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Deep inspiration volume and the impaired reversal of bronchoconstriction in asthma

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ABSTRACT

It is unclear whether the failure to reverse bronchoconstriction with deep inspiration (DI) in asthma is due to reduced maximal dilatation of the DI. We compared the effect of different DI volumes on maximal dilatation and reversal of bronchoconstriction in nine asthmatics and ten non-asthmatics.

During bronchoconstriction, subjects took DI to 40%, 70% and 100% inspiratory capacity, on separate days. Maximal dilatation was measured as respiratory system resistance (R_{rs}) at end-inspiration and residual dilatation as R_{rs} at end-expiration, both expressed as percent of R_{rs} at end-tidal expiration prior to DI.

DI volume was positively associated with maximal dilatation in non-asthmatics (ANOVA $p = 0.055$) and asthmatics ($p = 0.023$). DI volume was positively associated with residual dilatation in non-asthmatics ($p = 0.004$) but not in asthmatics ($p = 0.53$). The degree of maximal dilatation independently predicted residual dilatation in non-asthmatics but not asthmatics.

These findings suggest that the failure to reverse bronchoconstriction with DI in asthma is not due to reduced maximal dilatation, but rather due to increased airway narrowing during expiration.

1. Introduction

Deep inspirations in healthy humans reverse existing bronchoconstriction and therefore play an important role in modulating airway calibre (Salome et al., 2003; Nadel and Tierney, 1961). In contrast, patients with asthma have a reduced ability to reverse bronchoconstriction with deep inspiration and this has been suggested to contribute to airway hyperresponsiveness (AHR) (Fish et al., 1981; Scichilone et al., 2001). Furthermore, the loss of deep inspiration reversal of bronchoconstriction is associated with worse clinical severity, worse asthma control and increased salbumatol use (Scichilone et al., 2007). At present the precise mechanism/s underlying the loss of deep inspiration reversal of bronchoconstriction in asthma is unclear.

In healthy humans, the reversal of bronchoconstriction following deep inspiration is likely due to the effect of stretch on the airway smooth muscle. Recent studies of precision cut human lung slices from healthy volunteers indicate that the degree to which the deep breath actually dilates the airway is a critical determinant of the reversal of bronchoconstriction (Lavoie et al., 2012). This is consistent with the *in vivo* findings that in healthy subjects the reversal of bronchoconstriction is reduced when the volume of the deep inspiration is reduced (Salerno et al., 2005; Duggan et al., 1990). If, in asthma, the ability to maximally dilate the airways by a deep inspiration is reduced (Jensen et al., 2001; Salome et al., 2003), then this may explain the loss of deep inspiration reversal of bronchoconstriction. However, the evidence for this is unclear, with one study reporting that baseline maximal airway dilatation correlates with the reversal of bronchoconstriction following deep inspiration in asthmatics (Pyrgos et al., 2011) whereas in another study, maximal dilatation during bronchoconstriction correlated poorly with the reversal of bronchoconstriction (Salome et al., 2003). Furthermore, direct assessment of airway calibre with computed tomography suggests that asthmatic subjects can have reduced reversal of bronchoconstriction despite normal dilatation at total lung capacity (Brown et al., 2001). To fully determine the association between maximal dilatation and reversal of bronchoconstriction in subjects with asthma requires an intervention in which maximal dilatation

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can be manipulated to determine the subsequent effect on deep inspiration reversal.

We hypothesised that in asthmatic subjects the extent of maximal dilatation during a deep inspiration determines the acute reversal of bronchoconstriction after a deep inspiration. Our aim was to examine the relationship between the extent of maximal dilatation and reversal of induced bronchoconstriction in asthmatic and non-asthmatic subjects, using different deep inspiration volumes to alter the extent of maximal dilatation. The forced oscillation technique (FOT) was used to measure respiratory system resistance (R_{rs}) before, during and after the deep inspiration. The extent of maximal dilatation was measured by the minimum R_{rs} during the deep inspiration, and the extent of reversal of bronchoconstriction was assessed by the residual dilatation following the deep inspiration, measured as R_{rs} at end-expiration of the deep inspiration.

2. Methods

2.1. Subjects

Asthmatic subjects and non-asthmatic subjects were recruited from the staff and students of the University of Sydney and the Woolcock Institute of Medical Research, and through the research volunteer database at the Woolcock Institute of Medical Research. Inclusion criteria for asthmatics were physician diagnosis of asthma and AHR plus either current symptoms or current treatment. Non-asthmatics had no history of, or past treatment for, respiratory disease and did not have AHR. Subjects were excluded if they were current smokers, had a smoking history greater than 10 pack years, had any other respiratory or major illness, or had a respiratory tract infection in the last month. Asthmatic subjects withheld the use of short acting β2-agonists for 6 h and long acting β2-agonists/inhaled corticosteroids for 24 h prior to testing. All subjects provided written informed consent. The study was approved by the Human Ethics Committee of The University of Sydney.

2.2. Study design

During the initial screening visit, asthmatic subjects had measurements of exhaled nitric oxide, and all subjects had measurements of spirometry and lung volumes before a methacholine challenge to determine the provocative dose that caused a 20% fall in FEV_1 ($PD_{20}FEV_1$). At the second visit, subjects performed baseline spirometry and baseline forced oscillation technique (FOT) measurements (60 s of tidal breathing and a full inspiratory capacity [IC] manoeuvre). The $PD_{20}FEV_1$ dose of methacholine (or 102.2 μmol in those subjects who failed to achieve a 20% fall in FEV_1) was administered as a single dose and, while bronchoconstricted, subjects performed a deep inspiration breathing protocol on the FOT device that consisted of 60 s of tidal breathing, a full IC manoeuvre (deep inspiration of 100%), passive exhalation to functional residual capacity (FRC) and 60 s of tidal breathing (Fig. 1A). R_{rs} was measured throughout (Fig. 1B). On the third and fourth visits, the protocol was repeated with deep inspirations equivalent to 70% IC and 40% IC, in random order. Subjects were instructed to refrain from deep inspirations between methacholine administration and FOT measurements, but were otherwise uninstructed in their breathing pattern throughout the protocol. All study visits were performed at the same time of day, less than a week apart.

2.3. Fraction of exhaled nitric oxide (FeNO)

The fraction of exhaled nitric oxide (FeNO) was measured, as a non-specific marker of inflammation, using an online technique

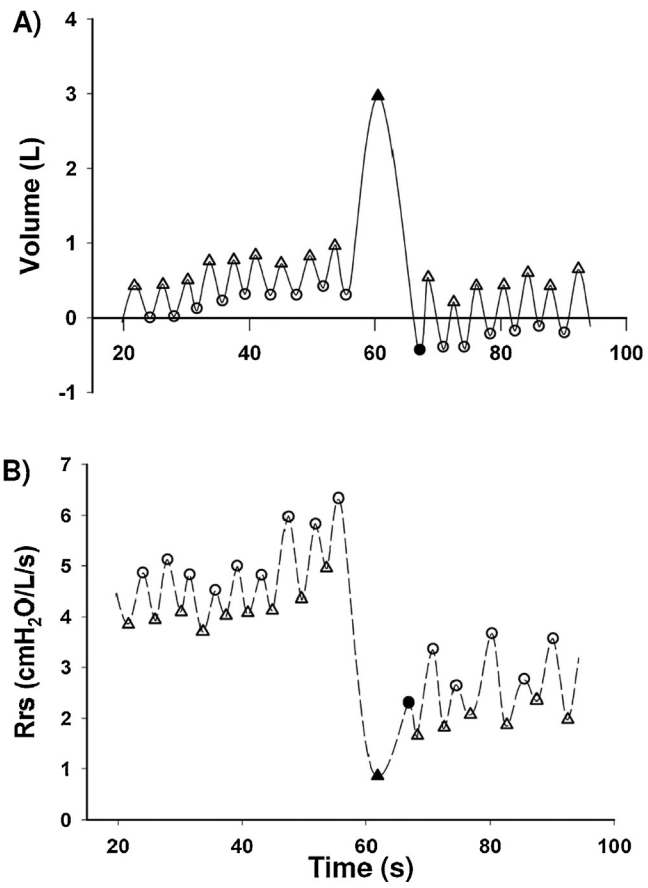

Fig. 1. A schematic representation of the breathing protocol (trace of volume showing tidal breathing with a single deep inspiration – A, solid) for measuring deep inspiration reversal of bronchoconstriction, and the corresponding measure of respiratory system resistance (R_{rs}) (B, dashed). R_{rs} at FRC prior to deep inspiration ($R_{Pre\text{-}DI}$) was calculated as the median R_{rs} measured at end-expiratory points during the 40 s prior to the deep inspiration (Δ). R_{rs} at end inspiration of the deep inspiration (R_{min}) was determined at the height of the deep inspiration (▲). R_{rs} at FRC after the deep inspiration ($R_{Post\text{-}DI}$) was taken as the first end-expiratory R_{rs} point following the deep inspiration (●). The relative extent of maximal dilatation was calculated as R_{min} expressed as a percentage of $R_{Pre\text{-}DI}$. The extent of residual dilatation following the deep inspiration was calculated as $R_{Post\text{-}DI}$ expressed as a percentage of $R_{Pre\text{-}DI}$.

(CLD88sp; Ecomedics, Duernten, Switzerland) at 50 mL/s for at least 10 s, according to ATS guidelines (1995).

2.4. Lung volumes and spirometry

Lung volumes and spirometry were measured using a constant-volume body plethysmograph that was calibrated daily (Medisoft BodyBox 5500, Medisoft Corporation, Sorrines, Belgium) according to ERS/ATS criteria (1995; Wanger et al., 2005). Baseline lung volumes (Crapo et al., 1982) and baseline spirometry (Hankinson et al., 1999) are reported as percent predicted.

2.5. Methacholine challenge

Subjects underwent cumulative methacholine challenges (MP Biomedicals LLC, Santa Ana, CA, USA) using a KoKo dosimeter (PDS Instrumentation Inc. Louisville, USA) (Boonsawat et al., 1992). Non-asthmatic subjects underwent a high dose challenge (dose range: 0.79–200 μmol) while asthmatic subjects underwent a standard dose challenge (dose range: 0.16–10.1 μmol). Doubling doses were administered until subjects reached either a 20% fall in FEV_1 or the end of the challenge. The $PD_{20}FEV_1$ was defined as the cumulative provoking dose of methacholine that caused a 20% fall