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, were excluded, 120 out of 175 constituting the study population. Dyspnoea following a 20% reduction in the baseline FEV₁, (Dys₁₀₀) was linearly interpolated, using the rating of dyspnoea and the FEV₁ at the two final concentrations of methacholine.

In the 120 asthmatic subjects, the mean intensity of dyspnoea was "moderate" (2.9, so 1.91; Borg 0–10) and the intensity across subjects was not significantly related to baseline FEV₁, vital capacity (VC), FEV₁/VC, DLCO, 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 (FEV₁ and DLCO), inspiratory muscle strength, and Dys₁₀₀: Dyspnoea = 3.8±0.07 MPO % pred - 0.02 FEV₁ % pred - 0.016 DLCO % pred - 0.02 MIP % pred + 0.19 (Dys₁₀₀) (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. Eur Respir J., 1993, 6, 1004–1010.

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 (DLCO) 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 (FEV₁), FEV₁/VC ratio, forced expiratory volume in one second (FEV₁), FEV₁/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 He¹6⁰⁹₁ (m) Age⁻⁰·₂³⁰¹, for males; and MIP=154 He¹₆⁰⁹₁ (m) Age⁻⁰·₃₃³, for females; 95% confidence 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 FEV₁ 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 FEV₁, 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 FEV₁ 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 FEV₁(Dys₂₀) was derived from a linear interpolation of dyspnoea and the FEV₁ recorded at the two final concentrations of methacholine (below and above that required to induce a 20% drop in FEV₁). Dys₂₀ was then used to characterize the patients. No attempt was made to curve fit the psychophysical relationship between FEV₁ and dyspnoea over the entire range of observed responses.

The provocative concentration of methacholine required to induce a 20% drop in FEV₁ (PC₂₀) was measured in the conventional manner from a linear interpolation of the FEV₁ 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.
Dyspnoea

Maximal
Very, very severe
Very severe
Severe
Somewhat severe
Moderate
Slight
Very slight
Very, very slight
Nothing at all

Dyspnoea

Maximal
Very, very severe
Very severe
Severe
Somewhat severe
Moderate
Slight
Very slight
Very, very slight
Nothing at all

Dyspnoea

Maximal
Very, very severe
Very severe
Severe
Somewhat severe
Moderate
Slight
Very slight
Very, very slight
Nothing at all

Fig. 1. — In the left panel, intensity of dyspnoea experienced at 80% of control forced expiratory volume in one second (FEV₁, 80% [Dys₃₅]) 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 FEV₁ and were rejected. One hundred and thirty eight of the 175 subjects achieved a 20% reduction in baseline FEV₁. 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 FEV₁ expressed as percentage of baseline, baseline FEV₁, TLC, DLCO and MIP were the independent contributors, alone and in combination; 2) during exercise, dyspnoea was the dependent variable and MPO%, baseline FEV₁, TLC, DLCO 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, DLCO, MIP and Dyşnoea (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 asthmatic subjects in table 1.

Dyspnoea during bronchoconstriction

Dyspnoea intensified significantly but variably as the FEV₁ decreased:
Dyspnoea= 7.75 - 0.06 FEV₁ % control (p<0.0001).

The addition of baseline FEV₁, FEV₁/VC, TLC, DLCO and MIP did not contribute to dyspnoea independent of the change in baseline FEV₁. There was no relationship between the intensity of dyspnoea following a 20% reduction in FEV₁ (Dysnoea) and the measured PC₂₀, alone or in combination with the baseline factors.

### Dyspnoea and Exercise

Dyspnoea intensified significantly and independently with power output (p<0.0001), increasing impairment in pulmonary function (FEV₁, p<0.0001; DLCO, p<0.001), and inspiratory muscle strength (MIP, p<0.0001), as described in the following multiple linear regression equation:

\[
\text{Dyspnoea} = 4.16 + 0.07 \text{ MPO} \% \text{ pred} - 0.02 \text{ FEV₁} \% \text{ pred} - 0.015 \text{ DLCO} \% \text{ pred} - 0.02 \text{ MIP} \% \text{ pred} (r=0.71).
\]

### Relationship between dyspnoea during bronchoconstriction and exercise

The subjects were characterized by the intensity of dyspnoea experienced during bronchoconstriction; Dysnoea ranged from 0–9. Dyspnoea intensified significantly and independently with power output (p<0.0001), and with increasing impairment in pulmonary function (FEV₁, p<0.0001; DLCO, p<0.001) and inspiratory muscle strength (MIP, p<0.0001), as described in the following multiple linear regression equation:

\[
\text{Dyspnoea} = 3.8 + 0.07 \text{ MPO} \% \text{ pred} - 0.02 \text{ FEV₁} \% \text{ pred} - 0.016 \text{ DLCO} \% \text{ pred} - 0.02 \text{ MIP} \% \text{ pred} + 0.19 \text{ Dysnoea} (r=0.72).
\]

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) (fig. 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 FEV₁, 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.
One hundred and thirty-eight of the 175 asthmatic subjects, 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} (Dysp_{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; 2) the tagging of the descriptive terms to numbers from 0–10 conforms on the numbers absolute and ratio properties, and allows the use of conventional statistics; 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. 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.

Table 2. – Characteristics according to dyspnoea status during bronchoconstriction (Dysp_{20}). Mean and sex (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).

<table>
<thead>
<tr>
<th>Characteristics according to dyspnoea status during bronchoconstriction (Dysp_{20}).</th>
<th>Low Borg &quot;0&quot;</th>
<th>Moderate Borg 0–5</th>
<th>High Borg &gt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>99</td>
<td>11</td>
</tr>
<tr>
<td>Age yrs*</td>
<td>63 (2.8)</td>
<td>41 (1.5)</td>
<td>47 (4.0)</td>
</tr>
<tr>
<td>Sex F/M</td>
<td>5/5</td>
<td>42/57</td>
<td>5/6</td>
</tr>
<tr>
<td>FEV, % pred</td>
<td>76 (6.3)</td>
<td>80.4 (1.6)</td>
<td>82 (10.0)</td>
</tr>
<tr>
<td>VC, % pred</td>
<td>89 (7.0)</td>
<td>88 (1.5)</td>
<td>89 (9.5)</td>
</tr>
<tr>
<td>FEV/VC%</td>
<td>69 (4.8)</td>
<td>75 (0.82)</td>
<td>73 (2.5)</td>
</tr>
<tr>
<td>TLC, % pred</td>
<td>94 (4.7)</td>
<td>97 (1.5)</td>
<td>101 (6.2)</td>
</tr>
<tr>
<td>Dlco, % pred</td>
<td>103 (6.2)</td>
<td>99 (1.6)</td>
<td>101 (5.9)</td>
</tr>
<tr>
<td>MIP, % pred</td>
<td>81 (6.2)</td>
<td>94 (2.7)</td>
<td>86 (8.5)</td>
</tr>
<tr>
<td>MPO, %</td>
<td>77 (6.3)</td>
<td>85 (2.1)</td>
<td>78 (6.2)</td>
</tr>
<tr>
<td>PC_{20}</td>
<td>3.9</td>
<td>3.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Range</td>
<td>0.14–32</td>
<td>0.04–32</td>
<td>0.04–28.5</td>
</tr>
</tbody>
</table>

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} (Dysp_{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.

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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. 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-
Severity of bronchoconstriction had little influence on the and/or respiratory muscle function decreases with prolonged duration, and is known as temporal accumulation. 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 FEV1, DLO 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.

References

20. Borg G. Psychophysical studies of effort and exertion: some historical, theoretical and empirical aspects. In: The perception of physical exertion in physical work. Proceedings of