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Deep inspiration-induced changes in lung volume decrease with severity of asthma ☆

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Summary
We have previously reported that the magnitude of deep inspiration (DI)-induced bronchodilation is only slightly reduced in mild asthmatics, compared to healthy subjects. The aim of this study was to evaluate whether increased severity of asthma is associated with impairment in the ability of DI to induce changes in lung volume. Thirty-six consecutive asthmatics recruited from the Pulmonary and the Allergy Outpatient Clinics of the Institute of Respiratory Diseases of the University of Palermo were divided into 3 groups: Intermittent (I), Mild Persistent (MP) and Moderate–Severe (MS), based on GINA guidelines. Single dose methacholine (Mch) bronchoprovocations were performed in the absence of DI, to induce at least 15% reduction in inspiratory vital capacity (IVC) from baseline. The post-Mch IVC was followed by 4 consecutive DI and by another IVC, to determine the bronchodilatory effect of DI. The bronchodilatory effect of DI was found to significantly decrease with increasing severity of asthma (I: $68\pm5.4\%$, MP: $45\pm7.2\%$, MS: $4\pm15.6\%$; ANOVA: $P<0.0001$). Bronchodilation by DI, but not FEV_1 or FEV_1/FVC, was also inversely correlated to symptom scores ($r=-0.42$, $P=0.01$) and to weekly salbutamol usage ($r=-0.47$, $P=0.004$). These observations provide support to the hypothesis that the attenuation of the bronchodilatory effect of DI contributes to the severity of the clinical manifestations of asthma.

Introduction

The fundamental abnormality of asthma is excessive baseline airway tone and narrowing in response to bronchoconstrictive stimuli. Deep inspirations have been demonstrated

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to counteract airway narrowing, in that, they are able to reverse bronchoconstriction that has been experimentally induced in healthy individuals.[1–6] In a previous study, we reported similar levels of deep inspiration-induced bronchodilation in healthy and in asthmatic subjects.[7] However, bronchodilation by deep inspirations was exclusively tested in asthmatics with mild disease. In 1980, Orehek and colleagues suggested that there are two populations of asthmatics: those in whom deep inspirations taken after the inhalation of carbachol caused bronchodilation, as measured by airway resistance, and those in whom deep inspirations had no effect.[8] The former group had milder disease than the latter, based on the frequency of dyspneic paroxysms. Recently, the bronchodilatory effect of deep inspirations was also investigated in children with different severity of asthma by using the ratio of maximal over partial forced expiratory flows[9]: in that study, the ability of a deep inspiration to improve expiratory airflows decreased with increasing severity of asthma, as assessed by international guidelines.

Our experimental design to test the effect of deep inspiration involves a single dose methacholine challenge model in which, after the induction of targeted bronchoconstriction, subjects are asked to take 5 consecutive deep inspirations with subsequent repetition of lung function measurement.[5,7,10–12] We have more recently introduced a spirometric inspiratory vital capacity (IVC) maneuver to provide us with the primary outcome in these studies. As will be discussed later, the measurement of IVC has the advantage of avoiding the inherent effect of a deep inspiration in the spirometric maneuver. However, IVC is a volume outcome and the question has been raised whether the findings reported in the above-cited work using airway resistance or flow characteristics can be confirmed with a volume measurement. We, therefore, designed the current study to test the hypothesis that the bronchodilatory effect of deep inspiration is impaired in adults with more severe asthma using IVC as the primary outcome. We used an unselected and consecutively recruited group of asthmatics and examined whether the bronchodilatory ability of deep inspiration was related to the severity of their disease, as assessed by the GINA guidelines,[13] as well as to the control of the disease, as assessed by the Asthma Control Questionnaire (ACQ),[14] which takes into account symptom scores and short-acting β agonist (reliever medication) usage.

Methods

Subjects

We recruited individuals attending for the first time the Pulmonary and the Allergy Outpatient Clinics of the Institute of Respiratory Diseases of the University of Palermo, Palermo, Italy and who received the diagnosis of asthma by a pulmonologist. The severity of asthma was determined in accordance with the GINA guidelines.[13] Because some individuals were already on asthma treatment, categorization by severity took into account their current therapeutic regimen, as required by the GINA guidelines.[13] All subjects were skin test positive to at least one aeroallergen that could explain the pattern of their lower airway symptomatology, and none was a current smoker (two subjects were former smokers). If an upper or lower respiratory infection was present, assessment was postponed for at least 4 weeks. All subjects were in stable condition and subjects allergic to pollen were studied out of season. Short-acting agonists were withheld for at least 12 h and long-acting agonists for 24 h prior to each evaluation. None of the subjects was receiving theophylline at the time of the study. Corticosteroid therapy and leukotriene modifiers were maintained throughout the study. Coffee or tea were not allowed before the bronchoprovocations. The study was approved by the Ethics Committee of the University of Palermo and all subjects gave written, informed consent prior to participation.

Study design

The study was designed to assess the association between the degree of deep inspiration-induced bronchodilation and the severity of asthma, and included both clinical and functional evaluations. Clinical evaluation consisted of the assessment of the frequency of daily and nocturnal symptoms, as well as recording of salbutamol usage. These assessments led to the categorization of asthma severity. Asthma control was measured by using a self-administered Asthma Control Questionnaire (ACQ). The ACQ is a validated 7-item instrument, each item (symptom) rated on a six-point scale, ranging from "none" to "extremely severe".[14] The questions addressed symptoms occurring within the week preceding the evaluation. The questionnaire was completed by each subject on the day of the evaluation.

Functional assessment included conventional spirometry and measurement of the bronchodilatory effect of deep inspiration. The bronchodilatory effect of deep inspiration was assessed as described before[5,7] by a series of single dose methacholine bronchoprovocations. First, the single dose of methacholine that, in a protocol completely devoid of deep inspirations, induces an at least 15% reduction in inspiratory vital capacity (IVC) from baseline, was determined. The protocol of the single dose methacholine bronchoprovocation (Fig. 1) consists of a 20-min period of deep-breath prohibition that begins after baseline spirometry. During this period, subjects are observed by a study staff member and are repetitively reminded of the need to abstain from any deep inspirations. At the end of this period, a single concentration of methacholine is administered through five tidal breaths; 3 min later, spirometry is repeated. The spirometric measurement is a combined maneuver (a partial

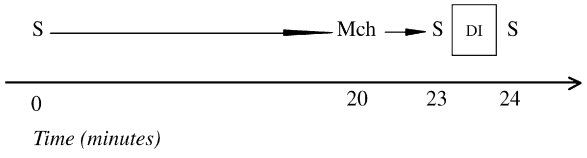

Figure 1 Depiction of the single dose-bronchoprovocation protocol that was employed to measure the bronchodilatory effect of deep inspiration. For details, see Section Methods. S = Spirometry; Mch = single dose Methacholine; DI = Deep inspiration.