Changes in respiratory drive account for the magnitude of dyspnoea during bronchoconstriction in asthmatics

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ABSTRACT: To evaluate whether the interindividual differences in dyspnoea perceived by asthmatic subjects for the same level of airway narrowing could depend on different changes in respiratory drive, we assessed the relationship between changes in airway calibre, changes in neuromuscular output, and dyspnoea rate during progressive bronchoconstriction induced by methacholine.

We studied 18 asymptomatic asthmatic subjects (aged 18–36 yrs; 11 males and 7 females) with normal lung function. Dyspnoea (Borg scale), mouth occlusion pressure ($P_{0.1}$), and forced expiratory volume in one second (FEV_1) were measured at baseline and after inhalation of aerosols of doubling concentrations of methacholine (MCh).

The progressive bronchoconstriction induced by MCh was associated with a progressive increase both of $P_{0.1}$ and dyspnoea. Dyspnoea score was linearly related either to the fall in FEV_1, or to the increase in $P_{0.1}$. However, the slope values of the relationship between dyspnoea score and the corresponding percent fall in FEV_1 showed a large interindividual variability (0.05–0.32; coefficient of variability (CoV) 43%). By contrast, the slope values of the relationship between dyspnoea score and the corresponding percent increase in $P_{0.1}$ ranged 0.02–0.05 (CoV=14%), indicating a more homogeneous response to dyspnoea for the same change in $P_{0.1}$. At the highest MCh concentration, the dyspnoea score was linearly related to the corresponding change in $P_{0.1}$ (r=0.91; p<0.01), but not to the corresponding percentage fall in FEV_1 (r=0.28).

These results show that the interindividual differences in dyspnoea perceived by asthmatic subjects for the same level of airway narrowing are associated with different changes in respiratory drive during bronchoconstriction.
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Dyspnoea is a common symptom experienced by asthmatic patients during episodes of bronchoconstriction. Although it has been reported that the magnitude of dyspnoea perceived is related to the severity of airflow obstruction [1, 2], patients with similar degrees of airflow obstruction experience different levels of dyspnoea during either spontaneously occurring asthma [3], or methacholine-induced bronchoconstriction [4]. The reason for such interindividual variability of intensity of dyspnoea is not known. The observation that patients with airflow obstruction have a higher threshold than normal subjects in detecting the addition of external resistive loads suggests that the presence of airway obstruction may be responsible for the underestimation of perceived dyspnoea [5]. Conflicting with this suggestion, however, is the observation that the presence of airflow obstruction does not result in an impaired perception of dyspnoea due to further airway narrowing induced by histamine [1].

It is known that methacholine-induced bronchoconstriction is associated with an increase in respiratory drive as assessed by mouth occlusion pressure [6, 7]. In addition, there is evidence that respiratory drive is a major determinant of the dyspnoea perceived during exercise or loaded breathing in normals [8, 9]. However, the relationship between the intensity of dyspnoea and the changes in respiratory drive during progressive bronchoconstriction has not so far been evaluated. Therefore, in this study, we wanted to determine whether interindividual differences in dyspnoea perceived by asthmatic subjects for the same level of airway narrowing could depend on different changes in respiratory drive during bronchoconstriction. We sought to answer this question by assessing the relationship between changes in airway calibre, changes in neuromuscular output, and dyspnoea rate during progressive bronchoconstriction induced by methacholine in asymptomatic asthmatic subjects.

Methods

Subjects

Eighteen asthmatic out-patients referred to our asthma clinic for assessment of airway responsiveness were studied. Asthma was diagnosed in accordance with American

Table 1. – Anthropometric, lung function data, and $PC_{20}FEV_1$ values of 18 asthmatic subjects

Sex	Age yrs	Height cm	Weight kg	FEV1 % pred	VC % pred	PC20FEV1 mg·mL⁻¹
M	21	185	83	76	93	0.03
F	34	155	64	93	98	0.03
M	21	180	75	85	91	0.03
M	19	187	85	119	100	0.60
M	25	177	80	80	82	0.07
M	18	157	57	112	120	1.49
M	30	182	70	90	93	6.64
M	17	170	62	78	80	0.48
F	31	180	75	94	109	0.21
M	22	154	49	86	91	0.45
F	18	165	65	109	94	0.60
M	21	180	70	80	86	0.06
M	31	161	62	82	86	1.65
M	27	190	102	121	117	0.16
F	32	173	78	93	95	1.20
M	33	150	45	86	96	0.04
M	26	172	85	99	107	0.72
M	36	184	81	91	118	0.03
Mean	26	172	71	93	98	0.27*
±SD	6	12	14	14	12	

M: male; F: female; FEV1: forced expiratory volume in one second; VC: vital capacity; % pred: percentage of predicted value; PC20FEV1: cumulative provocative concentration of methacholine provoking a 20% fall of FEV1. *: geometric mean.

Thoracic Society (ATS) guidelines [10]. All subjects had a history of episodic wheezing and 12 were atopic. Anthropometric and lung function data of all subjects are presented in table 1. All subjects had baseline forced expiratory volume in one second (FEV_1) values above 75% of predicted. Subjects were asymptomatic and had not taken any medication for 2 weeks before the study. All subjects had been free of respiratory tract infections for at least 6 weeks prior to the study. No subject had ever had previous experience of sensory testing or was aware of the purpose of the study. The investigation was approved by the Research Ethics Committee of our hospital, and subjects gave their written consent to the methacholine provocation test.

Study design

After 5 min of resting breathing through the respiratory apparatus, subjects were asked to quantify their sensation of breathing effort by using a modified Borg scale. Thereafter, neuromuscular output was assessed by performing 10 measurements of mouth occlusion pressure ($P_{0.1}$). Three reproducible forced expiratory manoeuvres, from which FEV_1 values were derived, completed each set of measurements. The sensation of dyspnoea, $P_{0.1}$, and FEV_1 were measured at baseline and 3 min after inhalation of saline and of each methacholine concentration. Postsaline values were used as control values.

Methacholine challenge

Methacholine hydrochloride (MCh) was dissolved in a phosphate-buffered isotonic solution (NaH_2PO_4 1.808 g,

NaH_2PO_4 7.576 g and NaCl 4.4 g, in 1,000 mL of distilled water) and aerosolized using a Hudson nebulizer (Hudson Ltd, Temecula, CA, USA; output 0.16 mL·min⁻¹) driven by a compressed air source (20 pounds per square inch (psi)). Aerosols of phosphate-buffered saline and of doubling concentrations of MCh were inhaled at tidal breathing for 2 min periods. The starting concentration of MCh was 0.03 mg·mL⁻¹, and the challenge was ended when a 50% fall in FEV_1 was achieved or when the subject experienced excessive discomfort. The cumulative provocative concentration of MCh that provoked a 20% fall in FEV_1 ($PC_{20}FEV_1$) was computed by linear interpolation from the concentration-response curve.

Measurements

Subjects were seated in a comfortable chair, with their nose occluded by a noseclip, and breathed *via* a mouthpiece through a pneumotachograph (Fleisch No. 3; Dynasciences, Blue Bell, PA, USA) mounted in series with a two-way breathing valve. The apparatus dead space was 168 mL. Airflow (V') was measured by the pneumotachograph connected to a differential pressure transducer (Statham PM45 ±3.5 cmH₂O; Hato Rey, PR). Mouth pressure (P_m) was measured by means of a differential pressure transducer (143PC03D ±150 cmH₂O; Honeywell, Denver, CO, USA) connected through a noncompliant small-bore tube to the mouthpiece. Electrical signals of V' and P_m were amplified, filtered through a low-pass filter, converted into digital signals through a 12-bit analogue-to-digital converter (DT2801-A, Data Translation Inc., Marlboro, MA, USA) and sampled at 500 Hz using a personal computer. Data were stored on diskette for successive analysis.

$P_{0.1}$ was measured by occluding the inspiratory line of the breathing valve and by measuring the P_m generated during the first 0.1 s of the occluded inspiration. Occlusions were performed by silently turning a three-way tap during expiration so that the next inspiration was occluded from functional residual capacity. Occlusions were performed randomly so that the subject was not able to predict which breath would be occluded. Ten occlusions were performed, each being maintained for 0.25–0.30 s.

Sensation of dyspnoea was assessed by using a modified Borg scale [9]. This is a category scale in which verbal notations describing increasing levels of breathing effort are anchored to numbers from 0 (none) to 10 (maximal). Subjects were asked to score their perceived breathing effort by pointing to a number whose verbal notation most appropriately described intensity of their sensation at that particular time. Subjects were allowed to select either whole numbers or fractions, and they were carefully instructed to score only their sensation of breathing effort and to ignore other sensory perception, such as dry mouth or sore throat.

Data analysis

Values are reported as mean±SEM, unless otherwise stated. The dyspnoea rates observed after each MCh inhalation were related either to the corresponding percentage
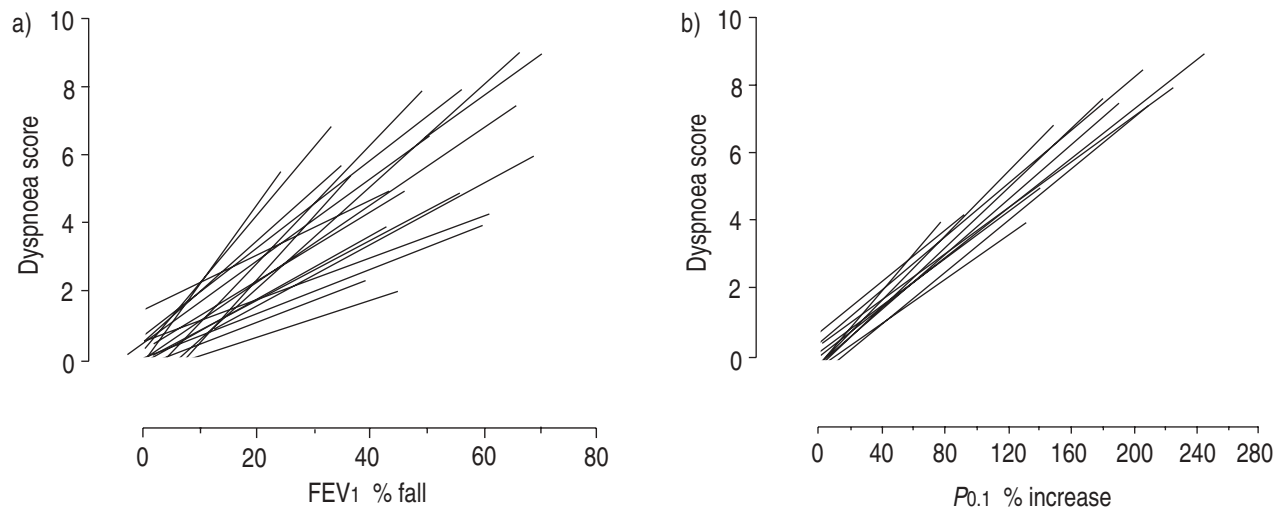
Fig. 1. – Individual regression lines between: a) percentage fall in FEV_1 and dyspnoea score; and b) between percentage increase in $P_{0.1}$ and dyspnoea score. FEV_1: forced expiratory volume in one second; $P_{0.1}$: mouth occlusion pressure.

fall in FEV_1 or to the corresponding percentage increase in $P_{0.1}$ by least squares linear regression. Coefficients of regression and slope values were calculated for each subject. The variability of the slope values of the relationships between dyspnoea score and changes in FEV_1 or $P_{0.1}$ were compared by analysis of variance (ANOVA). The intensity of dyspnoea perceived at the 20% fall in FEV_1 was linearly interpolated from the dyspnoea score *versus* percentage fall in FEV_1 plot. Statistical significance was accepted for p-values less than 0.05

Results

The progressive bronchoconstriction induced by MCh was associated with progressive increases both in dyspnoea score and $P_{0.1}$ values. In each subject, dyspnoea score was linearly related to the percentage fall in FEV_1, the individual coefficient of correlation ranging 0.72–0.99. The dyspnoea score was also linearly related to the percentage increase in $P_{0.1}$ in each subject (coefficient of correlation range 0.74–0.98). Correlations between dyspnoea score and percentage fall in FEV_1 or percentage increase in $P_{0.1}$ were calculated over at least five data points. The individual regression lines for dyspnoea score *versus* percentage change in FEV_1 or in $P_{0.1}$ are reported in figure 1. The individual slope values of the regression lines for dyspnoea score *versus* percentage change in FEV_1 showed a large variability (coefficient of variation (CoV) 43%) (fig. 2). In contrast, the variability of the slope values of the regression lines between dyspnoea score and percentage change in $P_{0.1}$ was significantly lower (CoV 14%; $p < 0.01$) (fig. 2).

The log-transformed values of $PC_{20}FEV_1$ were linearly related to the dyspnoea scores calculated at the 20% fall in FEV_1 ($r = 0.60$; $p < 0.01$), but not to the slope values of the relationship between dyspnoea and percentage fall in FEV_1 ($r = 0.39$ NS).

At the highest MCh concentration, dyspnoea score was linearly related to the corresponding percentage increase in $P_{0.1}$ ($r = 0.91$; $p < 0.01$), but not to the corresponding percentage fall in FEV_1 ($r = 0.28$, fig. 3).
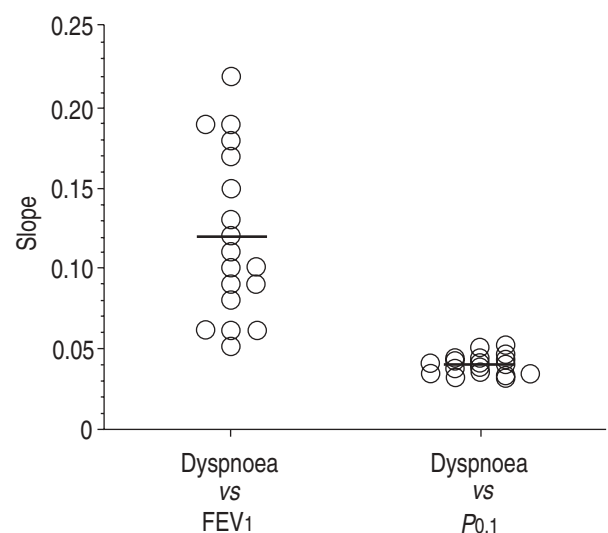

Fig. 2. – Individual slope values of the regression lines between dyspnoea score and percentage fall in FEV_1, and between dyspnoea score and percentage increase in $P_{0.1}$. For definitions see legend to figure 1.

Discussion

This study shows that the interindividual differences in dyspnoea perceived by asthmatic subjects for the same level of airway narrowing depend on different changes in respiratory drive during bronchoconstriction. In fact, we have demonstrated that the intensity of dyspnoea sensation experienced by asthmatic subjects during progressive bronchoconstriction induced by methacholine is related both to the magnitude of airway narrowing and the increase in neuromuscular output. We also observed, however, a large interindividual variability of the dyspnoea perceived at any given level of airway narrowing, indicating that the perception of dyspnoea during bronchoconstriction is highly variable among asthmatic subjects. In contrast, we observed a lesser interindividual variability of the relationship between dyspnoea and changes in neuromuscular output, thus indicating that during progressive bronchoconstriction, for the same
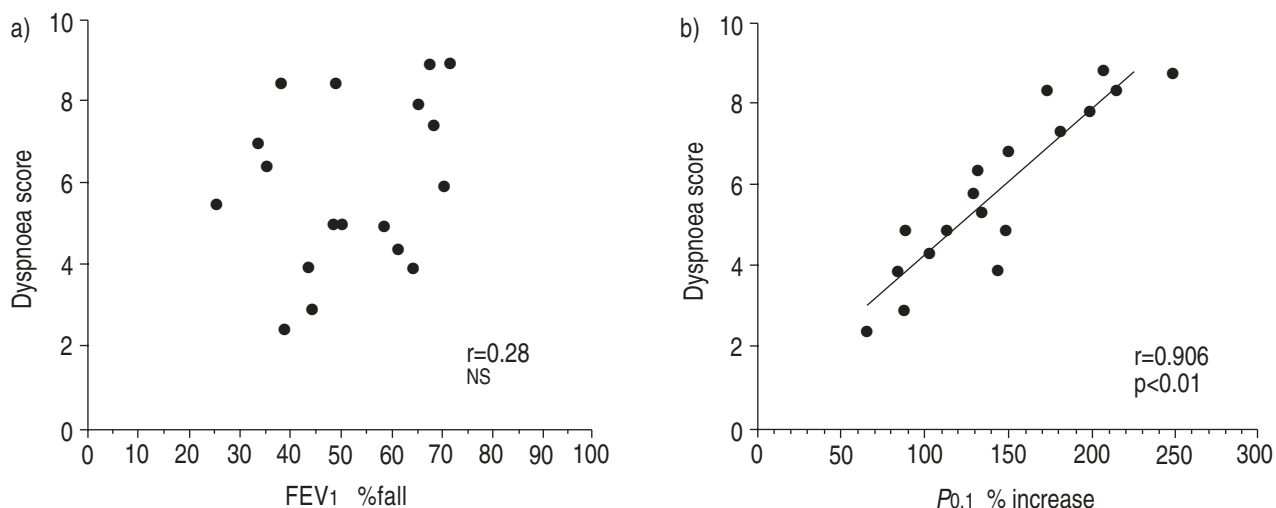
Fig. 3. – Relationship between: a) dyspnoea score and percentage fall in FEV1; or b) percentage increase in $P0.1$ measured at the highest concentration of methacholine. For definitions see legend to figure 1.

change in neuromuscular output the intensity of perceived dyspnoea is the same among different subjects. Of relevance to the interpretation presented here is the observation that at the maximal degree of bronchoconstriction there was a significant relationship between dyspnoea score and the corresponding changes of $P0.1$, whereas no correlation was observed between dyspnoea score and the percentage fall in FEV1 (fig. 3).

The large interindividual variability in dyspnoea response to progressive airway narrowing observed in our study is similar to that previously reported by other investigators [1, 2, 11, 12]. In particular, in the study by BURDON *et al.* [1], the average slope of the relationship between dyspnoea score, as measured by the Borg scale, and percentage fall in FEV1 was 0.13±0.06 SD, similar to the average value of 0.12±0.05 SD observed in our study (fig. 2). In addition, our data provide further insight into the relationship between dyspnoea and changes in airway calibre, in that we demonstrated that dyspnoea score and changes in FEV1 were linearly related not only at 20% fall in FEV1 as reported previously [1, 12] but also at higher levels of bronchoconstriction.

Although it has long been recognized that the dyspnoea associated with a given level of bronchoconstriction varies widely among subjects [3, 4], the determinants of this variability are still poorly understood. It has been suggested that the differences in resting airway calibre could account for the differences in the sensation of dyspnoea associated with bronchoconstriction. It has been shown that asthmatics with airway obstruction, but not asthmatics with normal airway calibre, have an impaired perception both of external resistive loads [5] and carbachol-induced bronchoconstriction [13]. These findings have been interpreted as the result of an adaptation to prolonged stimulation of structures or mechanisms giving rise to the sensation of dyspnoea. In contrast with this interpretation, it has been observed that the presence of moderate airflow obstruction does not result in a blunted sensation of dyspnoea to further bronchoconstriction induced by histamine [1]. Our findings that only some of the subjects with normal resting airway calibre had a low dyspnoea response to bronchoconstriction indicate that resting airway calibre *per se* does not account for the

variability in the perception of dyspnoea to progressive airway narrowing.

Another factor that has been suggested to be involved in the perception of dyspnoea is the degree of airway hyperresponsiveness. The significant relationship between the PC20FEV1 and the intensity of dyspnoea sensation at the 20% fall in FEV1 observed in this study, as well as in a previous study [1], indicates that subjects with higher airway hyperresponsiveness have a lower intensity of perceived dyspnoea during provoked bronchoconstriction. This finding has been interpreted as a tolerance to airway narrowing developed in response to increased frequency and severity of spontaneous asthma attacks [1]. On the other hand, it is also possible that subjects with higher hyperresponsiveness adopt breathing strategies that result in lower levels of dyspnoea.

Finally, recent evidence suggests that lung hyperinflation occurring during acute bronchoconstriction contributes to dyspnoea in asthma, and that the level of hyperinflation is partially responsible for the variability of perceived dyspnoea for a given level of bronchoconstriction [14]. This contribution of lung hyperinflation to perception of dyspnoea appears to be related to the changes in respiratory drive [14].

It is well-known that both spontaneous and provoked bronchoconstriction are associated with an increase in respiratory drive [6, 15]. The increase in $P0.1$ observed in the present study during MCh-induced bronchoconstriction was similar to that previously reported by others [6, 16], and by ourselves [7]. The increase in respiratory drive during bronchoconstriction has been suggested to be due to the activation of reflexes arising from muscular and joint receptors stimulated by hyperinflation [16, 17], and from airway receptors stimulated by inhaled substances and by bronchoconstriction [18–20]. The results of this study suggest that changes in respiratory drive are major determinants of the intensity of the sensation of dyspnoea experienced during progressive bronchoconstriction in asthmatic subjects. Our findings are in agreement with previous observations by KELSEN and co-workers [17]. These authors observed that both $P0.1$ and the sensation of breathing effort increased to a greater extent during MCh-induced bronchoconstriction than during

breathing against an external resistance, thus indicating that the sense of breathing effort is related to the intensity of the respiratory drive rather than to the resistive load applied to respiratory system. This is not surprising, in that it has been observed that asthmatic subjects adopt different ventilatory strategies in response both to airway narrowing [15, 21] and the addition of external resistive loads [17, 21]. On the other hand, it has been shown that the sensation of dyspnoea experienced during exercise [9], loaded breathing [8], or progressive bronchoconstriction [14] is a function of the intensity of respiratory drive. The importance of respiratory drive in determining the sensation of dyspnoea observed in our study is underlined by the recent observation that in patients with near-fatal asthma the reduced ability to perceive dyspnoea during resistive loading was associated to a blunted increase in $P0.1$ to hypoxia [22].

In summary, the results of the present study indicate that in asymptomatic asthmatic subjects, the dyspnoea elicited by progressive bronchoconstriction is linearly related to the degree of airway narrowing and to the magnitude of changes in neuromuscular output. Most importantly, this study also shows that the intensity of the sensation of dyspnoea for a given level of bronchoconstriction depends on the degree of activation of the neural motor command to the inspiratory muscles. These observations may have clinical implications in that they further support the concept that asthmatic subjects with blunted increases in respiratory drive, and therefore with lower intensity of dyspnoea perceived upon acute bronchoconstriction, are more prone to have fatal or near-fatal asthma attacks.

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