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*Original articles*

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## Perception of breathlessness during bronchoconstriction induced by antigen, exercise, and histamine challenges

Hélène Turcotte, François Corbeil, Louis-Philippe Boulet

### Abstract

Perception of breathlessness was studied in eight patients with mild, stable asthma after a histamine and exercise challenge performed before and 24 and 48 hours respectively after an antigen challenge. FEV<sub>1</sub> and perception of breathlessness, evaluated by Borg's 10 point category scale, were measured after each administration of doubling antigen or histamine concentrations to achieve a greater than 20% fall in FEV<sub>1</sub>, and after six minutes of steady state exercise at 80% of maximal oxygen consumption ( $\dot{V}O_{2,max}$ ). The geometric mean provocative concentration of histamine causing a 20% fall in FEV<sub>1</sub> (PC<sub>20</sub>) fell from 1.67 mg/ml before antigen challenge to 0.52 mg/ml 24 hours after the challenge. The median maximal % fall in FEV<sub>1</sub> with exercise was 24.9% (range 10.5-40.5%) before and 30.6% (range 13.8-52.3%) 48 hours after antigen challenge. The median maximum % fall in FEV<sub>1</sub> after antigen inhalation was 20.1% (range 13.3-35.2%) within the first hour; only two subjects had a late fall in FEV<sub>1</sub> (23% and 58%). The median (range) of Borg scores obtained when FEV<sub>1</sub> was reduced by 20% did not differ significantly for the three types of acute challenges: 1.25 (0.5-2.5) and 1.0 (0.5-3.0) after histamine tests, 1.0 (0.5-4.1) and 1.55 (0.5-2.0) after exercise, and 1.5 (0.3-3.0) after antigen challenge. In the two subjects who had a late response to antigen the Borg score was reduced for the same % fall in FEV<sub>1</sub> as with the early response. It is concluded that the perception of breathlessness does not differ appreciably during the early response to histamine, antigen exposure, or exercise, but that it is reduced during the late asthmatic response. It was not influenced by previous antigen exposure, despite an increase in airway responsiveness.

patients do not sense a major reduction in respiratory function, and others perceive a small change.<sup>1-4</sup> We do not know whether the perception of dyspnoea is affected by the stimulus responsible for the bronchoconstriction. Clinical observations have suggested that antigen may cause more dyspnoea for a given fall in FEV<sub>1</sub> than chemical agents such as histamine. The difference may be related to the type of airways constricted, the rapidity with which the constriction develops, or perhaps the presence or absence of an inflammatory component. There are no data on perception of bronchoconstriction during the late asthmatic responses. These responses may be underrecognised clinically if the perception of breathlessness is less at this time than during the early asthmatic response.

The aims of this study were to determine whether subjects with stable asthma perceive acute bronchoconstriction differently when it is induced by histamine, exercise, and antigen, and to determine whether the perception that follows histamine and exercise is altered when these are carried out after antigen challenge. We have also compared perception during the early and late asthmatic responses in two subjects with a dual response.

### Methods

#### SUBJECTS

Eight non-smokers with asthma (five of them female), aged 18 to 38 (mean 26) years took part in the study (table 1). They were recruited from the respiratory clinic at Laval Hospital, Quebec City. Subjects were studied while taking part in a study on the influence of exposure to antigen on the pattern of response to non-specific stimuli.

The subjects had mild stable asthma, controlled by a beta<sub>2</sub> agonist on an "as required" basis only. None was taking sodium cromoglycate, theophylline, inhaled corticosteroids or an oral antihistamine. All had a history of exercise induced asthma and all were atopic, with at least one positive skinprick reaction (weal diameter over 2 mm) on being tested with 26 common aeroallergens. The study was approved by the local ethics committee and all subjects gave written informed consent to the procedures.

Unité de Recherche,  
Centre de  
Pneumologie, Hôpital  
Laval, Hôpital et  
Université Laval,  
Sainte-Foy, Québec,  
Canada  
H Turcotte  
F Corbeil  
L-P Boulet

Address for reprint requests:  
Dr Louis-Philippe Boulet,  
Centre de Pneumologie,  
Hôpital Laval,  
2725 Chemin Sainte-Foy,  
Sainte-Foy, Québec,  
Canada G1V 4G5.

Accepted 12 September 1990

Patients with asthma show considerable variation in their perception of breathlessness for a given degree of bronchoconstriction. Some

Table 1 The subjects' characteristics

Patient No	Age (y)	Sex	FEV <sub>1</sub> (l (% pred))	FVC (l (% pred))	Source of antigen*	Baseline PC <sub>20</sub> (mg/ml)	PC <sub>20</sub> 24 h after antigen (mg/ml)
1	20	M	4.19 (96)	5.06 (95)	Cat	5.38	0.36
2	21	F	2.66 (82)	4.19 (105)	Cat	0.46	0.32
3	21	F	2.74 (81)	3.19 (79)	Grass	1.64	1.21
4	38	M	4.41 (106)	5.52 (101)	Cat	3.25	Saline
5	30	F	3.35 (99)	4.30 (101)	Cat	2.87	1.28
6	26	F	3.29 (103)	4.07 (102)	Dog	11.4	Saline
7	34	F	3.09 (101)	3.71 (101)	Ragweed	0.73	0.34
8	18	M	4.12 (88)	4.55 (82)	Cat	2.63	0.32
Geometric mean						1.67	0.52

\*The actual antigens were cat and dog epidermis and grass and ragweed pollen.

#### CHALLENGE TESTS

Non-specific airway responsiveness to histamine was measured according to the method described by Cockcroft *et al.*<sup>5</sup> After determination of baseline FEV<sub>1</sub> and forced vital capacity (FVC) the subject inhaled saline (0.9%) followed by progressive doubling concentrations of histamine (0.03–8 mg/ml) to obtain a 20% fall in FEV<sub>1</sub>. Histamine aerosols were generated by a Wright nebuliser and inhaled for two minutes at five minute intervals. The FEV<sub>1</sub> was measured 30, 90, and 120 seconds after each inhalation or until it started to increase. The provocative concentration of histamine giving a 20% fall in FEV<sub>1</sub> (PC<sub>20</sub> FEV<sub>1</sub>) was obtained by interpolation of the last two points on the log concentration-response curve.

A six minute steady state exercise test was carried on a cycle ergometer at 80% of the maximum oxygen consumption ( $\dot{V}O_2$  max) determined on a previous visit.<sup>6,7</sup> The FEV<sub>1</sub> was measured before and 1, 3, 5, 7, 10, 12, 15, 20, 25, 30, 40, 50, 60, 90, and 120 minutes after exercise, and then hourly for 7–8 hours. Change in FEV<sub>1</sub> was expressed as % fall from baseline FEV<sub>1</sub>.

An antigen challenge was carried out with cat epidermis in five subjects and dog epidermis and grass and ragweed pollen in one each (Omega Laboratories, Montreal). Antigen was diluted in 0.9% saline without preservative. The initial concentration of antigen inhaled was determined according to the method of Cockcroft on the basis of skin test titration and the PC<sub>20</sub> histamine.<sup>8</sup>

Antigen challenge was performed in a provocation chamber as described previously.<sup>9</sup> Aerosols were generated by a Wright nebuliser with an output of 0.13 ml/min. Doubling concentrations of antigen were inhaled for 30 seconds at 10 minute intervals, until the FEV<sub>1</sub> had fallen by more than 15% from baseline or until the undiluted concentration was given. The FEV<sub>1</sub> was measured before each dose of antigen; 10, 20, 30, 40, 50, 60, 90, and 120 minutes after each dose; and every hour up to 6–8 hours after the final dose of antigen.

The intensity of breathlessness was measured before each measurement of FEV<sub>1</sub> with a modified Borg scale labelled from 0 (no symptoms) at one end to 10 (maximum bearable) at the other, the subjects pointing to a category on a vertical list.<sup>10</sup> Measurements were made before and after each inhalation of histamine or antigen and before and after

exercise. Borg scores corresponding to a fall in FEV<sub>1</sub> of 20% were calculated by interpolation and in a few cases by extrapolation.

#### PROTOCOL

Before the tests inhaled beta<sub>2</sub> agonists were withheld for at least eight hours. The test was postponed if baseline FEV<sub>1</sub> was less than 65% of predicted normal. Temperature was kept constant in the laboratory at 22 ( $\pm 2$ )°C and humidity at 40% ( $\pm 10$ %) during the study. All tests started in the morning between 0800 and 0900 hours. During the study subjects stayed in the laboratory, withheld all medication, and took no caffeine.

On day 1 a histamine challenge test was carried out and on day 2 an exercise challenge test. An antigen challenge was then carried out on day 3 followed by a further histamine challenge 24 hours and an exercise challenge 48 hours after the antigen challenge ("histamine 2" and "exercise 2").

#### ANALYSIS

PC<sub>20</sub> was measured from individual histamine log dose-response curves, and geometric mean values were calculated. PC<sub>20</sub> values for the first and second tests (H1 and H2) and the % falls in FEV<sub>1</sub> after the first and second exercise tests were compared by paired *t* tests. Borg scores at a 20% fall in FEV<sub>1</sub> after the two histamine inhalation tests, exercises, and the antigen inhalation test were compared by Friedman non-parametric tests. Values are expressed as medians with ranges or means with standard errors. A *p* value of less than 0.05 was taken as significant.

#### Results

Individual baseline FEV<sub>1</sub> values before the study ranged from 81% to 106% and FVC from 79% to 105% predicted. Mean pre-challenge FEV<sub>1</sub> did not differ significantly on the study days. In individual subjects FEV<sub>1</sub> changed by less than 20% on the different days except for subject 1, whose prechallenge FEV<sub>1</sub> values before histamine 2 and exercise 2 were 67% and 76% of the initial baseline value (table 1).

#### ANTIGEN CHALLENGE

The maximum % fall in FEV<sub>1</sub> after antigen challenge ranged from 13.3 to 35.2 and occurred between five and 40 (median 20)

Figure 1 Perception of bronchoconstriction after antigen challenge: FEV<sub>1</sub> (◇) (median ◇; range light shading) and Borg scores (◆) (median ◆; range dark shading).

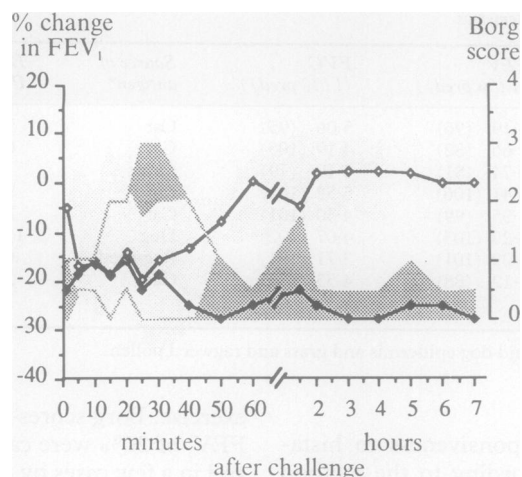
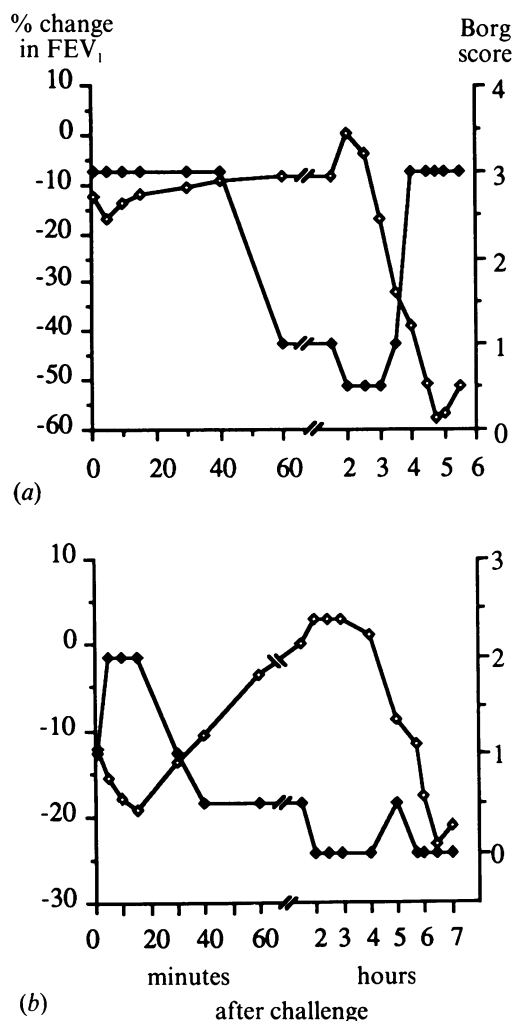


Figure 2 Relation of FEV<sub>1</sub> (◇) to Borg score (◆) during a dual asthmatic response after antigen challenge in subjects 1 (a) and 2 (b).



minutes. The maximum fall in FEV<sub>1</sub> for the group occurred at 25 minutes (median 19.6, range 8.0–33.0) and at this time the median Borg score was 0.50 (range 0–3). In the six subjects who did not have a late bronchoconstrictor response the perception of breathlessness started to decrease before the FEV<sub>1</sub> started to recover and the mean Borg score remained under 0.3 (median <0.25) between two and eight hours after the challenge (fig 1).

Two subjects (Nos 1 and 2) had a late response to antigen. In these subjects the early asthmatic response was associated with a 17.2% and 19.3% fall in FEV<sub>1</sub> and a Borg score of 3 and 2 respectively. Subject 1 had a late fall in FEV<sub>1</sub> of 57.8% with a corresponding score of 3 on the Borg scale (fig 2a). Subject 2 had a late fall in FEV<sub>1</sub> of 23.3% and a Borg score of 0 (fig 2b).

#### HISTAMINE CHALLENGE

The geometric mean baseline PC<sub>20</sub> histamine was 1.67 mg/ml (range 0.46–11.4 mg/ml). This fell after antigen exposure to a mean value of 0.52 (range 0.32–1.28) mg/ml ( $p < 0.05$ ); in two subjects FEV<sub>1</sub> fell by more than 20% after inhalation of saline 0.9%. The median Borg score for a 20% fall in FEV<sub>1</sub> was 1.25 (range 0.5–3.0) during the first histamine test and 1.0 (range 0.5–3) min during the second challenge (table 2). It was zero in most subjects before the tests, though a few scored 0.5.

#### EXERCISE CHALLENGES

After the first exercise test the maximum % fall in FEV<sub>1</sub> for each subject ranged from 10.5 to 40.5 (median 25.2) and occurred between three and 12 minutes. The maximum % fall in FEV<sub>1</sub> for the group occurred at five minutes (median 22.3, range 3.9–40.5). The Borg score was highest (median 2.5, range 0.5–5) immediately after the end of exercise and started to rise before the FEV<sub>1</sub> had fallen to its lowest level. There was no late response after the first exercise test (fig 3).

The maximum % fall in FEV<sub>1</sub> following the second exercise 48 hours after antigen varied from 13.8 to 52.3 (median 30.6) and occurred between three and 20 minutes. The maximum % fall for the group occurred at 10 minutes (median 25.0, range 11.7–39.8). This did not differ significantly from the fall in FEV<sub>1</sub> in the first exercise test. Before exercise 2 the Borg score was 0 in six subjects, 0.5 in one, and 1.0 in subject 1 (median 0). It increased to a maximum (median 2.0, range 0.5–4) three minutes after the end of exercise. Breathlessness then decreased progressively (fig 4a).

Subject 1 showed a late bronchoconstrictor response after exercise. The early bronchoconstriction was associated with a fall in FEV<sub>1</sub> of 52.3% and a Borg score of 4; the late response was associated with a Borg score of only 0.5 despite a fall in FEV<sub>1</sub> of 20.4% (fig 4b).

#### COMPARISON OF BORG SCORES WITH DIFFERENT TESTS

Although there were variations between individuals in the perception of breathlessness from one test to another, there were no sig-

Table 2 Borg scores for a 20% fall in FEV<sub>1</sub>

Subject No	H1	Ex1	Ag	H2	Ex2
1	2.5	4.1	3.0*	2.8	2.0
2	1.0	1.0*	2.0	1.0	1.7
3	1.5	2.1	2.0	3.0	2.0
4	1.2	0.8	1.0	1.0	1.5
5	0.5	1.0*	0*	1.0	0.7
6	0.5	1.0	0.5	1.5	0.5*
7	1.8	0.5*	2.0*	0.5	1.6
8	1.0	0.5	0.5	0.5	0.5
Median	1.25	1.0	1.50	1.0	1.55
Range	0.5–2.5	0.5–4.1	0.3–3.0	0.5–3.0	0.5–2.0

H—histamine test; Ex—exercise test; Ag—antigen challenge.

\*Borg score calculated by extrapolation.

Figure 3 Percentage change in FEV<sub>1</sub> from baseline (median  $\diamond$ ; range light shading) and Borg scores (median  $\blacklozenge$ ; range dark shading) in the eight subjects after the first steady state exercise.

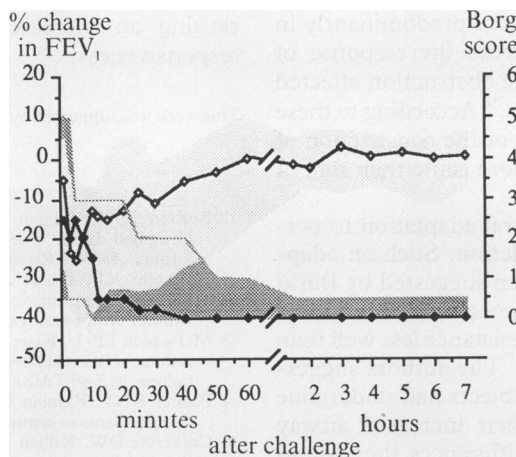
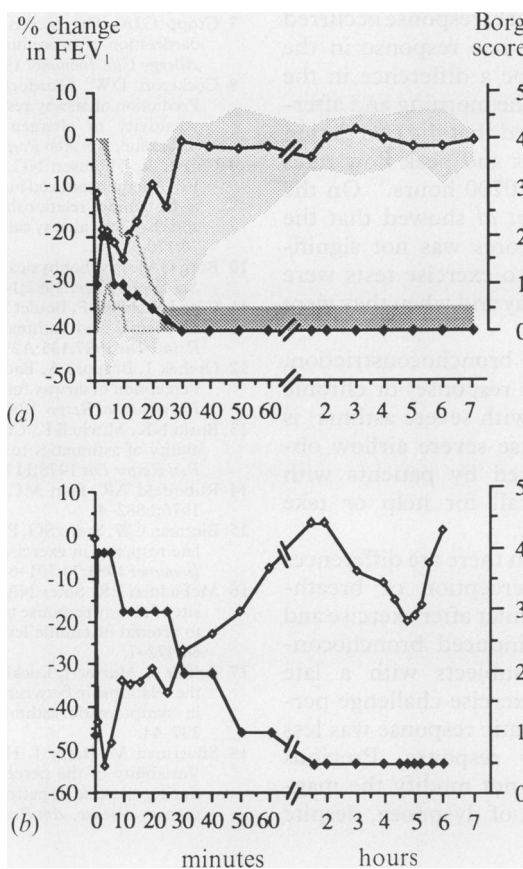


Figure 4 (a) Percentage change in FEV<sub>1</sub> ( $\diamond$ ) from baseline (median  $\diamond$ ; range light shading) and Borg scores ( $\blacklozenge$ ) (median  $\blacklozenge$ ; range dark shading) in the seven subjects without late bronchoconstriction after the second steady state exercise challenge. (b) Subject 1: Immediate and late bronchoconstriction after the second exercise challenge. The first bronchoconstriction was well perceived but the late fall in FEV<sub>1</sub> was not.



nificant differences in the median (range) of Borg scores obtained when FEV<sub>1</sub> was reduced by 20% for the three types of acute challenges: 1.25 (0.5–2.5) and 1.0 (0.5–3.0) after histamine tests, 1.0 (0.5–4.1) and 1.55 (0.5–2.0) after exercise and 1.5 (0–3.0) after antigen challenge (Friedman test,  $p > 0.05$ )—(see table 2).

**Discussion**

Our results show that, for a similar degree of induced bronchoconstriction, perception of breathlessness does not differ significantly after exercise or histamine or antigen inhalation. The perception of late asthmatic responses was, however, less than that of the early response in the two subjects with a late response. We conclude that exposure to antigen

does not modify the dyspnoea due to bronchoconstriction induced by exercise or histamine.

Although the perception of breathlessness for a given reduction in FEV<sub>1</sub> varied in the same subject for different challenges, the differences overall were not statistically significant. We also found, as reported previously, a wide variability between subjects in the intensity of breathlessness for the same degree of bronchoconstriction.<sup>1</sup>

Although the Borg scores were in the lower range of perception (usually less than 3), they were consistent in a given subject during a given challenge and they enable us to draw some conclusions about the perception of mild to moderate bronchoconstriction. The target fall in FEV<sub>1</sub> was at least 20% and in many cases the bronchoconstriction was more severe.

We asked the subjects to score only the sensation of breathlessness. After exercise various sensations from physical discomfort could, however, have influenced scoring of perceived breathlessness.

Burdon *et al* have suggested that the perception of breathlessness is associated with the degree of bronchial hyperresponsiveness to histamine, the more hyperresponsive subjects being poorer perceivers than those with a higher PC<sub>20</sub>.<sup>1</sup> Like Côté *et al*,<sup>11</sup> however, we found no relation between bronchial responsiveness to histamine and the intensity of breathlessness for a given fall in FEV<sub>1</sub>, though our subjects had only mild asthma. Such a relation may be detected only when subjects with a large difference in airway responsiveness are compared. In the current study we found no difference in perception of breathlessness for a given degree of airflow obstruction, even when the PC<sub>20</sub> histamine decreased in a subject after antigen challenge.

Late asthmatic responses following antigen challenge (two subjects) and exercise (one subject) were not perceived as well as early asthmatic responses. The late response following the antigen challenge was not perceived until 90 minutes after the onset of the fall in FEV<sub>1</sub> and the late bronchoconstrictor response after exercise was not perceived at all.

This impaired perception of the late response to antigen could be due to many factors. It was not due to differences in initial baseline airway obstruction in our study because in all cases there was a complete recovery from the fall in FEV<sub>1</sub> before the onset of the late response. Airways obstruction may impair the perception of changes in bronchial tone and the detection of inspiratory resistive loading.<sup>12–14</sup> The reduced perception of breathlessness after the late response could be due to differences in the type of airways constricted.

In a study designed to characterise the late response in exercise induced asthma, Bierman *et al* attempted to identify the airways affected in the immediate and the late response.<sup>15</sup> Their data suggest that both large and small airways were constricted in the early response whereas small airways appeared to be constricted primarily in the late response. McFadden *et al* found that when the response of asthmatic subjects to the exercise provocation test was

less severe the changes were predominantly in the larger airways, whereas the response of subjects with more severe obstruction affected mostly peripheral airways.<sup>16</sup> According to these observations, perception of the constriction of large airways could be more acute than that of peripheral airways.

There could be temporal adaptation to perception of airway obstruction. Such an adaptive mechanism has been suggested by Burki *et al* who found that asthmatic patients appear to detect an inspiratory resistance less well than non-asthmatic subjects.<sup>13</sup> The authors suggested that the asthmatic subjects had undergone chronic adaptation to their increased airway resistance, though the differences they found were not statistically significant.

Another difference between the early and the late response is that the early response occurred in the morning and the late response in the afternoon; there might be a difference in the quality of perception in the morning and afternoon. Peiffer *et al* reported that the correlation between dyspnoea scores and peak flow rates was less at 1500 than at 0700 hours.<sup>17</sup> On the other hand, Silverman *et al* showed that the variability in sensory scores was not significantly different when two exercise tests were performed on the same day and when they were done on different days.<sup>18</sup>

Altered perception of bronchoconstriction, whether short term (late response) or chronic (as in some individuals with severe asthma) is clinically relevant because severe airflow obstruction may be ignored by patients with consequent failure to call for help or take medication appropriately.

In conclusion, although there are differences between individuals, perception of breathlessness was generally similar after exercise and histamine and antigen induced bronchoconstriction. In the two subjects with a late response to antigen or exercise challenge perception of the late asthmatic response was less than that of the early response. Previous exposure to antigen did not modify the magnitude of the perception of dyspnoea, despite

causing an increase in non-specific airway responsiveness.

This work was supported by the Quebec Lung Association.

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