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Should We Measure the FEV_1 or the Specific Resistance of the Airways? An Evaluation in Patients with Either COPD, Chronic Dyspnea or Chronic Cough*

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ABSTRACT

Background: The purpose of this study was to evaluate the relative contribution of measuring the forced expiratory volume in one second (FEV_1) or the specific resistance of the airways (sRaw) in adults referred for chronic obstructive pulmonary disease (COPD), chronic dyspnea or chronic cough. **Methods:** This was a prospective study of 321 subjects referred for lung function testing, in a setting of routine clinical management, for suspicion of COPD (or follow-up of known COPD), chronic dyspnea or chronic cough. The proportions of FEV_1 values below the normal range and of sRaw values above the normal range were compared using a Chi-square exact test of Fisher. **Results:** In the COPD and chronic dyspnea groups, sRaw was as frequently abnormal as FEV_1. In the chronic cough group, sRaw was increased in 56.5% of subjects, while FEV_1 was decreased in solely 34.8% ($p = 0.059$). **Conclusions:** This study suggests that sRaw may be a better tool than FEV_1 to detect bronchial obstruction in patients presenting with chronic cough.

Keywords: Body Plethysmography; Chronic Cough; Specific Airway Resistance

1. Introduction

Spirometry is often considered as the gold standard for determination of obstructive pulmonary disease. This method has however several limitations, which has led to resistance measurements used to clarify lung pathophysiology [1]. In the recent years, there has been a progressive disinterest in resistance measurements, at least in adults. As an illustration, the 2005 American Thoracic Society and European Respiratory Society statements did not address resistance measurements [2]. In contrast, resistance measurements are still considered to be particularly relevant in pediatric patients [3,4].

The present study was designed to evaluate the relative contribution of measuring the forced expiratory volume in one second (FEV_1) or the specific resistance of the airways (sRaw) in adults referred for lung function testing (LFT) because of chronic obstructive pulmonary disease (COPD), chronic dyspnea or chronic cough. These indications were chosen because the Belgian authorities recently suggested that the usefulness of assessing airway resistance is not proven in subjects with either COPD, chronic dyspnea or chronic cough [5]. We hypothesized that sRaw may be more sensitive than FEV_1 in detecting bronchial obstruction in these groups of patients. The study was performed in a setting of routine clinical management and aimed to evaluate the percentage of subjects with an abnormal test, namely a decreased FEV_1 or an increased sRaw.

2. Patients and Methods

2.1. Study Design

In the present study, we prospectively evaluated the sRaw and the FEV_1 in three groups of subjects (as defined underneath) in a setting of routine clinical management. The patients were referred by their physician for LFT because of either COPD (group 1), chronic dyspnea (group 2) or chronic cough (group 3). The study protocol was approved by the Ethics Committee of the CHU Brugmann and each subject gave written informed consent to the analysis of his (her) lung function data.

2.2. Patients

The study was performed at the Pulmonary Division of the CHU Brugmann between 26/10/2009 and 16/07/2010. All males and females between 18 and 70 years old, referred for LFT because of COPD, chronic dyspnea or chronic cough, were eligible provided they gave informed consent and were able to perform technically

*Conflict of interest: There is no conflict of interest.

acceptable spirometry and plethysmography. Exclusion criteria included age less than 18 or more than 70, being referred for LFT because of another diagnosis, being unable to perform either spirometry or plethysmography, as well as having any contra-indication to LFT (recent heart attack or pneumothorax, recent ocular, abdominal or thoracic surgery, suspicion of tuberculosis, severe claustrophobia).

2.3. Constitution of Groups

The classification into three groups was made on basis of the requests for LTF, written by the referring physicians. Subjects were put into group 1 (COPD) when the request mentioned a clinical suspicion of COPD or follow-up of a known COPD. When the request mentioned several respiratory diseases, subjects were included provided COPD was listed as the first diagnosis (e.g. COPD plus bronchectasis). Subjects were put into group 2 (chronic dyspnea) and into group 3 (chronic cough) when the request respectively mentioned chronic breathlessness or chronic cough as the first reason to perform LTF. Patients referred for LFT for other indications (e.g. preoperative work-up), or for several indications with another diagnosis listed first (e.g. known lung fibrosis and chronic cough) were not included.

2.4. Lung Function Testing

A Zan (Waldfenster, Germany) body plethysmograph was used. Patients were instructed in the correct technique while the plethysmography door was open. During the maneuvers, patients were asked to firmly seal their lips around the mouthpiece. Airflow at the mouth was displayed against box pressure and their relationship was computed according to an automated procedure. Signals were digitized over a period of five breaths, with a sampling rate of 50 Hz. After correction for the thermal drift induced by the subject's heat production, a loop was obtained and midpoints at flows of +0.5 (point A) and −0.5 $l \cdot s^{-1}$ (point B) were obtained. The slope of the line between points A and B defined the sRaw. At least two technically satisfactory five breath-loops were obtained and the reported sRaw was an arithmetical mean. Spirometry was performed with the door of the box open. The subject was instructed to slowly inspire up to the total lung capacity and to subsequently expire a forced vital capacity. In each subject, two to three technically acceptable curves were obtained. Optimization of the reading of the expiratory curves was performed as recommended by Peslin *et al.* [6]. The FEV_1 was defined as the volume exhaled in one second during the performance of the forced vital capacity maneuver. When a bronchodilation or a provocation test was performed, only the baseline values were retained for analysis.

2.5. Interpretation of Lung Function Data

To calculate the predicted values for FEV_1, the regression equations of Quanjer *et al.* [7] were used. An individual FEV_1 value was considered as below the normal range if it was lower than the mean predicted minus 1.64 × standard deviation (SD). The data of Pelzer and Thomson [8] were used as mean predicted values for sRaw, depending on gender. An individual sRaw value was considered as above the normal range if it was higher than the mean predicted value plus 2 × SD.

2.6. Statistical Analyses

The variables recorded in the three groups were compared using either an ANOVA procedure (means comparisons in case of continuous variables) or a Chi-square exact test (proportions comparisons in case of discrete variables). More particularly, the proportions of FEV_1 values below the normal range and of sRaw values above the normal range were compared using a Chi-square exact test of Fisher. The analysis was made separately in the three groups (COPD, chronic dyspnea, and chronic cough). The statistical software used was SPSS version 17.0.

2.7. Retrospective Review of Medical Charts

Twelve months after the study had been completed, medical charts were examined to check for the final cause retained for chronic dyspnea and for chronic cough, in the chronic dyspnea and chronic cough groups.

3. Results

During the study period, 321 subjects were included. The allocation into the three groups is listed in **Table 1**, as well as the mean (SD) values obtained for FEV_1 and sRaw. COPD subjects were older than subjects with chronic dyspnea or chronic cough. The proportion of males in the COPD group was higher than in the chronic dyspnea group, and tended to be higher ($p = 0.074$) than in the chronic cough group. As expected, FEV_1 was lower, and sRaw higher, in the COPD group than in the other two groups (**Table 2**).

Individual FEV_1 values were plotted against predicted values, separately in males and females. As shown in **Figure 1**, measured values were predominantly under the identity line in the COPD group, while a large proportion of values were near the identity line in the chronic dyspnea and chronic cough groups (**Figures 2** and **3**). The proportions of subjects with FEV_1 within versus under the normal range, as well as those of subjects with sRaw within or above the normal range, are shown in **Table 3**. In the chronic dyspnea and COPD groups, sRaw was as frequently abnormal as FEV_1 (exact Fisher test, $p = 1.000$

Table 1. Allocation of 321 subjects into three groups.

	Group 1 (COPD) n = 177	Group 2 (Chronic dyspnea) n = 98	Group 3 (Chronic cough) n = 46
Age (years)	58.1 (7.6)	46.5 (13.3)	50.0 (14.2)
Gender	114 M/63 F	45 M/53 F	23 M/23 F
FEV_1 (% predicted)	53.0 (22.7)	81.1 (19.8)	84.9 (19.4)
sRaw (kPa.s)	3.21 (2.27)	1.44 (1.16)	1.44 (0.57)

M = males, F = females; Data in the table (continuous variables) are mean (SD).

Table 2. Comparison of age, gender, FEV_1 and sRaw among groups, two by two.

	COPD Chronic dyspnea	COPD Chronic cough	Chronic dypsnea chronic cough
Age (years)	<0.001	<0.001	0.166
Gender	0.003	0.074	0.647
FEV_1 (% predicted)	<0.001	<0.001	0.590
sRaw (kPa.s)	<0.001	<0.001	0.999

Data in the table are p values (Student *t*-test for age, FEV_1, sRaw; Chi-square test for gender).

Table 3. Proportions of abnormal tests in 321 subjects.

	Group 1 (COPD) n = 177	Group 2 (Chronic dyspnea) n = 98	Group 3 (Chronic cough) n = 46
FEV_1 normal	20.3%	59.2%	65.2%
Decreased	79.7%	40.8%	34.8%
sRaw normal	14.1%	59.2%	43.5%
Increased	85.9%	40.8%	56.5%

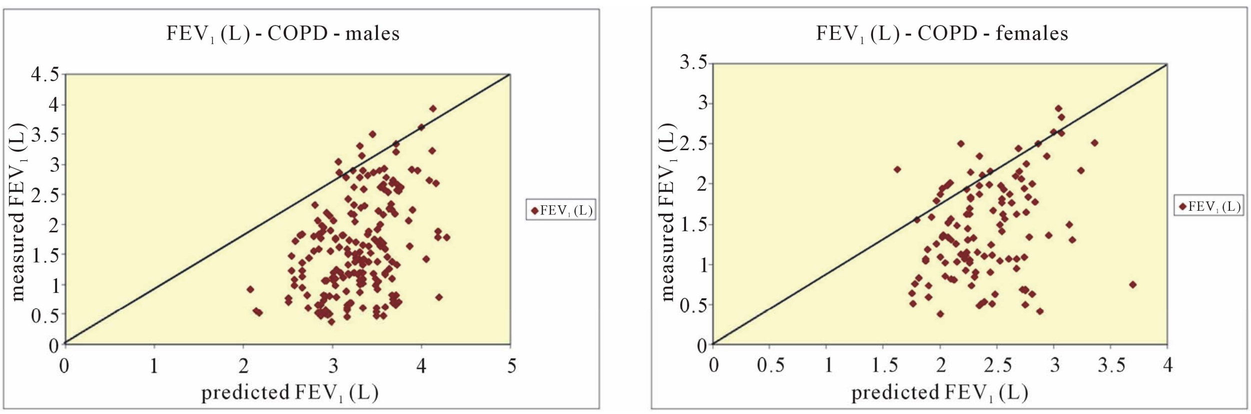

Figure 1. Measured values of forced expiratory volume in one second (FEV_1) are plotted against predicted values, separately in males and females, in the COPD group.

and p = 0.159, respectively). On the other hand, in the chronic cough group, sRaw was increased in 56.5% of subjects, while FEV_1 was decreased in only 34.8% of subjects; this difference reached near significance (exact Fisher test, p = 0.059).

In the chronic dyspnea group, dyspnea remained unexplained in 18 subjects (18%), including 10 subjects lost for follow up. In the remainders, asthma, COPD, heart failure and hyperventilation syndrome emerged as main diagnoses (in, respectively, 32, 28, 7 and 6 subjects). Less frequently, chronic dyspnea was ascribed to obesity or beta blocker therapy (two subjects each) and to lung

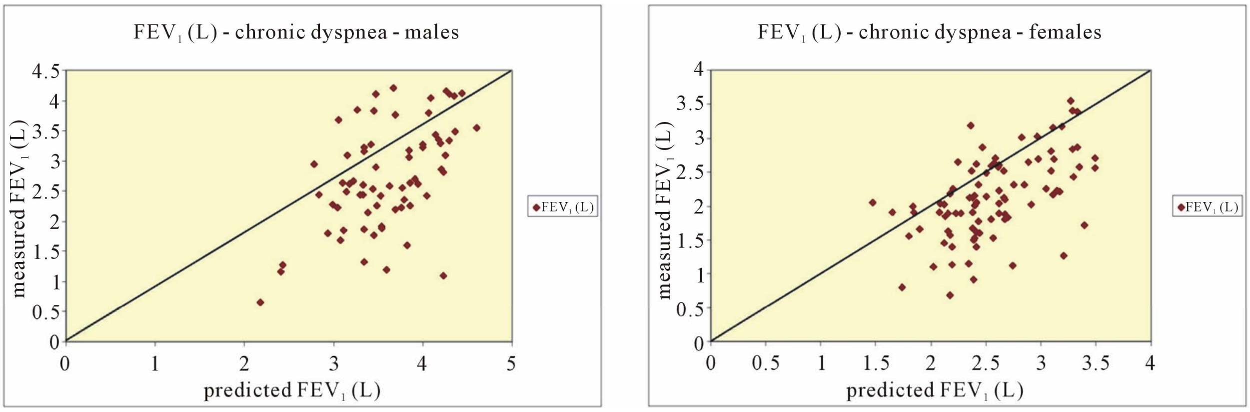

Figure 2. Same legend as Figure 1, in the chronic dyspnea group.

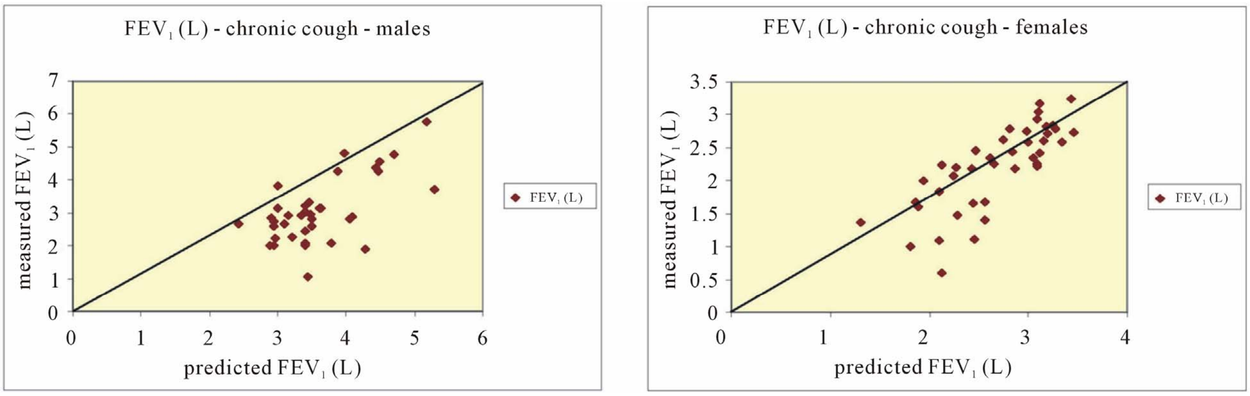

Figure 3. Same legend as Figure 1, in the chronic cough group.

atelectasis, pericarditis or sarcoidosis (in a single subject each). In the chronic cough group, cough remained unexplained in 10 subjects (22%), including 5 subjects lost for follow up. In the remainders, the main diagnoses were cough-variant asthma, chronic rhinitis and sinusitis, COPD, active smoking without COPD and post-infectious cough (in respectively 12, 6, 4, 3 and 3 subjects). Finally, angiotensin converting enzyme inhibitor-induced cough, bronchectasis, gastroesophageal reflux and sarcoidosis were diagnosed each in two subjects.

4. Discussion and Conclusions

Currently accepted indications for resistance measurements include the evaluation of airflow limitation beyond spirometry, the differentiation between different types of obstructive pulmonary diseases having similar spirometric profiles, as well as the distinction of respiratory muscle weakness from obstruction as the cause of low flow rates [9]. In asthma, sRaw has been shown to be increased in patients with no or few symptoms and normal spirometric values [10]. In these particular patients, resistance measurement is crucial to correctly diagnose asthma. Similarly, the assessment of sRaw is useful in patients with tracheal stenosis, compressive goiter or other obstructive lesions of the larynx and the trachea [11]. On the other hand, it is unknown whether measuring sRaw in addition to FEV_1 in patients with COPD, chronic dyspnea or chronic cough caries relevant additional information. As sRaw is measured during tidal (or near tidal) breathing maneuvers, it may reflect the functional breathing status in current everyday life better than FEV_1, which is closer to breathing associated with coughing, singing or laughing. Where lung pathophysiology is concerned, sRaw is thought to predominantly reflect the resistance of the large proximal airways [12]. Small distal airways may however contribute to some extent, as sRaw is sensitive to a small airway disease like bronchiolitis obliterans syndrome [13]. On these grounds, it may be hypothesized that assessing sRaw may be relevant in subject attending for COPD, chronic dyspnea or chronic cough.

Determination of FEV_1 has several advantages. Spirometry requires only a simple equipment and FEV_1 shows a rather good reproducibility. In our lung function laboratory, the mean coefficient of variation of FEV_1 amounts 5.0% in a population of COPD patients [14]. Furthermore, reduced FEV_1 carries additional relevant information, as FEV_1 has been shown to be an independent marker for cardiovascular mortality [15]. On the other hand, spirometry is in a large extent dependent on the subject cooperation. As an illustration, as many as 11.5% of subjects are unable to perform correct forced expiratory maneuvers, even in a young population with little or no chronic lung disease [16]. Similarly, measuring sRaw via plethysmography has advantages and disadvantages. The equipment is more sophisticated, more expensive and the reproducibility is somewhat weaker than that of FEV_1, with e.g. a mean coefficient of variation of 9.3% in COPD patients in our laboratory [14]. On the other hand, sRaw is more sensitive than FEV_1 in a large variety of clinical conditions. Studying the acute effect of physiotherapy on lung function in patients with copious sputum production, Cochrane *et al*. found a greater change in sRaw than in FEV_1 [17]. In patients with heart-lung or bilateral lung transplantation, Bassiri et al found that serial measurements of sRaw were more useful than those of FEV_1 for early detection of bronchiolitis obliterans syndrome [13].

In the present study involving three groups of patients with respectively COPD, chronic dyspnea and chronic cough, we were able to show a larger proportion of subjects with increased sRaw than that of subjects with decreased FEV_1 only in chronic coughers. The difference drew near statistical significance. On retrospective examination of medical charts, cough-variant asthma emerged as the most frequent diagnosis retained to explain chronic cough. Cough-variant asthma is known to be a frequent cause of chronic cough, particularly in nonsmokers. It may be either a precursor of typical asthma, or persist lifelong as the sole symptom of asthma [18]. Definite diagnosis is usually based on both histamine or metacholine inhalation testing and on resolution of cough with anti-asthmatic therapy [19]. Studies on larger groups of patients are needed to evaluate whether sRaw may be a better tool than FEV_1 to detect mild bronchial obstruction in patients presenting with chronic cough.

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List of Abbreviations

COPD: chronic obstructive pulmonary disease
FEV_1: forced expiratory volume in one second
LFT: lung function testing
SD: standard deviation
sRaw: specific resistance of the airways

