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Small airway impairment in moderate to severe asthmatics without significant proximal airway obstruction

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Summary
Asthma is a disease characterized by inflammation which affects both proximal and distal airways. We evaluated the prevalence of small airway obstruction (SAO) in a group of clinically stable asthmatics with both normal forced expiratory volume in the first second (FEV_1) and normal FEV_1/forced vital capacity (FVC) and treated with an association of inhaled corticosteroids (ICSs) and long acting β_2-agonists (LABAs). Clinical evaluation included the measurement of dyspnea, asthma control test and drug compliance.

The prevalence of SAO was estimated by spirometry and plethysmography and defined by the presence of one or more of the following criteria: functional residual capacity (FRC) > 120% predicted (pred), residual volume (RV) > pred + 1.64 residual standard deviation (RSD), RV/total lung capacity (TLC) > pred + 1.64 RSD, forced expiratory flow $(FEF)_{25-75\%}$ < pred − 1.64 RSD, $FEF_{50\%}$ < pred − 1.64 RSD, slow vital capacity (SVC) − FVC > 10%.

Among the 441 patients who were included, 222 had normal FEV_1 and FEV_1/FVC. At least one criteria of SAO was found in 115 (52%) mainly lung hyperinflation (39% based on high FRC, RV or RV/TLC) and more rarely distal airflow limitation (15% based on $FEF_{25-75\%}$ or $FEF_{50\%}$) or expiratory trapping (10% based on increased SVC − FVC). In the patients with only SAO (no PAO), there

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was no relationship between SAO, asthma history and the scores of dyspnea, asthma control or drug compliance.

These results suggest that in asthmatics with normal FEV_1 and FEV_1/FVC, treated with ICSs and LABAs, SAO is found in more than half of the patients indicating that the routinely used lung function tests can underestimate dysfunctions occurring in the small airways.

Introduction

Asthma is characterized by a chronic inflammatory process which affects the whole respiratory tract, from central to peripheral airways, and the site of this involvement determines the resulting pathophysiology of the disease. The peripheral airways, commonly defined as small airways, are those with less than 2 mm in internal diameter and may account for up to 50—90% of total airflow resistance in asthmatics [1]. However, studies of distal airways have proven difficult likely explaining why their role in the natural history of asthma has been neglected for a long time.

Spirometry and plethysmography are the most widely available noninvasive pulmonary function tests (PFTs) to assess distal airway impairment. During the forced expiratory maneuver, the volume of air expired in the first second of a forced expiration, known as FEV_1 reflects mostly the proximal airway assessment, whereas distal airways contribute mainly to the second part of expiration [2]. An obstruction in distal airways causes a slowing of expiratory flows in the terminal portion of the spirogram and a concave shape on the flow-volume curve. Accordingly, the forced expiratory flow (FEF) between 25% and 75% of forced vital capacity ($FEF_{25-75\%}$) and $FEF_{50\%}$ have been regarded as a more sensitive measure of small airways narrowing than FEV_1. Unfortunately $FEF_{25-75\%}$ has a broad range of normality, is less reproducible than FEV_1, and is difficult to interpret if the forced vital capacity (FVC) is reduced or increased [3].

A characteristic of small airway obstruction includes premature airway closure and air trapping [4]. In this regard, Sorkness et al. [3] have partitioned airway obstruction into components of air trapping (indicated by a reduced FVC) and airflow limitation (indicated by FEV_1/FVC). Severe asthma was associated with prominent air trapping whereas non severe asthma did not exhibit air trapping, even at $FEV_1/FVC < 75\%$ predicted. Air trapping was further confirmed with measures of residual lung volume (RV)/total lung capacity (TLC) [3]. An increase in RV and RV/TLC represents a marker of hyperinflation and air trapping, and this pattern has been proposed as an early detector of peripheral airways disease [5]; the ratio of FVC to slow vital capacity (SVC) has also been suggested to be an indirect marker of distal airway abnormalities, reflecting either distal airway obstruction or loss of elastic recoil in the parenchyma [6].

In addition, ventilation heterogeneity is a sensitive marker of abnormal small airway function which can be measured by using the single-breath washout [7] or multiple-breath washout techniques [8—12]. Although nitrogen multiple-breath washout appears an appealing technique for measurement of distal airway abnormalities, the lack of standardization precludes its use in clinical routine [13].

The first aim of the study was to assess the prevalence of small airway obstruction (SAO) in clinically stable moderate-to-severe asthmatics without proximal airway obstruction (PAO). SAO was assessed, with both spirometry and plethysmography, based on the following parameters:

(1) functional residual capacity (FRC), RV, RV/TLC as marker of lung hyperinflation;
(2) $FEF_{25-75\%}$ and $FEF_{50\%}$ to detect distal airflow limitation;
(3) the difference between SVC and FVC to detect expiratory air trapping.

The second aim of the study was to identify possible relationships between SAO and asthma clinical history and phenotypic characteristics such as age, gender, smoking history, asthma control and compliance.

Material and methods

In this cross-sectional study, chest physicians have been randomly selected in a French national list and were offered to participate by post-office mail followed by a phone call. They had to include five consecutive patients with clinically stable moderate-to-severe asthma treated with an association of ICSs and LABAs and referred to the chest physicians for PFTs. The main exclusion criteria were a smoking history equivalent to $\geq$10 pack-years or in the month prior to screening, an hospitalization or emergency department visit for asthma, a clinically significant respiratory tract infection or the need for systemic corticosteroid.

After reading an information leaflet, patients gave their consent for the use of the data for research purpose, then spirometry and plethysmographic lung measurements were conducted. According to the French law on observational studies, the study was approved by the CNOM (Conseil national de l'Ordre des Médecins).

PAO was defined as a FEV_1 less than 80% of pred and a $FEV_1/FVC < 0.7$. SAO was defined by the presence of one or more of the following criteria:

(i) FRC > 120% pred, based on the official statement of the ERS [14],
(ii) RV > RV pred + 1.64 residual standard deviation (RSD),
(iii) RV/TLC > pred + 1.64 RSD,
(iv) $FEF_{25-75\%}$ < pred − 1.64 RSD,