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Respiratory mechanics in children with cystic fibrosis

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ABSTRACT

When a nonlinear biological system is under analysis, one may employ linear and nonlinear tools. Linear tools such as fractional order impedance models have not been previously employed to characterize difference between healthy volunteers and patients diagnosed with cystic fibrosis (CF). Nonlinear tools such as detection lines from nonlinear contributions in frequency domain have also not been employed previously on CF patient data. CF is an irreversible inflammatory disease, of genetic origin. The forced oscillation technique (FOT) is a non-invasive, simple lung function test suitable for this class of patients with breathing difficulties, since it does not require any special maneuvre. In this work we bring additional evidence that the FOT method combined with both linear and nonlinear tools reveals important information which may be used as complementary to the standardized lung function tests.

1. Introduction

When extracting information from complex nonlinear biological systems, it is important to decide whether a linear or a nonlinear analysis is envisaged. The respiratory system is a complex nonlinear system, which changes its properties with disease, i.e. the nonlinear behavior may become more pronounced. A combination of both linear and nonlinear tools may be beneficial for extracting the maximum amount of information. In this work, we employ linear impedance extraction and detection of nonlinear distortions in the impedance signals from patients diagnosed with cystic fibrosis (CF). Additionally, we employ a parametric model of fractional order which is directly linked to mechanical properties in the lungs, to identify quantitative differences between healthy volunteers and CF patients.

Biological systems modeled by fractional order impedance models have received significant interest in the research community [1,9,10,23,33]. Initial characterizations of the lungs mechanical properties have been reported in several invasive animal studies, showing the necessity of a fractional order (FO) integral [11,12]. Recent studies led to the conclusion that a FO model outperforms most of the integer-order models for characterizing the frequency-dependence in human respiratory input impedance. The major advantage of the FO models over the integer order counterpart is not only their low number of parameters, but also their intrinsic capability to characterize the viscoelastic properties and the recurrent structures of biologic materials [2,7,16,17,32].

Fractional order models have been employed previously in both healthy subjects group [15] and various pathologies, such as asthma [19], Chronic Obstructive Pulmonary Disease (COPD) [18]. The respiratory impedance poses several resonant frequencies [22] and the validity of one fractional order impedance model is restricted to the frequency range where its parameters have been identified [26]. As soon as the frequency range, in which the lung function is evaluated, changes, important variations in the frequency-dependence of the respiratory impedance may occur and the structure of the model must be revisited.

Hitherto, to our knowledge, there is a lack of information on CF patients from the linear and nonlinear tools employed in this work. The forced oscillation technique is a non-invasive, simple lung function test suitable for this class of patients with breathing difficulties, since it does not require any special maneuvre. In this work we show that the forced oscillation technique (FOT) combined with both linear and nonlinear tools revels important information which may be used as complementary to the standardized lung

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Table 1
Biometric and spirometric parameters of the children diagnosed with cystic fibrosis and the healthy children used for comparison. Values are presented as mean ± standard deviation values; % pred: predicted values; VC: vital capacity; FEV1: forced expiratory volume in one second; FEF: forced expiratory flow; MEF75/25: mean expiratory flow at 75%, respectively at 25% capacity; NA: data not available

	Cystic fibrosis (10)	Healthy (16)
Female/male	4/6	13/3
Age (years)	14.44 ± 6.21	9.66 ± 0.47
Height (m)	1.49 ± 0.15	1.39 ± 0.07
Weight (kg)	39.89 ± 11.67	32.3 ± 6.34
FEF/*VC* % pred	86.51 ± 36.12	NA
FEV_1/*VC* % pred	95.71 ± 9.42	NA
*MEF*75/25 (l)	2.08 ± 1.13	NA

function tests (e.g. spirometry). The only work which uses FOT in CF patients are those reported in [4,13,24]. There, the authors showed the ability of FOT to distinguish between various values of respiratory resistance in asthma and cystic fibrosis.

The work presented in this paper aims to provide the reader with a proof of concept on the added value of using FOT as a complementary lung function test to the standardized spirometry test and particularly suited for measurements in children [6,27]. The added value is shown by means of linear non-parametric identification of the respiratory impedance, further parameterization with a FO model. The FOT data is also processed for the detection of nonlinear contributions from the lungs in the measured air-pressure.

The paper is organized as follows: the methods, patients and measurement protocol are described in the next section. Third section presents the results and a fourth section discusses these results. A conclusion section summarizes the main outcome of this work.

2. Methods

2.1. Patients

This study was approved by the local Ethics Committee of Antwerp University Hospital and informed consent was obtained from all volunteers before inclusion in the study. The study involved healthy and cystic fibrosis subjects. Exclusion criteria were the inability to perform technically adequate spirometry or FOT measurements, evidence of current airway infection, acute exacerbation and any respiratory disease other than CF. All patients were in stable clinical condition at the moment of measurement. The study involved 16 healthy children and their corresponding biometric values are given in Table 1, their impedance was referenced to the values published in [28]. The measurements were performed in May 2009, at the St. Vincentius Basis School in Zwijnaarde, Belgium. The study involved also 10 children diagnosed with cystic fibrosis and their corresponding biometric and spirometric values are given in Table 1. The measurements were performed during the December 2008–March 2009 time interval.

Using a closed circuit spirometer (JAEGER MasterLab, Germany) measurements for forced vital capacity (FVC), FEV1, the ratio FEV1/FVC and the ratio of forced expiratory flow (FEF) between 25% and 75% of FVC to FVC (FEF/FVC) were obtained for the CF patients in a sitting position. These parameters were presented as raw data and percentile of the predicted values (% pred) in a healthy subject with the same biometric details. Quality control of spirometry is given by the ATS criteria (American Thoracic Society), with the software allowing detection of non-acceptable manoeuvres. The details from the CF patients are given in Table 1.

2.2. Input impedance measurement

The impedance was measured using the Forced Oscillation Technique (FOT) setup, commercially available, assessing respiratory mechanics in the 4–48 Hz frequency band. The device complies with the standard FOT guidelines [27]. The subject is connected to the setup via a mouthpiece as in Fig. 1. The oscillation pressure is generated by a loudspeaker, with the membrane moving according to the fed voltage from a computer. This in turn generates a multisine signal, resulting in air pressure oscillations. Opening of the main tubing via a bias tube allows the patient to have fresh air circulation, designed carefully not to lose significant air pressure power. During the measurements, the patient wears a nose clip and keeps the cheeks firmly supported.

The FOT lung function tests were performed according to the recommendations described in [27]. The sampling period of the measurements was 500 Hz and the duration of one test was 30 s. Three consecutive tests were performed, to allow the estimation of an averaged impedance data. The multisine signal was kept within a range of a peak-to-peak size of 0.1–0.3 kPa to avoid lung injury.

Apart from this device, we also used a prototype device which is able to deliver lower excited frequencies, between 0.1 and 10 Hz. The device complied with the same recommendations as in [27] and works based on the same principles as the one described in Fig. 1. The sensors, signal amplitudes and sampling period are also the same [21].

All patients were tested in the sitting position, with cheeks firmly supported and elbows resting on the table. Each and every group of patients and volunteers has been tested in its unique location, using the same FOT devices, and under the supervision of the same FOT team.

2.3. Respiratory impedance

The spectral representation of the respiratory impedance Z_r is a fast, simple and fairly reliable evaluation [25,27]. Since the multisine signal is optimized such that it does not contain components of the breathing frequency of the patient, one can calculate the respiratory impedance as in:

$$Z_r(j\omega) = \frac{S_{PU_g}(j\omega)}{S_{QU_g}(j\omega)} \quad (1)$$

whereas U_g is the input signal send to the patient (i.e. sinusoidal variations in the air-pressure), the P corresponds to pressure (its electrical equivalent is voltage) and Q corresponds to air-flow (its electrical equivalent is current), the respiratory impedance Z_r can be defined as their spectral (frequency domain) ratio relationship, with $S_{ij}(j\omega)$ the cross-correlation spectra between the various input–output signals, ω is the angular frequency and $j = (-1)^{1/2}$ [27].

2.4. Parametric model and relation to lung properties

In our previous work, we had shown that anatomical and morphological models of the respiratory tract [14] lead to ladder network models [16], which in their lumped representation contain fractional order Laplace terms. In short, we found that the FO terms in the impedance models arise either from intrinsic viscoelastic (at low frequencies), either intrinsic fractal structure of the airway tree. From a manifold of possible FO models [20], the FO model proposed for evaluation in this paper is:

$$Z_{FO4}(s) = L_r s^{\alpha_r} + \frac{1}{C_r s^{\beta_r}} \quad (2)$$