderate ($n = 19$) and severe ($n = 19$) airflow obstruction. The exclusion criteria for patients in this study included a history of tobacco use, evidence of current airway infection, acute exacerbation, or any cardiorespiratory disease other than asthma.

The control group was composed of 22 healthy subjects with no history of pulmonary or cardiac disease or tobacco use. The study conformed to the principles outlined in the Declaration of Helsinki and have been approved by the Medical Research Ethics Committee of the State University of Rio de Janeiro. The baseline data, including age, height and weight, were obtained from each subject at the time of the procedures. Informed consent was obtained from all volunteers before inclusion in the study.

Using a closed circuit spirometer (Vitrace VT-139; Pro-médico, Rio de Janeiro, Brazil), the following measurements were obtained for all subjects while they were in a sitting position: forced expiratory volume in the first second (FEV_1), forced vital capacity (*FVC*), forced expiratory flow (*FEF*) between 25% and 75% of the *FVC*, the *FEF*/*FVC* ratio and the FEV_1/FVC ratio.

2.2. Respiratory impedance measurements

The respiratory system impedance was measured between 4 and 32 Hz with 2-Hz increments using a pseudorandom noise forced oscillation system that was built in our laboratory and described previously [26,27]. Briefly, pressure oscillations, which were produced by a loudspeaker coupled to the respiratory system by means of a mouthpiece, were applied with amplitude of approximately 2 cmH_2O. The resulting flow (V') and pressure (*P*) signals were measured near the mouth by means of a screen pneumotachograph (PT-36 Jaeger-Tonnies)