The bronchodilatory effect of deep inspiration diminishes with aging

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Summary Deep inspirations have the ability to dilate constricted airways. The impairment of this function has been associated with the occurrence of asthmatic symptoms. We evaluated whether the bronchodilatory effect of deep inspiration (DI) is affected by aging. We tested 25 healthy subjects (median age: 54 yrs, range: 25–83 yrs). Single dose methacholine (Mch) provocations were performed in the absence of DI, which induced at least 15\% reduction in inspiratory vital capacity (IVC) from baseline. The post-Mch IVC measurement was followed by 4 DIs and by another IVC (post-DI IVC). The fractional difference between post-DI IVC and post-Mch IVC represented the \% bronchodilation by DI. The \% bronchodilation significantly diminished with aging ($r = 0.65$, $P = 0.0005$). The bronchodilatory ability of DI was also positively associated with the degree of Mch-induced reduction in IVC ($r = 0.84$, $P < 0.0001$). In multiple regression analysis, where \% bronchodilation was the dependent variable, both \% reduction in IVC ($P < 0.0001$) and age ($P = 0.02$) entered the model. Our data raise the hypothesis that aging is associated with reduction in DI-induced bronchodilation.

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Introduction

Deep inspirations have been shown to exert beneficial effects on the airways of healthy subjects.\textsuperscript{1–7} In addition to their protective effects against spasmogen-induced bronchoconstriction, deep inspirations are able to partly reverse bronchoconstriction in healthy subjects and, to a lesser extent, in subjects with asthma.\textsuperscript{1,2,4–7} Within the asthmatic population, we have observed a large variability in deep inspiration-induced bronchodila-

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has reached complete maturation and all functions are fully effective. The respiratory system undergoes structural changes associated with aging.\(^9\)–\(^11\) The most important physiological alterations occur in the connective tissue of the lungs, with a consequent reduction in the elastic recoil pressure.\(^12\) The re-arrangement of the elastic fiber network in the lungs of elderly individuals contributes to reduced mechanical interdependence between the airway and the parenchymal structures. The present study was designed to test the hypothesis that the age-related alterations of the lung attenuate the bronchodilatory ability of deep inspiration.

**Methods**

**Subjects**

We studied 25 healthy subjects. To ensure that none of the subjects included in the study suffered from respiratory diseases, he or she underwent clinical evaluation that included a questionnaire that derives from the International Union Against Lung and Tuberculosis Disease (IUALTD) bronchial symptom questionnaire\(^13\) and a physical examination. None of them reported chronic respiratory symptoms of any sort or had any diagnosis of respiratory disease. All but 2 subjects were non-smokers and those who smoked had 1.25 and 2 pack-years history of smoking, respectively, with current consumption of less than 10 cigarettes per day. None received any medications that could interfere with this study. Functional assessment also included conventional methacholine bronchoprovocation, during which he or she received the highest dose of methacholine (25 mg/ml) without reaching the conventional threshold of a 20% fall in FEV\(_1\). If an upper or lower respiratory infection was present, the assessment was postponed until at least 4 weeks after the event. The study was approved by the ethics committee of our Institution and all subjects gave written, informed consent prior to participation.

**Study design**

To measure the effects of deep inspiration, we have developed a procedure that involves single dose methacholine (Mch) challenges. This procedure has been extensively described and validated.\(^3\)–\(^4\),\(^14\) Recently, we have improved this procedure by utilizing the inspiratory vital capacity (IVC), as described below, as the primary outcome in the single dose Mch challenge.\(^15\),\(^16\) Following the screening procedures, a series of single dose Mch bronchoprovocations were performed. These aimed at identifying the single dose inducing at least 15% reduction in IVC from baseline, under deep breath prohibition. The protocol for the single dose Mch bronchoprovocation is depicted in Fig. 1. Three combined partial followed by maximal forced expiratory maneuvers were performed at baseline, and the best IVC (defined as the volume from the end of the partial forced expiratory maneuver to TLC) was retained for analysis. Subjects were then instructed not to take deep breaths for a period of 20 min. Thereafter, a single concentration of methacholine was administered as five tidal breaths and, 3 min later, lung function measurement was repeated, with a single spirometric maneuver, as described above. The single dose bronchoprovocation was repeated with increased doubling doses until the expected level of reduction in IVC was attained.

The second part of the study aimed at determining the bronchodilatory effect of deep inspirations. The single dose Mch bronchoprovocation in which the targeted reduction in IVC was obtained was extended with 4 deep inspirations performed immediately after the post-Mch spirometry. Following these deep inspirations, a single IVC maneuver was repeated. The ability of deep inspiration to reverse the induced bronchoconstriction was calculated by using the ratio of the difference between post-deep inspiration (DI) IVC and post-methacholine (Mch) IVC over the post Mch IVC; this was termed % bronchodilation (% BD). The formula is:

\[
\% \ BD = \frac{\text{post-DI IVC} - \text{post-Mch IVC}}{\text{post-Mch IVC}} \times 100.
\]

Since the residual volume on which IVC depends is reached with a maneuver that does not involve a deep inspiration (partial expiratory maneuver from end-tidal volume to residual volume), IVC has an advantage over FVC (or FEV\(_1\)), in that the latter

![Figure 1](image-url)
outcomes may be affected by the deep inspiration that precedes their recording. In validating the use of IVC, we have demonstrated that it has less inter- and intra-individual variability than FVC or FEV₁ and that it can quantitate the beneficial effects of deep inspiration in healthy subjects, as well as in subjects with asthma.¹⁵,¹⁶

Mch was delivered through a ampul-dosimeter (Mefar Elettromedicali; Bovezzo, Italy), which was activated by an inspiratory effort for 0.5 s at a time. All spirometric measurements were obtained from a computerized water-sealed spirometer (Biomedin; Padua, Italy), allowing for compliance with ATS criteria¹⁷ to be checked on-line.

Data analysis

Results are expressed as median with 25 and 75 percentiles, unless otherwise indicated. In our primary analysis, we assessed the correlation between the bronchodilatory effect of deep inspiration and age by simple regression analysis. Also, to confirm previous findings,⁴ we assessed whether the bronchodilatory effect of deep inspirations is affected by the magnitude of Mch-induced bronchoconstriction. Finally, multiple linear regression analysis was constructed in which % bronchodilation was the dependent variable, and % reduction in IVC from baseline and age served as independent variables. In all analyses, P values ≤0.05 were considered statistically significant.

Results

Demographics and baseline lung function characteristics for all subjects are depicted in Table 1. The median single dose of Mch that induced ≥15% reduction in IVC from baseline in the absence of deep inspirations was 20 (20–75) mg/ml; the actual percent reduction in IVC attained by that single dose was 26 ± 2.1%. The deep inspiration-induced bronchodilation was 20 ± 3.3% (mean ± SEM) with a range of −3 to 62%.

Using simple regressions, we evaluated whether aging affects the ability of deep inspiration to dilate the Mch-constricted airways. Fig. 2 shows that the bronchodilatory effect of deep inspiration significantly diminishes with aging (r = 0.65, P = 0.0005). Similar results were obtained when the two smoker subjects were excluded (r = 0.62, P = 0.002). Confirming our previous findings,⁴ we found that the bronchodilatory ability of deep inspirations increases with increasing reduction in IVC from baseline (r = 0.84, P < 0.0001). Therefore, we further analyzed our data in a multiple regression model with the % bronchodilation by deep inspirations as the dependent variable and the Mch-induced bronchoconstriction and age as two

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Note that normative values for subject #8 and #25 were calculated based on the equations that derived from elderly population.³⁷

![Figure 2](http://example.com/figure2.png)
independent variables. This analysis yielded a strong relation \( r = 0.84, P < 0.0001 \), with the two factors being independent correlates of deep inspiration-induced bronchodilation (% induced bronchoconstriction in IVC: \( P < 0.0001 \); age: \( P = 0.02 \)).

Similar results were obtained when the analysis was performed by using a somewhat different measure of bronchodilation by deep inspiration, the % improvement in IVC over the % reduction from baseline.\(^{14} \) in this case, % bronchodilation significantly decreased with aging, again, \( r = 0.60, P = 0.002 \), but did not correlate with increasing reduction in IVC in the absence of deep breaths \( r = 0.28, P = 0.16 \).

**Discussion**

The ability of deep inspirations to dilate experimentally narrowed airways of healthy subjects and, to a lesser extent, of asthmatics is a well-known phenomenon. We have speculated that the first step required for bronchodilation by deep inspiration to take place is that lung inflation stretches the airways, and this can only occur if there is intact airway-to-parenchyma interdependence. Herein, we have provided evidence supporting the hypothesis that the bronchodilatory effect of deep inspirations diminishes with aging. As we will discuss, the possibility exists that structural alterations of the lung are involved in this age-related phenomenon.

The bronchodilatory effect of deep inspiration has been extensively assessed by many investigators.\(^{1,2,4-7,14} \) Once bronchoconstriction has been produced, deep inspirations can substantially reverse it. This function is similar in both healthy and mild asthmatic subjects, albeit somewhat decreased in the latter group. This phenomenon has been extensively studied by using partial expiratory flow-volume curves.\(^{18-27} \) Recently, Jensen and colleagues\(^{6} \) have shown that a single deep inspiration has the ability to dilate airways maximally in healthy subjects, whereas this effect is attenuated in asthmatics: the importance of this study lies in the fact that this phenomenon was demonstrated by using airway resistance, which represents a direct measurement of airway caliber. Our findings based on IVC are consistent with the previous observations.

The mechanisms underlying the beneficial effects of lung inflation have not been elucidated yet. It has been hypothesized that deep inspirations exert bronchodilation by stretching the airways;\(^{4} \) this can be attributed to the forces of interdependence between airways and parenchyma:\(^{28,29} \) airways modify their caliber with changes in lung volume, by virtue of a radial traction that is applied to the airway wall. This mechanism is sustained by the elastic connective tissue that surrounds the airways and is also responsible for the elastic recoil of the lungs. As proposed by Fredberg,\(^{30,31} \) the constricted airway smooth muscle approaches the latch-state equilibrium, in which the number of actin–myosin cross bridges has reached its highest value; large stretches of the airway smooth muscle are, therefore, required to overcome this contractile state. In other words, high forces need to be activated for bronchodilation to be effective. Any factor affecting the interdependence between airways and parenchyma might potentially interfere with the effectiveness of deep inspirations to distend airways. At least three conditions could result in the loss of lung inflation-induced bronchodilation: on one hand, increased thickness of the airway wall, such as that observed in the more severe stages of asthma, could induce greater stiffness of airways which, in turn, would oppose airway distension. On the other hand, reduction of elastic recoil could diminish the radial traction of the airway walls, allowing for loss of supporting tissue for peripheral airways with ease of airway closure.\(^{32} \) This would explain, for example, why bronchodilation by deep inspiration appears to be essentially absent in subjects with changes in lung parenchyma, such as emphysema.\(^{33} \) Finally, the possibility exists that the constricted smooth muscle is too stiff to relax in response to a deep inspiration.

The well-recognized, age-related structural alterations of the lungs provide support to the hypothesis that the loss of the bronchodilatory ability of deep inspiration in older healthy individuals may be due to reduced airway-parenchyma interdependence. The respiratory system undergoes structural changes associated with aging, which involve (1) the parenchyma, (2) the chest wall, and (3) the respiratory muscles. The lung parenchyma of the elderly is characterized by an exaggerated but homogeneous enlargement of airspaces without destruction.\(^{11} \) The senile lung can be, therefore, distinguished from the emphysematous lung, where the airspace enlargement has an irregular distribution with destruction. Albeit minimal, the age-dependent structural alterations are able to exert physiological changes in respiratory function, such as reduction in the static elastic recoil pressure of the lung.\(^{9,34} \) This is of functional significance if one considers that, in COPD, the loss of elastic recoil of the lung is one of the earliest functional abnormalities, even when
spirometric assessment is within the normal range and no macroscopic emphysema is noted. Saetta and coworkers\textsuperscript{35} showed that loss of elastic recoil in smokers represents an early stage in the destruction of lung parenchyma, possibly due to reduction in the content of alveolar attachments. In our study, the small number of current or ex-smokers renders the role of smoking of limited significance. Also, removal of the 2 smokers did not alter the findings of our study.

Other mechanisms that need to be considered in explaining the reduction of the bronchodilatory ability of deep inspirations as a function of age are that aging may result in chest wall stiffness and reduction in respiratory muscle strength\textsuperscript{34,36} that may have negative effects on force generation. The effect of the above-cited factors, although unlikely, cannot be ruled out.

The current findings confirm our earlier observations that the bronchodilatory effect of deep inspiration increases with increasing bronchoconstriction. However, the multiple regression analysis demonstrated that, even when bronchodilation is normalized for this confounding factor, the role of age on the ability of lung inflation to bronchodilate remains statistically significant.

In conclusion, we have provided evidence suggesting that the bronchodilatory effect of deep inspiration is reduced by aging. The attenuation of this deep inspiration-induced bronchodilation may compromise maintenance of airway patency in the elderly. Further studies to assess the role of age-related changes in the bronchodilatory effect of deep inspiration in elderly asthmatics are warranted.

References


