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Factors contributing to dyspnoea during bronchoconstriction and exercise in asthmatic subjects

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ABSTRACT: The purpose of the present study was to identify: 1) whether dyspnoea during bronchoconstriction and exercise is related, in asthmatic subjects; and 2) to what extent baseline pulmonary function and respiratory muscle strength contribute to dyspnoea under both conditions.

One hundred and seventy five consecutive subjects, referred with suspected asthma, rated the intensity of dyspnoea (Borg scale 0–10): 1) during the administration of doubling concentrations of methacholine to 32 mg·ml^{-1} methacholine, or until the baseline forced expiratory volume in one second (FEV_1) was reduced by 20%; and 2) during incremental cycle ergometry (100 kpm·min^{-1} each minute) to maximal capacity. 138/175 subjects achieved a 20% reduction in their baseline FEV_1; 18 of the 138 were excluded, 2 children and 16 with complicating pulmonary disorders (diffusing capacity of the lung for carbon monoxide (D_{LCO}) and/or total lung capacity (TLC) <70% predicted). The remaining 120 out of 175 constituted the study population. Dyspnoea following a 20% reduction in the baseline FEV_1 ($Dys_{20\%}$) was linearly interpolated, using the rating of dyspnoea and the FEV_1 at the two final concentrations of methacholine.

In the 120 asthmatic subjects, the mean intensity of dyspnoea was "moderate" (2.9, SD 1.91; Borg 0–10) and the intensity across subjects was not significantly related to baseline FEV_1, vital capacity (VC), FEV_1/VC, D_{LCO}, TLC and maximal static inspiratory pressure (MIP), alone or in combination. In the 120 asthmatic subjects, dyspnoea intensified significantly and independently with maximal power output (MPO), impairment in baseline pulmonary function (FEV_1, and D_{LCO}), inspiratory muscle strength, and $Dys_{20\%}$: Dyspnoea = 3.8+0.07 MPO % pred - 0.02 FEV_1 % pred - 0.016 D_{LCO} % pred - 0.02 MIP % pred + 0.19 ($Dys_{20\%}$) (r=0.72).

We conclude that asthmatic subjects who rate the intensity of dyspnoea high during bronchoconstriction also tend to report dyspnoea high during exercise. The high rating is not due to differences in baseline function.

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Clinicians have long suspected that dyspnoea varies widely in different subjects for the same severity of bronchoconstriction [1–5]. Psychophysical techniques to measure dyspnoea under standardized conditions of stimulation, using self-reported ratings, have not been widely used, because the ratings are considered suspect due to their variability. The averaged results across large groups of subjects are generally reliable in isolating factors contributing to dyspnoea, because positive and negative biases are balanced [6–8]. Hence, we conducted a formal psychophysical study to isolate the factors contributing to the variability in dyspnoea in asthmatic subjects.

One hundred and seventy five consecutive subjects, referred for methacholine challenge testing for suspected bronchial asthma, estimated the intensity of dyspnoea during induced bronchoconstriction and during incremental exercise, using the Borg scale. One hundred and twenty of the 175 subjects were considered to have asthma, based on hyperreactive responses to methacholine and the absence of other pulmonary disorders. We were particularly interested in the contribution of impaired baseline spirometry, diffusing capacity of the lungs for carbon monoxide (D_{LCO}) and inspiratory muscle strength to dyspnoea in these subjects. We were also interested in whether the asthmatic subjects who rated dyspnoea high during bronchoconstriction also rated dyspnoea high during exercise, and whether this was due to impairment in pulmonary and respiratory muscle strength.

Methods

Subjects

The study was carried out in 175 consecutive subjects (78 males, 97 females), referred for the measurement of

airway responsiveness to inhaled methacholine, because of suspected asthma. Inhaled bronchodilators were withheld for 12 h, oral bronchodilators for 24 h, and inhaled or oral steroids were continued.

Protocol and measurements

On arrival in the laboratory, the procedure and attendant risks were explained, and written informed consent was obtained. Height and weight were measured and age recorded. Baseline spirometry forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/VC ratio [9], single breath lung volume by helium dilution [10], DLCO [11], and maximal inspiratory pressure (MIP) were measured, and expressed as percentage of predicted normal values. Laboratory derived normal values were used for MIP: ($MIP=231\ Ht^{0.6459}\ (m)\ Age^{-0.3231}$, for males; and $MIP=154\ Ht^{0.6459}\ (m)\ Age^{-0.3231}$, for females; 95% confidence lower limit 60%)

Measurement of dyspnoea

The subjects were requested to rate discomfort experienced and associated with the act of breathing at each workload during exercise, and prior to each FEV_1 manoeuvre during the methacholine challenge test. The subject was free to interpret discomfort in any way he felt appropriate, and no further instructions were given. The subject rated the intensity of this discomfort by matching his subjective magnitude to a number on the Borg scale; the numbers on this scale are tagged to descriptive phrases, *e.g.* 0.5="very, very slight"; 2="slight"; 3="moderate"; 4="somewhat severe" *etc.* (fig. 1). Subjects were not restricted to the use of whole numbers.

Exercise test

The exercise test was a standardized incremental test, performed on an electrically-braked cycle ergometer [12]. The test was performed with electrocardiographic monitoring, under the supervision of a physician, and with defined criteria for stopping, such as serious cardiac arrhythmias, hypotension and electrocardiographic changes; termination of exercise by the supervising physician was not required in any patient. Before exercise, while seated comfortably on the cycle ergometer (Siemens Elema 370), subjects breathed for 1 min through a unidirectional valve (Hans Rudolph), with the expired air going to a universal exercise testing system (SensorMedics MMC Horizon System, Anaheim, CA, USA). After 1 min of loadless pedalling, subjects cycled at 60 revolutions·min^{-1}, at an initial power output of 100 kpm·min^{-1}. At the end of each minute, the power output was increased by 100 kpm·min^{-1}. Heart rate, blood pressure, ventilation, respiratory rate, and tidal volume were measured, and the subjects were asked to estimate the intensity of discomfort with breathing every minute, by matching their perceived discomfort to a number on the Borg scale. Subjects were encouraged to continue exercise until exhaustion. Maximal power output (MPO) was defined as the highest power output maintained for at least 30 s.

Because of the potential need for bronchodilator medication following the methacholine challenge, the exercise test was conducted 1–2 h prior to the methacholine challenge.

Baseline spirometry had returned to control values in all subjects prior to the methacholine challenge.

Methacholine inhalation

Methacholine inhalation was carried out according to the method described by COCKCROFT *et al.* [13]. Aerosols of the test solutions were generated by a Wright nebulizer, with an output of 0.13 ml·min^{-1}. After the initial control solution of phosphate buffered saline, doubling concentrations of methacholine (0.03–32 mg·ml^{-1}) were inhaled by tidal breathing for 2 min, at intervals of 5 min. The response was measured by a fall in FEV_1 at 0.5 and 1.5 min after the completion of the inhalation, and at 2 min intervals, if necessary, to record the lowest value after each inhalation. The test was stopped when the FEV_1 had fallen by >20%, or 32 mg·ml^{-1} of methacholine was delivered.

Analysis of results

Methacholine measurement

The intensity of dyspnoea experienced at a 20% drop in FEV_1($Dys_{20\%}$) was derived from a linear interpolation of dyspnoea and the FEV_1 recorded at the two final concentrations of methacholine (below and above that required to induce a 20% drop in FEV_1). $Dys_{20\%}$ was then used to characterize the patients. No attempt was made to curve fit the psychophysical relationship between FEV_1 and dyspnoea over the entire range of observed responses.

The provocative concentration of methacholine required to induce a 20% drop in FEV_1 (PC_{20}) was measured in the conventional manner from a linear interpolation of the FEV_1 against the logarithmic transformation of the methacholine concentration.

Exercise measurement

To compare dyspnoea at the same relative exercise intensity in all subjects, the rating of dyspnoea at 20, 40, 60, 80 and 100% of the predicted MPO was taken directly from the exercise record, and was linearly interpolated between consecutive loads where necessary; the rating of dyspnoea at maximal exercise, expressed as percentage of predicted MPO, was also taken from the record. Hence, six paired values were available in subjects who achieved a maximal power output >100% predicted, and the number of paired values was less in those subjects who failed to achieve their predicted power output.

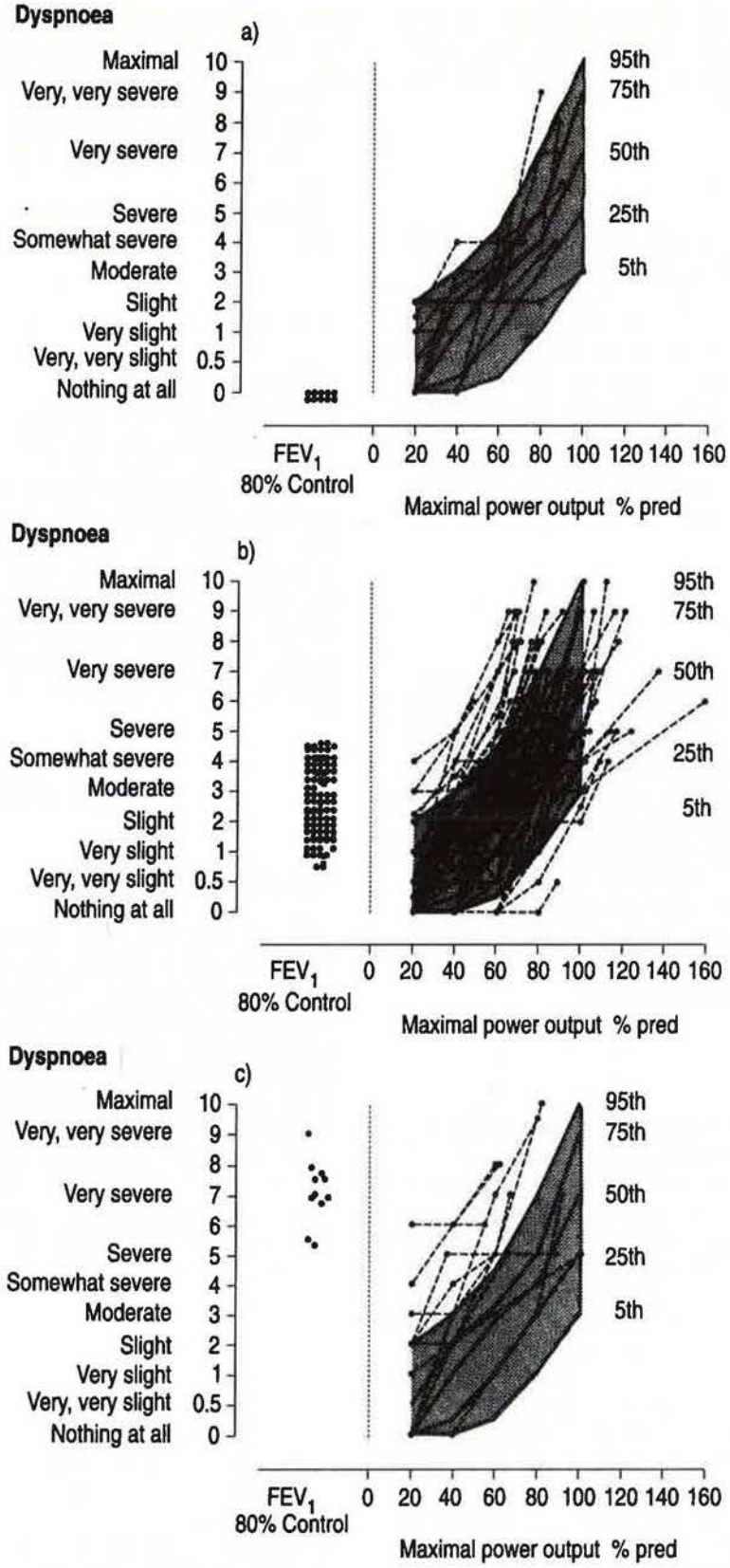

Fig. 1. – In the left panel, intensity of dyspnoea experienced at 80% of control forced expiratory volume in one second (FEV_1 80% ($Dys_{20\%}$) is plotted: a) Group 1 "low" asthmatic perception (dyspnoea 0, nothing at all); b) Group 2 "moderate" asthmatic perception (dyspnoea 0.5–5); and c) Group 3 "high" asthmatic perception (dyspnoea > 5) ratings. In the right panel, intensity of dyspnoea experienced during exercise is plotted *versus* levels of maximal power output, responses as % of predicted maximum. The shaded areas indicate the 95% confidence limits for the normal expected responses. Excessive dyspnoea during exercise was experienced in the subjects with higher asthmatic perception.

The predicted MPO (MPO% pred) for each subject was determined based on the normal expected power output for age, height and sex [14].

Selection criteria

Thirty seven of the 175 subjects did not achieve a 20% reduction in baseline FEV_1 and were rejected. One hundred and thirty eight of the 175 subjects achieved a 20% reduction in baseline FEV_1. Two of the 138 were less than 15 yrs old, and 16 of the 138 had other abnormalities of baseline pulmonary function, consistent with complicating pulmonary impairment, and so were also excluded. Analysis was conducted in 120 of the 175.

Statistical analysis

Linear and multiple linear regression analysis were used: 1) during bronchoconstriction, dyspnoea was the dependent variable and the FEV_1 expressed as percentage of baseline, baseline FEV_1, TLC, D_{LCO} and MIP were the independent contributors, alone and in combination; 2) during exercise, dyspnoea was the dependent variable and MPO%, baseline FEV_1, TLC, D_{LCO} and MIP the independent contributors; and 3) to analyse the interrelationship between dyspnoea during bronchoconstriction and exercise, dyspnoea during exercise was taken as the dependent variable and MPO%, baseline spirometry, TLC, D_{LCO}, MIP and $Dys_{20\%}$ (during bronchoconstriction) as the independent contributors. The partial F was calculated for each independent variable, and the p value was determined. For illustrative purposes, the 120 asthmatic subjects were divided into three groups, based on the intensity of dyspnoea during bronchoconstriction. Group 1 was asymptomatic, rating 0 (low). Group 2 rated dyspnoea from 0.5, "just noticeable", to 5, "severe" (moderate). Group 3 rated dyspnoea greater than 5 (high).

Results

Anthropomorphic characteristics, and baseline pulmonary function and exercise tolerance expressed as percentage of predicted normal values, are shown for the 120 asthmatics subjects in table 1.

Dyspnoea during bronchoconstriction

Dyspnoea intensified significantly but variably as the FEV_1 decreased:

Dyspnoea= 7.75 - 0.06 FEV_1 % control ($r=0.31$; $p<0.0001$).

The addition of baseline FEV_1, FEV_1/VC, TLC, D_{LCO} and MIP did not contribute to dyspnoea independent of the change in baseline FEV_1. There was no relationship between the intensity of dyspnoea following a 20% reduction in FEV_1 ($Dys_{20\%}$) and the measured PC_{20}, alone or in combination with the baseline factors.

Table 1. – Baseline characteristics of asthmatic subjects

	n	Mean	SD	Minimum	Maximum
Age yrs	120	44	15.8	16	76
FEV_1 % pred	120	80	18.5	31	138
VC % pred	120	89	17.6	44	147
FEV_1/VC %	120	74	9.0	32	93
MIP % pred	120	92	26.5	38	164
D_{LCO} % pred	118	99	16.5	72	149
TLC % pred	118	97	14.9	72	149
MPO % pred	120	84	20.5	31	159

Mean, SD, minimum and maximum values for age, forced expiratory volume in one second (FEV_1) vital capacity (VC), FEV_1/VC ratio, maximal inspiratory pressure (MIP), diffusing capacity of the lung for carbon monoxide (D_{LCO}), total lung capacity (TLC), and maximal power output (MPO) of the 120 asthmatic patients.

Dyspnoea and exercise

Dyspnoea intensified significant and independently with power output ($p<0.0001$), increasing impairment in pulmonary function (FEV_1, $p<0.0001$; D_{LCO}, $p<0.001$), and inspiratory muscle strength (MIP, $p<0.0001$), as described in the following multiple linear regression equation: Dyspnoea = 4.16 + 0.07 MPO % pred - 0.02 FEV_1 % pred - 0.015 D_{LCO} % pred - 0.02 MIP % pred ($r=0.71$).

Relationship between dyspnoea during bronchoconstriction and exercise

The subjects were characterized by the intensity of dyspnoea experienced during bronchoconstriction; $Dys_{20\%}$ ranged from 0–9. Dyspnoea intensified significantly and independently with power output ($p<0.0001$), and with increasing impairment in pulmonary function (FEV_1, $p<0.0001$; D_{LCO}, $p<0.001$) and inspiratory muscle strength (MIP, $p<0.0001$), and with $Dys_{20\%}$ ($p<0.0001$), as described in the following multiple linear regression equation: Dyspnoea = 3.8 + 0.07 MPO % pred - 0.02 FEV_1 % pred - 0.016 D_{LCO} % pred - 0.02 MIP % pred + 0.19 $Dys_{20\%}$ ($r=0.72$).

Dyspnoea ratings during exercise are shown in figure 1, superimposed on the normal expected responses (95% confidence limits) [15]; 10 out of 120 subjects were asymptomatic and rate dyspnoea 0, "nothing at all" (fig. 1a); 99 out of 120 rated dyspnoea "moderate", (range 0.5–5) (fib. 1b); and 11 out of 120 rated dyspnoea between >"severe" and "very, very severe" (range 5–9) (fig. 1c).

Whereas patients who indicated no dyspnoea during methacholine-induced bronchoconstriction experienced an intensity of dyspnoea during exercise, that was in the range expected in normal subjects (fig. 1a); most patients experiencing severe dyspnoea for the same fall in FEV_1, indicated an intensity of dyspnoea, during exercise, that was greater than 95% of the normal population (fig. 1c). Eighteen patients with moderate dyspnoea on bronchoconstriction were also excessively breathless on exertion

Table 2. – Characteristics according to dyspnoea$_{20\%}$

	Low Borg "0"	Moderate Borg 0–5	High Borg >5
n	10	99	11
Age yrs*	63 (2.8)	41 (1.5)	47 (4.0)
Sex M/F	5/5	42/57	5/6
FEV_1 % pred	76 (6.3)	80.4 (1.6)	82 (10.0)
VC % pred	89 (7.0)	88 (1.5)	89 (9.5)
FEV_1/VC%	69 (4.8)	75 (0.82)	73 (2.5)
TLC % pred	94 (4.7)	97 (1.5)	101 (6.2)
DLCO % pred	103 (6.2)	99 (1.6)	101 (5.9)
MIP % pred	81 (6.2)	94 (2.7)	86 (8.5)
MPO %	77 (6.3)	85 (2.1)	78 (6.2)
PC_{20}	3.9	3.1	2.8
Range	0.14–32	0.04–32	0.04–28.5

Characteristics according to dyspnoea status during bronchoconstriction ($Dys_{20\%}$). Mean and SEM (in parenthesis) for all parameters, except for the PC_{20}, where the median and range are given. *: statistical significance across the three groups ($p<0.05$).

(fig. 1b). There was no significant difference in height, sex, FEV_1, VC, FEV_1/VC, TLC, DLCO, MIP, PC_{20}, alone or in combination, between subjects. Subjects with low dyspnoea ratings were significantly older (table 2).

Discussion

Self-reported ratings of the intensity of dyspnoea were made during induced bronchoconstriction and exercise in 120 asthmatic subjects, in an effort to identify the factors contributing to increased dyspnoea in these settings. As expected, dyspnoea intensified during bronchoconstriction and during exercise. Dyspnoea was significantly more intense in subjects with impairment of baseline pulmonary function (FEV_1, DLCO) and inspiratory muscle strength (MIP) during exercise. Dyspnoea was not more intense in subjects with impairment of baseline pulmonary function (FEV_1, DLCO) and inspiratory muscle strength (MIP) during bronchoconstriction. This was surprising, but the induced bronchoconstriction was modest and the impairment in baseline function was modest. Excessive dyspnoea during bronchoconstriction was significantly related to excessive dyspnoea during exercise, and was not due to impairment in pulmonary or inspiratory muscle function. A heightened level of awareness to sensory stimuli was present in both conditions, perhaps due to anxiety.

Some comments are required about the conduct of the study. The study population was selected from 175 consecutive patients, referred for the measurement of bronchial reactivity (PC_{20}) because of suspected bronchial asthma. These subjects were referred by respiratory consultants operating in a university hospital. Not all patients were asthmatic. One hundred and thirty eight of the 175 subjects had a PC_{20} <32 mg·ml^{-1} methacholine (potentially asthmatic), and 37 of the 175 had a PC_{20} >32 mg·ml^{-1} and were unreactive (not asthmatic). The reactivity threshold value PC_{20} of 32 mg·ml^{-1} was taken, rather than the less sensitive but more specific threshold value of 8 mg·ml^{-1} because the presence of asthma was not essential. We were primarily interested in bronchoconstriction, and not in the dose at which it was achieved. Many of the patients were taking inhaled steroids, and the PC_{20} might have been lower without treatment. There was no relationship between the intensity of dyspnoea following a 20% reduction in FEV_1 ($Dys_{20\%}$) and the measured PC_{20}. Of the reactive subjects (138), two children were excluded because of concern regarding the ability to rate dyspnoea, and 16 had reductions in TLC and DLCO incompatible with uncomplicated asthma. The residual 120 out of 175 constituted the population on which the results are based.

Comment is also required regarding self-reported symptom ratings of dyspnoea as a measure of the intensity of dyspnoea. The subjects were simply requested to rate the intensity of discomfort experienced and associated with breathing, regardless of its qualitative features, by matching its intensity to a number on the Borg scale. Hence, the number and the intensity were considered synonymous for the purposes of the study. The subjects were free to select fractions if considered appropriate. The Borg scale (0–10) was used for the following reasons: 1) the scale is based on quantitative semantics familiar to everyone, and is easy to use [16–18]; 2) the tagging of the descriptive terms to numbers from 0–10 confers on the numbers absolute and ratio properties, and allows the use of conventional statistics [6, 19, 20]; and 3) the scale has proved to be reliable and successful in our hands in answering questions about sensory phenomena, such as the one addressed [15, 21–24]. The technique is not absolutely precise or reliable in all subjects, but in large numbers of subjects positive and negative rating biases are generally balanced, and it is sufficiently precise and reliable to identify and to reject factors contributing to dyspnoea. Magnitude scaling of dyspnoea in this way appeared to work, in that the intensity of dyspnoea increased during acute bronchoconstriction and exercise, and intensified with impairment in baseline pulmonary and inspiratory muscle function during exercise, in accordance with all reasonable expectations.

In this study, we controlled for sex, age and stature by expressing all values as a percentage of normal predicted. During exercise, dyspnoea intensifies with power output, is higher in females than males, increases with age, and decreases with stature [15]. The 95% confidence limits for dyspnoea expressed in this way are shown in figure 1 by the shaded areas. The population of 120 asthmatics has been illustrated in figure 1, based on the intensity of dyspnoea experienced during bronchoconstriction (low, moderate and high). The mean intensity of dyspnoea experienced after a 20% fall in baseline FEV_1 was close to "moderate". The low group was asymptomatic (Borg "0"); the middle group was moderate (Borg "0.5–5"); and the final group was high, (Borg ">5"). Baseline spirometry, MIP, sex or stature were not significantly different between the low, moderately symptomatic, and high groups. Older subjects were less symptomatic during bronchoconstriction (table 2). Baseline pulmonary and respiratory muscle function (FEV_1% pred, DLCO% pred and MIP% pred) did not contribute to the intensity of dyspnoea dur-

pred) did not contribute to the intensity of dyspnoea during bronchoconstriction. This was unexpected but was also found in a previous study of similar design [25].

Multiple linear regression analysis provides greater statistical power than analysis of variance. Hence, multiple linear regression was used, with sequential introduction of independent variables likely to contribute to dyspnoea. Direct measurement of pulmonary and chest wall impedance, ventilation, the efficiency of gas exchange, and inspiratory muscle strength would have been more direct, but all of these measurements were not possible. FEV_1, DLCO and maximal inspiratory muscle pressure (MIP) were used to reflect these factors indirectly, and contributed significantly to dyspnoea during exercise, as expected [26].

Central motor output, which is associated with a sense of effort [6, 21–23, 27], afferent activity from muscle spindles, joint receptors and tendon organs, which are associated with perceived force and displacement [28], and chemoreceptor stimulation [29–34] are the sensory receptors commonly postulated to contribute to dyspnoea [28]. While these receptors are stimulated in widely different patterns during exercise and bronchoconstriction, the perception of dyspnoea during bronchoconstriction, and the perception of dyspnoea during exercise, were significantly related, such that subjects excessively dyspnoeic during bronchoconstriction were also excessively dyspnoeic during exercise. To formally address this question, we isolated the intensity of dyspnoea following a 20% reduction in baseline FEV_1 in all subjects (range 0–9 on the Borg scale), and its magnitude was added as an independent contributor to dyspnoea during exercise, following the prior introduction of power output, FEV_1, DLCO and MIP. Its introduction constituted a significant independent contribution to dyspnoea during exercise ($p<0.0001$); for every Borg unit increase in dyspnoea experienced during bronchoconstriction, dyspnoea increased by 0.19 units on average during exercise. We interpreted this as a heightened awareness of sensory stimuli, which is a feature of anxiety. Ventilatory pattern was not measured, but an abnormal pattern of breathing is often noted in such patients, due to an aberrant behavioural response [2, 25].

The perceptual response to all sensory stimuli is dependent on the duration of the stimulus. Perceptual magnitude initially increases with the duration of stimulation, and is known as temporal accumulation. Perceptual magnitude decreases with prolonged duration, and is known as temporal adaptation. Temporal adaptation was extremely effective in minimizing the sensory consequences associated with chronic stimulation. The patients who had impaired baseline function were all asymptomatic prior to bronchoconstriction. Any patients referred for testing in an unstable state were stabilized prior to the conduct of the methacholine and exercise tests. Surprisingly, the baseline severity of bronchoconstriction had little influence on the symptomatic response to bronchoconstriction.

In summary, dyspnoea associated with methacholine induced bronchoconstriction and a reduction in FEV_1 by 20% was unaffected by differences in baseline pulmonary and/or respiratory muscle function in asthmatic subjects. Dyspnoea associated with exercise intensified as the baseline FEV_1, DLCO and MIP decreased in the same asthmatic subjects. Excessive dyspnoea during bronchoconstriction was associated with excessive dyspnoea during exercise, and could not be explained on mechanical grounds. The state of arousal, particularly the heightened state of arousal associated with anxiety, may be an important contributor to dyspnoea in these subjects.

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