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Tracheal section is an independent predictor of asthma in patients with nasal polyposis

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ABSTRACT

Airway anatomy could be a risk factor for asthma in susceptible patients with airway hyperresponsiveness. This anatomy can be described by only two parameters, the tracheal cross-sectional area and the homothety ratio, which describes the reduction of calibre at each subsequent generation. Thus, we hypothesized that the tracheal area would be linked to the risk of asthma presence.

Tracheal area (measured by acoustic reflexion method) and airway responsiveness to metacholine (expressed as Dose Response Slope) were evaluated in 71 consecutive adult patients with nasal polyposis and normal baseline lung function.

Hyperresponsiveness was evidenced in 30/71 patients (42%), and 20/71 patients (28%) were asthmatics. Forced expiratory flows were related to tracheal areas (mean value: $3.22 \pm 1.32\ cm^2$). In a logistic multivariate analysis, tracheal area and the degree of responsiveness were independent predictors of asthma.

In conclusion, this study suggests that airway anatomy, crudely assessed by tracheal section, is an independent determinant of asthma.

1. Introduction

Impaired lung function is a consistent finding in asthmatic patients (Sears et al., 2003). But whether this impairment is a consequence or a cause of asthma is open to debate. There are several arguments sustaining the hypothesis that airway morphology is a risk factor for asthma (presence of symptoms) in susceptible patients with airway hyperresponsiveness (AHR). The study of Sears and colleagues showed that lung function is constantly impaired throughout childhood in patients with persistent asthma in adulthood, a phenomenon known as tracking (Sears et al., 2003). However, the slopes of change in FEV_1/FVC were similar in asthmatic patients and healthy controls (Sears et al., 2003). Subsequently, Haland and colleagues demonstrated that reduced lung function at birth was associated with an increased risk of asthma by 10 years of age (Haland et al., 2006), strongly suggesting that underlying anatomy is a main risk factor for asthma. Based on theoretical arguments, the whole human bronchial tree anatomy can be described by only two factors, the tracheal cross-sectional area and the homothety factor (diameter of daughter bronchus over diameter of parental bronchus), which describes the reduction of calibre at each subsequent generation (Bokov et al., 2010). The tracheal section is highly variable from subject to subject, which partly explains the wide variability of instantaneous flows in the healthy population (Osmanliev et al., 1982), which is further sustained by the wide standard deviations of their predicted values (Stanojevic et al., 2008). Consequently, one may hypothesize that the tracheal area is a determinant of the calibres of the whole bronchial tree and would be linked to the risk of asthma development in susceptible patients with AHR.

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To evaluate this hypothesis, patients with nasal polyposis prospectively underwent lung function assessment including spirometry and a metacholine challenge test, and non invasive tracheal section measurement using acoustic reflexion method (Hoffstein and Fredberg, 1991). We selected this specific population because the prevalence of both AHR and asthma is elevated in this setting (Delclaux et al., 2008; Mahut et al., 2012), and because nasal polyposis would not constitute a bias for airway anatomy, which may allow the generalization of the results to the whole asthmatic population.

2. Patients and methods

2.1. Design

We prospectively enrolled patients referred to our lung function testing unit between February 13, 2012 and December 15, 2013. Inclusion criteria were: age > 18 years, nasal polyposis and the absence of other respiratory disease than asthma or condition associated with AHR. The patients gave their informed consent to the study, which was approved by an ethics committee (CPP IDF VI, no. 48-10).

They underwent lung function assessment according to recommendations (Crapo et al., 2000; Miller et al., 2005; Pellegrino et al., 2005) including spirometry and a metacholine challenge test (with appropriate withholding of asthma treatment (Crapo et al., 2000)) allowing the calculation of the Dose Response Slope (DRS), as previously described (Essalhi et al., 2013; Mahut et al., 2012). AHR was defined by a DRS $\geq$ 2.39% decrease per μmol (Essalhi et al., 2013). Spirometry results were expressed as percentages of predicted values (Stanojevic et al., 2008). Abnormal lung function (FEV_1 below the lower limit of normal value (Stanojevic et al., 2008)) was the only non inclusion criterion.

2.2. Acoustic pharyngotracheometry

The Eccovision Acoustic Pharyngometer (Sleep Group Solutions, North Miami Beach, FL, USA) was used for tracheal section measurements. The results of in vitro and in vivo validation studies, with particular attention to the reproducibility, accuracy and variability of the technique have been reviewed by Hoffstein and Fredberg (Hoffstein and Fredberg, 1991). A figure of a normal pharyngotracheogram obtained with this apparatus can be found in the study of Friedman and colleagues (Friedman et al., 2014). Four acoustic measurements were performed during tidal breathing at functional residual capacity (avoiding neck flexion) (Friedman et al., 2014). The mean extrathoracic tracheal section (obtained from at least three reproducible measurements) was calculated from a 4 cm segment starting at a point located 2 cm beyond the glottal minimum, which could be easily identified on all area functions (Hoffstein et al., 1987).

2.3. Asthma diagnosis

Asthma diagnosis relied on GINA criteria (http://www.ginasthma.org/: history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough with variable expiratory flow limitation [bronchodilator reversibility testing or positive metacholine challenge test]) and ongoing treatment (either on demand or daily preventive treatment). Asthma severity was scored using GINA criteria in mild, moderate and severe asthma.

2.4. Statistical analyses

The sample size was calculated to allow a logistic multivariate analysis with two independent factors (AHR and anatomy) for the variable of interest (asthma). As a consequence, a minimum of 20 asthmatic patients had to be enrolled.

The variables are expressed as mean ± SD or median (interquartile range) where appropriate. Percentages are expressed with 95% confidence interval. Variables were normally distributed with the exception of DRS, which was log-transformed for the analyses (Pearson coefficient for correlations, Student *t*-tests and chi-square test). In order to avoid multiple testing, the statistical analyses were designed to assess: (i) our ability to reproduce findings of the literature (validation process for tracheal area measurement) and (ii) our hypothesis (tracheal section and susceptibility (AHR) as independent risk factors for asthma).

Statistical analyses were performed using StatView software (SAS Institute Inc., Cary, NC, USA) or OpenStat®. A p-value < 0.05 was deemed significant.

3. Results

During the study period, 83 patients were screened (10 patients had baseline airflow limitation and 2 patients refused to consent) and 71 were enrolled. Their characteristics are described in Table 1. The prevalence of AHR was 30/71 (42%, 95% confidence interval [CI] 31–54%) and asthma was 20/71 (28%, 95% CI 18–39%). Thirteen patients had mild asthma, 6 had moderate asthma and one had severe asthma.

The degree of responsiveness ($\log_{10}$ DRS) was linked to $FEF_{75-25\%}$/FVC ($R = -0.346$, $p = 0.003$) and to baseline FEV_1 (L) ($R = -0.278$, $p = 0.019$).

The tracheal section was not significantly lower in women than in men ($2.90 \pm 1.20\,cm^{-2}$ versus $3.40 \pm 1.37\,cm^{-2}$, $p = 0.128$) and was significantly but weakly related to the height of the subject ($R = 0.251$, $p = 0.034$). Forced expiratory flows were related to tracheal areas: PEF ($L\,s^{-1}$), $R = 0.338$, $p = 0.004$; FEV_1 (L), $R = 0.292$, $p = 0.013$; and $FEF_{75-25\%}$ ($L\,s^{-1}$), $R = 0.252$, $p = 0.034$.

In a multivariate analysis (backward selection) with tracheal area as dependent variable and height, PEF, $FEF_{25-75\%}$ and FEV_1 as independent variables, we show that only tracheal area and PEF remained independently related (adjusted $r^2 = 0.101$, $p = 0.004$).

Tracheal area and $\log_{10}$ DRS remained independent predictors of asthma in a logistic multivariate analysis (area: odds ratio 0.545, 95% CI: 0.31–0.956, $p = 0.034$; $\log_{10}$ DRS: odds ratio 2.160, 95% CI: 1.002–4.655, $p = 0.049$; model: $r^2 = 0.13$, $p = 0.004$).

4. Discussion

The main result of our cross-sectional study is to show that both airway size and the degree of AHR determine the presence of symptoms (asthma) according to our hypothesis, at least in patients with nasal polyposis. It also suggests the validity of the homothety concept for the description of airway anatomy.

4.1. Spirometry and AHR

It has been established for a long time that, for the same dose of metacholine, airways with the smallest calibre will undergo greater relative reduction in airway diameter than those with the largest initial calibre. Accordingly, both FEV_1 and $FEF_{75-25\%}$/FVC ratio are linked to the degree of AHR, as previously demonstrated (Delclaux et al., 2008; Litonjua et al., 1999; Mahut et al., 2012). This latter result has often been attributed to asthma induced remodelling (consequence rather than causal factor). That is why we investigated the same relationship with the most proximal airway segment, i.e. the trachea, which would not be affected by the remodelling process.