Respiratory Physiology & Neurobiology 192 (2014) 23–29

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

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

Regional differences in bronchial reactivity assessed by respiratory impedance

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ARTICLE INFO

Article history:
Accepted 2 December 2013

Keywords:
Respiratory resistance
Respiratory reactance, Asthma
Small airways
Sensitivity
Specificity

ABSTRACT

We used the Impulse Oscillometric System (IOS) to gain information concerning the distribution of hyper-reactivity along the bronchial tree during methacholine challenge test (MCT).

37 subjects underwent MCT until reaching the provocative dose (PD20). At each dose, we estimated respiratory resistance at 5 and 20 Hz (R_5, R_{20}), and reactance at 5 Hz (X_5). In non-responsive subjects ($N = 14$) no changes in R_5, R_{20}, and X_5 were observed during MCT. In responsive subjects, a wide spectrum of responses was found concerning frequency dependence and PD20. We describe two phenotypes representing the extremes of response. For PD20 > 400 μg ($N = 13$), MCT caused equal changes of resistance/reactance on varying oscillation frequencies, suggesting a homogeneous bronchoconstriction along the bronchial tree. For PD20 < 200 μg ($N = 10$), a remarkable frequency dependence was observed, with increase in R_5, no change in R_{20}, and decrease in X_5, suggesting hyper-responsiveness of the distal airways paralleled by a change in visco-elastic properties of lung parenchyma.

1. Introduction

Bronchial hyper-responsiveness (BHR) is a pre-clinical condition characterized by an excessive bronchial narrowing in response to various inhaled stimuli. BHR is frequently associated with airway inflammation preceding clinical manifestations, such as asthma (Koskela et al., 2003).

An appropriate broncho-provocation testing is of high clinical relevance particularly to detect the early phase of the developing disease. Indications for broncho-provocation also include assessment of the response to asthma therapy, and, less commonly, the identification of triggers or cases involving environmental or occupational asthma (Laprise et al., 1999; Weiss et al., 2000).

The clinical diagnosis of BHR is currently performed by measuring the decrease in FEV_1 as percent of baseline value, caused by a direct activation of airway smooth cells (Cockcroft and Davis, 2006) following inhalation of aerosolized bronco-constrictor agents, such as methacholine (methacholine challenge test, MCT) (Crapo et al., 2000). However, the fact that for many patients it is relatively difficult to perform reliable spirometric forced maneuvers, has led to combine the measurement of FEV_1, with the measurement of airways resistance (Raw) assessed by body plethysmography (Nensa et al., 2009) that is less dependent on patient's cooperation. The real problem underlying the response to MCT remains the lack of information concerning the distribution of the broncho-reactivity along the bronchial tree down to the terminal lung units. Indeed, neither FEV1 nor plethysmography does really allow the identification of sites of bronchoconstriction that is known to vary in the clinical context. Thus, the general diagnosis of hyper-reactivity remains nonspecific as far as the location of the reaction is concerned. This point is of great interest given the fact that BHR is a complex inflammatory process affecting to a various extent both the large airways as well as the distal lung that includes the terminal airways as well as the surrounding interstitial microenvironment.

The aim of this study was to assess inter-individual differences concerning the longitudinal distribution of airways flow resistive properties as well as the viscoelasticity of the lung tissue in response to methacholine stimulation. We relied on the use of impedenzometric indexes as a powerful tool to describe the lung mechanical response to methacholine. In particular, we adopted the Impulse Oscillometric System (IOS), a non-invasive method that has been widely used to study the lung function in children (Tomalak et al., 2006; Schulze et al., 2012; Shi et al., 2012), as well as in adults (Aronsson et al., 2011; Skloot et al., 2004).

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http://dx.doi.org/10.1016/j.resp.2013.12.002

2. Materials and methods

2.1. Study subjects

Subjects ($N = 37$) were recruited among people undergoing functional evaluation for clinical purposes at the pneumological service of the San Gerardo Hospital. At time of examinations, none of the subjects had any cardiac or pulmonary disease other than suspected asthma and none was receiving any treatment. Methacholine challenge test was requested to assess bronchial hyper-reactivity.

Subjects were informed in detail about the operation of the equipment and it was proved that they were able to perform the required maneuvers correctly. We obtained informed consent from subjects for the procedure/treatment and for their medical data to be used in this study. The project was approved by the Ethics Committee of the San Gerardo Hospital.

Methacholine challenge test was performed according to standardized protocols through deep inhalations using a dosimeter method (Crapo et al., 2000). Subjects abstained from using β2-agonists or other drugs 24 h prior to the challenge. Subjects underwent 0.9% saline aerosol bolus (assumed as baseline) and after increasing doses of methacholine (corresponding to cumulative doses of 50, 100, 200, 400, 800, 1600 and 2400 μg, respectively) administered through aerosol inhalation (Markos Mefar Dosimeter MB3). Respiratory mechanics was evaluated by Impulse Oscillometric System (IOS, Jeager, MasterScreen System). The sequence of maneuvers was as follows: (a) three consecutive runs of IOS (Oostveen et al., 2003), (b) determination by plethysmography of total gas volume (ITGV) and airways resistance (Raw), (c) FEV_1, which currently represents the gold standard. This sequence was chosen to avoid influences by spirometric maximal maneuvers on the bronchial tone (Skloot et al., 2004). Tests were performed and reported by at least 2 physicians experienced in the field. At each methacholine dose, all measurements were performed within 5 min.

The methacholine dose was increased until the provocative dose was reached, corresponding to a 20% decrease in FEV_1 from baseline (PD20) or to a maximal dose of 2400 μg. PD20 was estimated from the linear interpolation of the measured FEV_1 values with the corresponding methacholine dose for a 20% decrease in FEV_1 relative to saline solution.

2.2. Plethysmography

The plethysmographic method (Bodyscope Ganshorn Medizin Electronic) was used to measure intra thoracic gas volume (ITGV) and airways resistance (Raw): while closing a shutter at functional residual capacity (FRC), the subject was invited to make a series of weak inspiratory and expiratory efforts against the shutter. The patients were instructed to support the cheek with the palms of the hands to minimize the artifacts due to cheek motion. We derived ITGV as the slope of the resulting correlation between variation of box pressure and the corresponding variation in pressure measured at mouth. FEV_1 and FVC were measured from a flow-volume forced maximum expiratory maneuver. Raw was obtained as a ratio between specific airways resistance and lung volume at FRC during panting.

2.3. Impulse Oscillometric System (IOS)

This technique is based on the superimposition of small pressure oscillations with multiple frequency contents on the spontaneous breathing of the patient. The resulting changes in pressure and the corresponding flow, measured at the mouth of the subject under examination, depend on mechanical properties of airways, lung tissue and chest wall. To avoid interference from spontaneous breathing, the measurements are performed at frequencies at least one order of magnitude above normal breathing frequency. The technique allows estimating the absolute value of the impedance (Z_{rs}) of the respiratory system at different frequencies (in the range 5–20 Hz) that is given by the vector sum of resistance (R_{rs}) and reactance (X_{rs}). A full run of oscillation lasts 40 s. Subjects were instructed to support their cheeks with the palms of their hands to minimize shunt effects.

We considered the following IOS parameters: (a) resistance at 5 Hz (R_5), an index of total respiratory resistance, (b) resistance at 20 Hz (R_{20}), reported by most researchers as an index of resistance of the large airways; (c) the difference R_5–R_{20} (R_{5-20}), index of frequency dependence of respiratory resistance, (d) reactance at 5 Hz (X_5), index of mechanical properties of the distal lung (Goldman et al., 2005). We considered the average inspiratory–expiratory values of resistance and reactance. In the case of reactance, on occasion we considered the expiratory value, X_{5exp}, that was proposed as a useful index to permit the early detection of flow limitation (Dellacà et al., 2004; Paredi et al., 2010).

2.4. Statistics

We performed linear regression and assessed the normality test for distribution as well as coefficient of skewness using Origin 8 software. To define the sensitivity and specificity of some IOS indexes, a receiver-operating characteristic (ROC) curve was plotted (Sigma plot 8). Cut-off levels at 95% confidence interval were calculated with the optimal combination of sensitivity and specificity using the Youden (Youden, 1950) index (sensitivity + specificity − 1).

3. Results

Patient recruitment and data collection and analysis extended from March 2012 to April 2013.

Table 1 reports the baseline subject's values of FEV_1, IOS indexes, as well as Raw and ITGV, and PD20. The first 3 lines report data concerning 3 subjects: a non-responsive control subject (A), and two patients whose response differed in terms of degree of frequency dependence of the impedenzometric indexes on increasing the methacholine dose: frequency dependence was not detectable in subject B-like while it was present to a various degree in subjects C-like. All other subjects were ranked in Table 1 based on increasing dose of PD20; considering this ranking, 62% of the subjects were considered positive (23 out of 37) having a PD20 lower than 2400 μg.

Fig. 1A shows R_{rs} and X_{rs} values at different oscillation frequencies for the three representative subjects. In a non-responsive subject (A) the R_{rs} and X_{rs} values (top and bottom panels, respectively) remained substantially unchanged at all frequencies of oscillation on increasing the methacholine dose up to 2400 μg. In subject B (Fig. 1B), the response to methacholine caused a similar increase in R_{rs} and corresponding decrease in X_{rs} at all frequencies. This caused a parallel shift upward and downward respectively for R_{rs} and X_{rs}, up to a maximal dose of 400 μg. In subject C (Fig. 1C), we observed a remarkable frequency dependent change in both R_{rs} and X_{rs} on decreasing frequency of oscillation upon reaching the maximal dose of 50 μg. The phenotypes of the two responsive subjects shown, essentially represent the extremes of a wide spectrum of response, characterized by a variable degree of frequency dependence and PD20 values.

Fig. 2A shows that a significant correlation was found by plotting R_{5-20} at PD20 *vs.* the basal value of R_5. Furthermore, Fig. 2B shows that remarkable inter-individual differences were found when plotting the increase in R_{5-20} at PD20, relative to baseline