TECHNICAL NOTE

Effects of lung volume and thoracic gas compression on maximal and partial flow-volume curves

R. Pellegrino*, P. Confessore**, A. Bianco**, V. Brusasco+


ABSTRACT: Comparing isovolume flows, measured at the mouth during forced expiratory manoeuvres as started from maximal or partial lung inflation, is a means of assessing the effects of deep inhalation on airway calibre. The aim of this study was to investigate whether the assessment of the effect of deep inhalation during induced bronchoconstriction is influenced by the lung volume at which it is determined and by volume differences due to thoracic gas compression that occur during forced expiratory manoeuvres.

Four healthy subjects and six subjects with mild-to-moderate asthma subjects performed partial and maximal forced expiratory manoeuvres in a flow-type body plethysmograph at control and during a methacholine (MCh) inhalation challenge. Mouth flow (V̇₉) was plotted against both the expired volume (V₀) and the simultaneous thoracic volume measured by plethysmography (Vₚ) changes (V⁹-V₀, V⁹-Vₚ loop, respectively). The effects of deep inhalation were quantified by determining 1) the ratio of maximal to partial expiratory flows (M/P) at 30, 40 and 50% of control forced vital capacity (FVC) both on V⁹-V₀ loops (M/P₀) and V⁹-Vₚ loops (M/Pₚ) at control and at MCh end-point; and 2) the slope of the linear regression of maximal vs partial expiratory flows at 30, 40 and 50% of control FVC both on V⁹-V₀ loops (M/P₀) and V⁹-Vₚ loops (M/Pₚ) over the entire challenge.

At control, M/P₀ and M/Pₚ were similar. At MCh end-point, M/P₀ and M/Pₚ increased more than twofold (p<0.002), with M/P₀ consistently exceeding M/Pₚ (p<0.001). In addition, both M/P₀ and M/Pₚ varied inversely with lung volume (p<0.001). By contrast, MP₀ₚ and MPₚₚ were not significantly different from each other (p=0.8), and were also similar at the different lung volumes (p=0.6).

We conclude that during induced bronchoconstriction, the bronchodilation following a deep inhalation, expressed as maximal to partial flow ratio is dependent both on lung volume and volume differences due to thoracic gas compression. The use of expired flow and volume measurements may lead to a small but systematic overestimation of the bronchodilator effect of a deep inhalation. On the contrary, maximal to partial flow slope is insensitive either to lung volume or volume differences due to thoracic gas compression and can, therefore, be fairly determined from expired flow-volume loops.

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occurs during forced expiratory manoeuvres [10], thus causing a difference between expired volume and thoracic volume changes. This study was devised to investigate the extent to which lung volume and the volume differences due to thoracic gas compression occurring at control and during induced bronchoconstriction influence the assessment of the effect of deep inhalation on airway calibre when flow-volume curves recorded at the mouth are used.

Methods

Subjects

The study was conducted on four healthy volunteers and six mild-to-moderate asthmatic subjects. Their anthropometric and functional characteristics are presented in table 1. All subjects underwent a methacholine (MCh) inhalation challenge. For the asthmatics, this was part of a routine diagnostic procedure. The diagnosis of asthma was made according to the criteria of the American Thoracic Society (ATS) [11]. None of the asthmatics was on steroids or long-acting β2-agonists at the time of the study. Short-acting β2-agonists were withheld at least 8 h before the study [12]. None of the subjects had had an upper respiratory tract infection in the previous 4 weeks. Asthmatics were required to be in a stable clinical condition and to have a forced expiratory volume in one second (FEV1) > 80% of predicted [13]. All individuals were informed of the purpose of the study and gave their consent.

Methacholine inhalation challenge

MCh was administered in doubling doses during quiet tidal breathing by using an ampul-dosimeter system (Mefar, Brescia, Italy), which delivers particles with an aerodynamic mass median diameter of 1.53–1.61 µm, according to the manufacturers. During inspiration, a breath-activated solenoid valve was open for 1 s and delivered 5 µL of solution. The starting doses of MCh were 0.02 mg for the asthmatic subjects and 0.3 mg for the healthy volunteers. The challenge ended when the FEV1 decreases by ≥20% of control, or upon request, by the subject, or when a noncumulative dose of 24 mg was necessary. At the end of the challenge, the subjects were given a β2-agonist to inhale and dismissed when the FEV1 had returned to within 10% of control value. No complications occurred during the challenges.

Pulmonary function measurements

Mouth flow was measured through a heated screen-type pneumotachograph (Hans Rudolph Inc., Kansas City, MO, USA) linear up to 12 L·s⁻¹, connected to a differential pressure transducer (SensorMedics Inc., Yorba Linda, CA, USA), and expired volume was obtained by integration of flow. FEV1 was taken from the best of three acceptable expiratory manoeuvres according to the guidelines of the ATS. Thoracic gas volume at end-tidal expiration was measured in duplicate in a constant volume body plethysmograph (2800 Transmural Body Box; Sensormedics Inc. Yorba Linda, CA, USA) by panting at a frequency <1 Hz against a closed shutter. The response of this system is accurate up to 12 Hz. Expiratory reserve volume and inspiratory vital capacity were measured immediately after the opening of the shutter, thus allowing residual volume (RV) and total lung capacity (TLC) to be calculated.

Partial and maximal flow-volume curves were determined with the subjects sitting in the body plethysmograph, which also functions as a flow-type plethysmograph, and mouth flow was measured by the pneumotachograph. Expired lung volume (Vono) was obtained by integrating the mouth flow (V') signal, while thoracic volume (Vpl) changes were obtained from the plethysmograph. The box flow signal was calibrated by using a sinusoidal signal generated by a 50mL piston pump at 2 Hz. The mouth flow signal was calibrated by a 3 L syringe attached to the pneumotachograph. A spiographic tracing was continuously displayed on the screen of a Windograph™ recorder (Gould Inc., Walley View, OH, USA) to provide a visual feedback for the subject and was then printed on paper. All signals were processed by an IBM PS-2 computer and the V-Vono and V-Vpl loops were superimposed on paper by an Epson EX-1000 graphic printer.

For controls, three repeatable maximal forced expiratory manoeuvres preceded by quiet breathing were obtained at intervals of at least 2 min, in order to calculate inspiratory capacity (IC) and forced vital capacity (FVC). The subjects then performed two sets of three

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H/A: healthy/asthmatic; Y/N/EX: smoker/nonsmoker/former smoker; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; PD20: noncumulative dose of methacholine that reduced the FEV1 by 20% of control; % pred: percentage of predicted volume.
repeatable manoeuvres a minimum of 2 min apart. The first set consisted of quiet breathing, a forced expiration from about 70% of FVC to RV, and an inhalation to TLC. The second set consisted of a maximal forced expiratory manoeuvre from TLC to RV, followed by another inhalation to TLC to check for drift. Two minutes after inhaling each dose of MCh, IC was measured in order to calculate the volume between functional residual capacity (FRC) and 70% of control FVC. Two minutes later, the subjects performed a partial forced expiratory manoeuvre from about 70% of control FVC to RV and then inhaled to TLC. Two minutes later, the subjects inhaled to TLC and then performed a maximal forced expiration to RV, followed by another inhalation to TLC to check for drift.

Data analysis

Expiratory flows at 30, 40 and 50% of control FVC on partial and maximal manoeuvres were measured, assuming that TLC was unchanged over the whole MCh challenge [14]. The ratios of isovolume maximal to partial flows both on \( \dot{V}'-V_{mo} \) loops at 30, 40 and 50% of control FVC (\( M/P_{30,mo}, M/P_{40,mo}, \) and \( M/P_{50,mo} \) and \( \dot{V}'-V_{pl} \), loops (\( M/P_{30,pl}, M/P_{40,pl}, \) and \( M/P_{50,pl} \)) were then computed at control conditions and at each step of the challenge.

For each individual, maximal flows at 30, 40 and 50% of control FVC measured over the entire MCh challenge were plotted against the partial flows at the same lung volumes both on \( \dot{V}'-V_{mo} \) and \( \dot{V}'-V_{pl} \) loops, in order to calculate the slope of their linear regression. Thus, the \( M/P_{30,sl,mo}, M/P_{40,sl,mo}, \) and \( M/P_{50,sl,mo} \) on the \( \dot{V}'-V_{mo} \) loops, and the \( M/P_{30,sl,pl}, M/P_{40,sl,pl}, \) and \( M/P_{50,sl,pl} \) on the \( \dot{V}'-V_{pl} \) loops were calculated for each individual. The slopes of such linear regressions are a measure of the bronchodilator effect of deep inhalation over the entire challenge [6, 9]. For example, if the slope is zero, then for any decrement of partial flow there is no change of maximal flow, indicating that deep inhalation fully reverses the induced bronchoconstriction. If the slope is one, then for any decrement of partial flow there is an equal decrement of maximal flow, indicating that the effect of deep inhalation on airway calibre does not change during the challenge, even when airways narrow.

Airway sensitivity to MCh was inferred from the non-cumulative dose of MCh that decreased FEV\(_1\) by 20% of control. This was obtained by linear interpolation between two adjacent points of the dose(log)-response curve.

Statistics

Data are expressed as mean±SD. Comparisons between all measurements were made by two- or three-factor analysis of variance (ANOVA) for repeated measures. The differences between \( M/P_{mo} \) and \( M/P_{pl} \) and between \( M/P_{sl,mo} \) and \( M/P_{sl,pl} \) values were appraised by plotting them against their averages and calculating mean differences ±2 SD [15] and linear regression coefficients. Probability values of less than 0.05 were considered statistically significant.

Results

At MCh end-point, FEV\(_1\) and FVC decreased on average by 20±12 and 5±7% of control, respectively. Maximal forced expiratory flows at 30, 40 and 50% of the \( \dot{V}'-V_{mo} \) loop decreased by 43±17, 45±18 and 44±23% of control, respectively. Figure 1 shows typical examples of partial and maximal flow-volume curves measured at the mouth and in the plethysmograph at control and at the end of the challenge in an asthmatic individual.

Both \( M/P_{mo} \) and \( M/P_{pl} \) values increased with bronchoconstriction at all lung volumes (p<0.002), with the former being slightly but significantly (p<0.001) greater than the latter both in asthmatics and normals (table 2). At MCh end-point, both \( M/P_{mo} \) and \( M/P_{pl} \) were less at high than low volumes in all subjects (p<0.001). In all but one case, in which it increased, the difference between \( M/P_{mo} \) and \( M/P_{pl} \) did not change significantly with the average \( M/P \).

![Fig. 1.](#)
Both MP$_{30,mo}$ and MP$_{50,pl}$ values were consistently lower in the healthy than in the asthmatic subjects (fig. 2), indicating greater increment of bronchodilatation after deep inhalation as the bronchial tone increased. The MP$_{30,mo}$ values were similar ($p=0.8$) to those for MP$_{50,pl}$ (fig. 3), with no significant effect ($p=0.6$) of the lung volume at which they were determined.

**Discussion**

The main findings of this study are that during MCh-induced bronchoconstriction: 1) M/P increases with decreasing lung volume, and is slightly but consistently greater when calculated from the flow-volume curves measured at the mouth than by body plethysmography; and 2) MP$_{50}$ is independent of lung volume, and similar when determined at the mouth or by body plethysmography.
The volume of thoracic gas compressed during forced expiration at a given lung volume depends on airway resistance [10]. This predicts that the volume difference due to gas compression increases during bronchoconstriction. Furthermore, as deep inhalation may cause either bronchodilatation or bronchoconstriction [2–6, 9], the volume of thoracic gas compression may differ during maximal and partial forced expiratory manoeuvres. Consistent with this prediction, gas compression was greater during maximal than partial manoeuvres in subjects with chronic airway obstruction and deep inhalation induced bronchoconstriction [8]. The opposite might be expected during induced bronchoconstriction, when deep inhalation has a bronchodilator effect [2].

M/P has been widely-used to assess the effect of deep inhalation under different conditions [2–5, 8]. Generally, the lung volume at which M/P was determined ranged 30–50% of FVC. It can be assumed that M/P is independent of lung volume only if partial and maximal flow-volume curves have linear downslopes and terminate at the same RV. This may be the case in healthy or mild asthmatic individuals under control conditions, but not during induced bronchoconstriction when deep inhalation increases both expiratory flows and FVC [5]. Under these circumstances, unless the downslopes of partial and maximal manoeuvres are substantially different, M/P increases as lung volume decreases. This was indeed the case in the present study. Accordingly, the volume change due to thoracic gas compression after MCh caused M/Pmo values to exceed those of M/Ppl, the former actually being measured at lower lung volumes. However, a greater thoracic gas compression on partial than maximal manoeuvres would also have resulted in M/Pmo values larger than those of M/Ppl s.

MPsl is an index which has recently been proposed to quantify the bronchodilator effect of deep inhalation during bronchial challenge [6, 9]. It has the advantage of taking into account the dilator response at all steps of the challenge, which makes it independent of the level of airway narrowing at which the response is considered. It is assessed from the slope of the linear regression of the maximal and partial expiratory flows [9] or their percentage changes from control [6]. In the present study, MPsl measurements were independent of the lung volume at which they were taken, and similar when measured at the mouth or by plethysmography. The insensitivity of MPsl to lung volume is likely because it is calculated on absolute differences between maximal and partial flows, which are not affected by changes in FVC. The similarity between MPsl,mo and MPsl,pl values suggests that thoracic gas compression was similar on partial and maximal manoeuvres throughout the challenge, as greater volume differences due to thoracic gas compression on partial than maximal manoeuvres with bronchoconstriction would have caused MPsl,mo to exceed MPsl,pl. Indeed, no differences in the amount of thoracic gas compressed was detectable between maximal and partial manoeuvres.

Reliable assessment of the effects of deep inhalation during induced bronchoconstriction may predict the level at which bronchoconstriction is limited, as well as exaggerated airway narrowing [6]. Moreover, the changes of airway calibre after deep inhalation represent a potential and useful means for evaluating the benefits of the

![Figure 3](image-url)
anti-inflammatory therapy in subjects with chronic bronchoconstriction [16].

The present study shows that measuring maximal to partial flow ratio at the mouth may result in a systematic overestimation of the bronchodilator effect of deep inhalation because of the volume difference due to thoracic gas compression. This error is, however, relatively small (10–12%) and may not lead to substantially erroneous conclusions. Nevertheless, the bronchodilator effect of deep inhalation during induced bronchoconstriction can be more reliably inferred from maximal to partial flow slope, as this is not sensitive to lung volume or to volume changes due to thoracic gas compression.

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References


