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Changes in neural drive (EMGd) and neuromuscular coupling during histamine-induced bronchoconstriction in patients with asthma

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ABSTRACT: This study was undertaken in order to assess the neural drive to the respiratory muscles and the inspiratory neuromuscular coupling in patients with bronchial asthma during histamine-induced bronchoconstriction. Bronchoconstriction was produced in a graded fashion, with histamine phosphate aerosol of increasing dose, in twelve asymptomatic asthmatic patients and was measured by FEV_1. Inspiratory drive was measured by electromyographic activity of the diaphragm (EMGd) and the coupling of the neural drive to the respiratory muscles was assessed by the relationship of mouth occlusion pressure ($P_{0.1}$) to EMGd. During the test we also measured electromyographic activity of the inspiratory intercostal (EMGint), sternomastoid (EMGsm) and expiratory abdominal (EMGab) muscles. Histamine caused a significant decrease in FEV_1, a significant increase in $P_{0.1}$, EMGd, EMGint, and a relevant increase in EMGsm, with no substantial increase in EMGab. An inverse significant relationship between the change in FEV_1 and changes in $P_{0.1}$, EMGd and EMGint and a significant correlation between the change in FEV_1 and in the $P_{0.1}$/EMGd ratio were observed. We conclude that a progressive increase in bronchospasm is accompanied by a progressive increase in respiratory neural drive and decrease in neuromuscular coupling. This could be caused both by an increase in lung volume and a lack of abdominal expiratory muscle recruitment.

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Neuromuscular inspiratory drive, assessed by mouth occlusion pressure ($P_{0.1}$) [1], is enhanced in patients with bronchial asthma, during both spontaneous [2] and induced bronchoconstriction [3, 4]. Mouth occlusion pressure ($P_{0.1}$) represents the product of neural drive to, and the resulting output force of, the respiratory muscles [1]. As this output depends on both length-tension and geometrical characteristics of the respiratory muscles [1, 5, 6], $P_{0.1}$ does not allow the assessment of neural drive to the respiratory muscles when changes in lung volume and chest-wall configuration occur [5–10]. Unlike $P_{0.1}$, electromyographic activity of the diaphragm (EMGd) allows the measurement of neural inspiratory drive to be taken [6, 8–17]. However, to our knowledge, no data exist concerning assessment of neural inspiratory drive by EMGd in patients with asthma during spontaneous or induced bronchoconstriction.

In normal man, the relationship between $P_{0.1}$ and EMGd allows the assessment of neuromuscular coupling, that is the neuromuscular inspiratory efficiency [6, 10, 14, 15].

In a previous paper [4] we found that $P_{0.1}$ increased in patients with asthma during histamine-induced bronchoconstriction. The present report was undertaken in patients with asthma in order to quantify the neural drive to the respiratory muscles and the neuromuscular coupling assessed by $P_{0.1}$ to EMGd ratio during histamine-induced bronchoconstriction.

Materials and methods

We studied twelve asymptomatic patients (seven males and five females; mean age 38 ± 10 yr). Asthma was diagnosed on the basis of the American Thoracic Society (ATS) criteria [18]. Eight of the twelve patients had biological findings of atopic asthma, as shown by immediate skin test reactions to an allergenic extract of either mite or cat. None of them had a current respiratory infection or had received any treatment in the 24 h preceding the test. Smokers were excluded.

Functional evaluation included routine pulmonary function tests by a water sealed spirometer (Pulmonet Godart). The normal values for lung volumes are those proposed by the European Community for Coal and Steel [19].

Mouth occlusion pressure against an occluded airway 0.1 s after the onset of inspiration, at functional residual capacity (FRC) ($P_{0.1}$) [1] was obtained as described previously [4, 10, 20]. This measurement is considered to be an index of the total inspiratory muscle output [6, 14, 15].

The measurement of the neural respiratory drive was assessed by electromyographic activity (EMG) of the respiratory muscles: diaphragm (EMGd), inspiratory intercostal (EMGint) in ten cases, sternomastoid (EMGsm) in five cases, and external oblique (EMGab). EMG was recorded by means of surface electrodes placed on the 6th to 7th intercostal spaces (EMGd), as proposed by GROSS *et al.* [13], on the second parasternal intercostal space (EMGint), on the sternomastoid (EMGsm), and on the external oblique a few centimetres below the umbilicus (EMGab). Muscle action potentials were differentially amplified and filtered between 80 and 1000 Hz in order to remove as much of the electrocardiogram signal as possible without significantly filtering EMG. EMG activity was then full-wave rectified and 'integrated' over time (time constant 200 msec) using a third order low-pass filter, in order to provide a measure of the change in average electrical activity as a function of time, referred to as 'moving time average' ($\bar{X}$) [14]. This method of analysis allows the description of the time course of inspiratory muscle activity, which shows a definable rate of increase reaching a peak of amplitude and then rapidly decreasing. Inspiratory activity was quantified both as peak activity ($\bar{X}P$) and rate of rise of inspiratory activity (slope). The $\bar{X}P$ amplitude was measured directly in cm and the slope was obtained by dividing $\bar{X}P$ by the inspiratory time of the respiratory cycle ($\bar{X}P/TI$). According to LOPATA *et al.* [14] slope activity ($\bar{X}P/TI$) may reflect actual inspiratory drive and peak activity ($\bar{X}P$) may reflect the inspiratory off-switch threshold.

As the EMG activity of an inspiratory muscle may include cardiac muscle activity, we checked for cardiac artefacts in order to manually gate the electrocardiogram signal from the EMG to ensure that the electrocardiogram was not contributing to the progressive increase of EMG.

Patients were studied under control conditions over a twenty minute period, firstly during inhalation of placebo (propellant) and then during a challenge-test with histamine from a metered-dose inhaler (MDI), which delivered 100 μg per puff, following a procedure described previously [4].

When a single dose of histamine was unable to reduce forced expiratory volume in one second (FEV_1) by more than 20% of control values, doubled doses of histamine phosphate were inhaled by the patient 10 min later, and at each following doubled dose, the measurements of respiratory cycle, $P_{0.1}$, EMG and FEV_1 were repeated. In four patients the first provocative dose of histamine (HPD) which caused a significant decrease in FEV_1 (>20% of the control value) was followed by further (two-fold) provocative doses which caused a further decrease in FEV_1; in the remaining eight patients clinical symptoms were induced by a single HPD. In each instance the test was held at the dose of histamine that caused expiratory wheezing, a sensation of respiratory distress and a significant decrease in FEV_1 (Hmax). The largest dose of inhaled histamine did not exceed 800 μg. During the histamine challenge test the patient was asked not to take deep breaths until respiratory cycle, $P_{0.1}$ and EMG had been recorded; then three consecutive forced expiratory manoeuvres preceded by a deep inspiration were made and an average FEV_1 value was calculated.

After each dose of histamine delivered, the patient breathed over five consecutive minutes and during this period of time all of the respiratory cycle, $P_{0.1}$ and EMG activities were recorded; this enabled us to measure ten to fifteen random occlusions for each step. Recording of three consecutive FEV_1 measurements followed the last occlusion.

For each subject the values calculated were the mean of: 1) approximately 50 random occlusions recorded under control conditions during the twenty minutes following the adaptation period; 2) all consecutive $P_{0.1}$ and EMG ($\bar{X}P/TI$) recorded over five minutes, two minutes after every dose of inhaled histamine. In order to eliminate the possible artefacts induced by occlusions the EMG that followed occlusion was not considered. The reproducibility of the histamine challenge test has been reported previously [4].

Changes in FEV_1 and $P_{0.1}$ with histamine are expressed in percentage of the prehistamine values. EMG activity ($\bar{X}P/TI$) of the respiratory muscles is presented either in actual value (arbitrary units, AU) obtained by dividing $\bar{X}P$ amplitude (in cm) by inspiratory time (in sec) (fig. 1) or in percentage of the prehistamine values (fig. 2).

To assess the coupling of inspiratory drive to output force of inspiratory muscles [6, 15] during each step of the histamine challenge test, changes in $P_{0.1}$ were plotted against changes in EMGd, for each subject.

In a complementary study, carried out in two patients, we compared surface EMGd and oesophageal EMGd activity. Oesophageal EMGd activity was recorded by means of a bipolar oesophageal electrode (DISA 13K63). An oesophageal lead was passed through the nose, positioned to obtain an optimal and reproducible signal to noise ratio at tidal volume and maximal inspiration, and then fixed at the nose with tape.

All results were compared by Student's paired t-test when variances were equal, and by the Wilcoxon test when variances were unequal. Regression analysis of the data was performed by the least-squares method.

Results

Functional data of the patients are summarized in table 1. The FEV_1/VC (vital capacity) ratio was found to be significantly decreased in seven patients

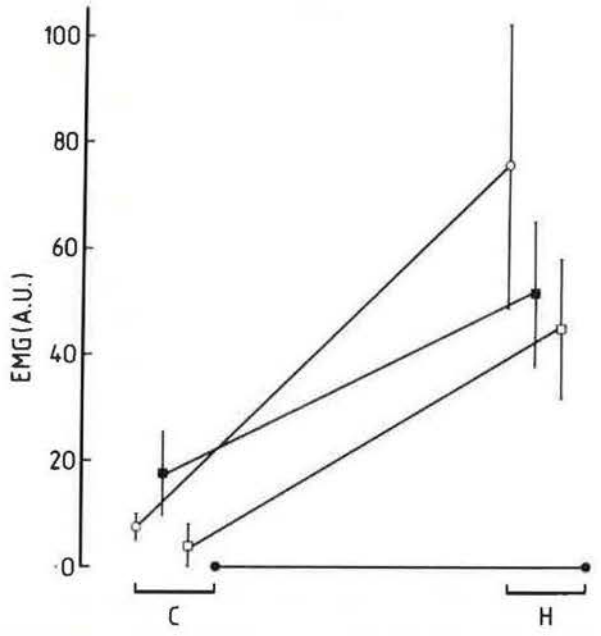


Fig. 1. Average EMG activity of the diaphragm (EMGd, ○——○), intercostal (EMGint, ■——■), sternomastoid (EMGsm, □——□), and abdominal (EMGab, ●——●) muscles before (C) and after histamine (H) inhalation. EMG activity is expressed in terms of slope of inspiratory activity ($\dot{X}P/T_I$, in arbitrary units).

whilst residual volume (RV) was significantly increased in six.

Compared to the control conditions, histamine induced a significant average decrease in FEV_1 (59.6% ± 17.8, at Hmax) and a significant average increase in EMGd (from 7.8 AU ± 2.4 SE to 75 AU ± 26 SE with $p<0.01$) and EMGint (from 17.3 AU ± 8.2 SE to 51.7 AU ± 14 SE with $p<0.05$). In three of the five patients we could not observe any EMGsm activity before histamine challenge, average value for the group being 4.1AU ± 4.1 SE; with histamine, average maximum value (at the final HPD) for the group being 45 AU ± 13 SE. Moreover, in the two patients who had received two consecutive HPD, progressive recruitment in EMGsm was observed: 30 and 64 AU in one case, and 18.9 and 50.9 AU in the second, for the first and second HPD respectively. In no patient could we observe any EMGab activity before or after histamine testing. Figure 1 summarizes all EMG changes with histamine (Hmax) from the control conditions.

Figure 2 shows the relationship of changes (posthistamine in % of prehistamine values) in FEV_1 to both log $P_{0.1}$ (panel A) and log EMGd (panel B) changes. Both relationships were found to be significant ($p<0.01$ and $p<0.001$, respectively). From figure 2 it can also be seen that in three patients a greater FEV_1 decrease with larger histamine provocative doses was accompanied by a further consistent increase in EMGd; this graded effect was less evident for $P_{0.1}$. Due to the small number of cases (five) we were unable to analyse both $FEV_1/P_{0.1}$ and FEV_1/EMGd relationships for the additional provocative doses of histamine separately. However, as shown in the left and middle panels of figure 2 this relationship tended towards significance. Furthermore (right panel of fig. 2) FEV_1 change was found to be significantly related to log EMGint change ($r=-0.76$; $p<0.01$); this relationship was computed in only seven of the ten cases owing to the lack, in three of them, of any relevant EMGint activity before histamine. The absence of EMGsm activity before histamine, found in three of the five patients, did not allow us to relate percentage FEV_1 changes to percentage EMGsm changes. Changes in FEV_1 with histamine were also

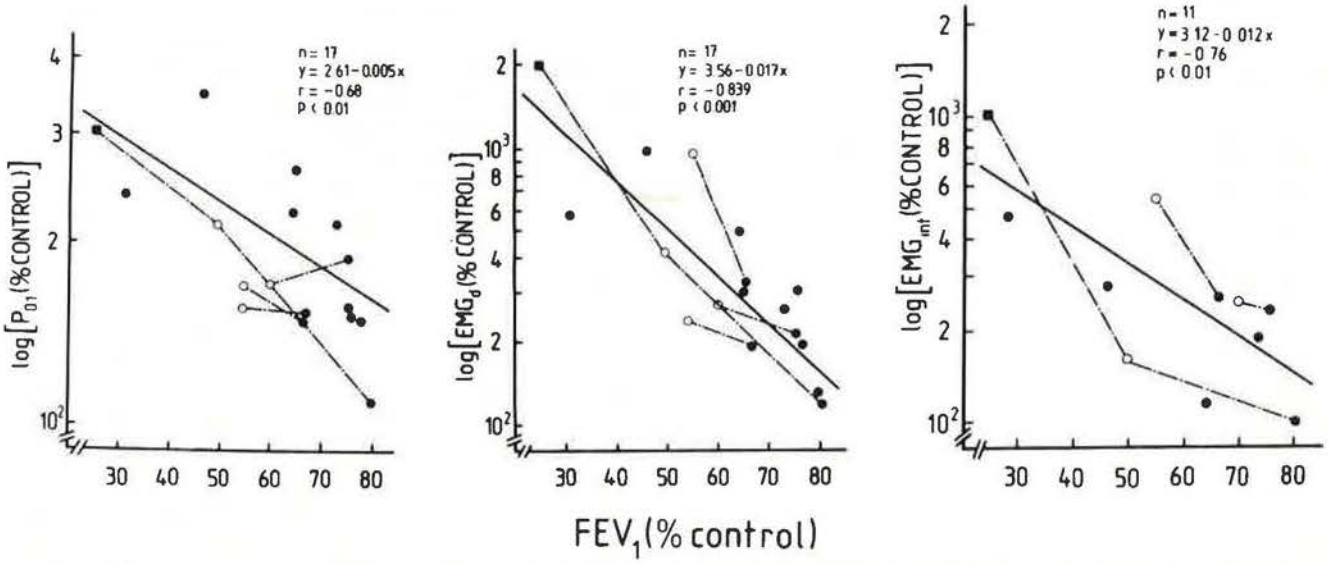


Fig. 2. Semilogarithmic representation (on the Y-axis) of the relationship of FEV_1 to $P_{0.1}$ (left panel), EMGd (middle panel) and EMGint (right panel) all expressed in % of control value. Eight patients were given a sole provocative dose of histamine (●); four patients had a second provocative dose of histamine (○) and one of the four had a third provocative dose of histamine (■). Continuous lines are the regression lines.

Table 1. – Anthropometric characteristics and functional data of the twelve patients studied

Patient n	Age yr	Sex	VC l	VC % pred	RV l	RV % pred	FRC l	FRC % pred	TLC l	TLC % pred	FEV_1 l	FEV_1 % pred	FEV_1/VC %
1	22	F	3.1	(82)	2.1	(176)	3.3	(136)	5.2	(104)	2.4	(74)	76
2	23	F	2.9	(84)	1.8	(155)	3.1	(124)	4.7	(103)	1.9	(63)	64
3	31	F	4.0	(103)	1.7	(111)	3.2	(116)	5.7	(105)	2.7	(80)	67
4	43	M	4.9	(100)	2.8	(130)	4.6	(120)	7.8	(112)	4.1	(105)	84
5	56	M	4.5	(111)	2.8	(145)	4.4	(131)	7.3	(119)	2.9	(98)	65
6	39	M	4.3	(92)	3.2	(164)	5.2	(142)	7.5	(119)	2.7	(73)	63
7	43	F	2.4	(76)	2.2	(138)	2.7	(100)	4.7	(96)	1.4	(67)	58
8	55	M	2.8	(89)	2.4	(120)	3.4	(113)	5.2	(98)	1.8	(70)	62
9	20	M	5.4	(86)	1.9	(114)	3.7	(106)	7.3	(96)	3.8	(75)	70
10	23	M	4.7	(92)	1.4	(92)	3.0	(96)	6.2	(97)	4.2	(99)	88
11	44	M	4.6	(95)	1.8	(99)	3.2	(95)	6.4	(95)	3.8	(98)	84
12	45	F	3.5	(129)	2.4	(159)	3.6	(146)	5.9	(138)	2.0	(87)	57

VC: vital capacity; RV: residual volume; FRC: functional residual capacity; TLC: total lung capacity; FEV_1: forced expiratory volume in one sec.

found to be significantly related ($p < 0.01$) to percentage changes in log $P_{0.1}$/EMGd ratio (fig. 3). From figure 3 it is evident that progressively greater levels of bronchoconstriction were accompanied by a progressive reduction in log $P_{0.1}$/EMGd ratio.

Heart rate was monitored before and during histamine challenge test. Before histamine challenge the heart rate was 69.6 ± 10.4 beats per min and afterwards it was 71.7 ± 10.9 beats per min ($p = NS$). In one case only, heart rate was found to substantially increase (from 53 to 68 beats per min).

In two patients we compared EMGd activities ($\bar{X}P/Ti$) as recorded by surface (EMGds) and oesophageal (EMGde) electrodes before and after histamine inhalation (table 2): in each case we found no significant difference between EMGds/EMGde ratio values as calculated before and after histamine (variance analysis).

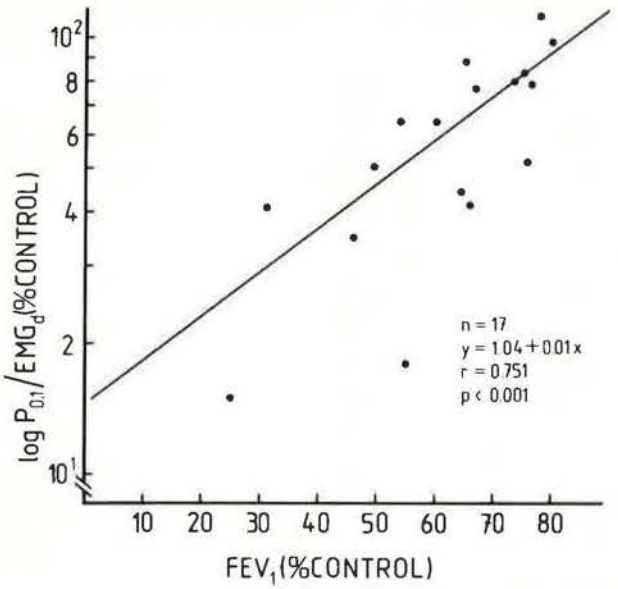


Fig. 3. Relationship of $P_{0.1}$/EMGd ratio (on semilogarithmic scale) to FEV_1 during histamine inhalation, all expressed in % of control value. The regression line is shown. Closed circles represent individual data for each histamine provocation dose. EMGd is expressed in terms of $\bar{X}P/Ti$ (arbitrary units).

Discussion

Firstly we will deal with the methods we used in assessing neural drive to the respiratory muscles: (i) processing the EMG 'raw' signal as proposed by LOPATA *et al.* [14] allowed the assessment of neural drive to the respiratory muscles [6, 8–17]. However, the employment of surface EMG to study the electrical activity of the diaphragm may be criticized, as chest-wall muscle EMG may interfere with EMGd recorded with surface electrodes. Nevertheless, previous studies, either in normal man [10, 12, 13, 17, 21] or in patients with chronic airway obstruction (CAO) [10, 22], seem to indicate that when EMGd activity is recorded by surface electrodes there is only minimal interference from the activity of other chest-wall muscles during either spontaneous breathing or presentation of fatiguing resistive respiratory loads; (ii) in studies where changes in FRC were observed to occur, as in the cases with histamine [23, 24], it is also possible that variations in pulmonary volume, by inducing changes in diaphragm position, do not allow surface EMG to maintain a good representation of diaphragmatic electrical activity. Nevertheless, in agreement with the data of BANZETT *et al.* [21], we showed in a previous study [10] that changes in lung volume, by voluntary manoeuvres, were not found to modify the agreement between EMGd as recorded by surface electrodes and EMGd as recorded by oesophageal electrodes. The present results (see table 2) confirm the quoted studies; (iii) the electrocardiogram signal represents an artefact on EMG signal and any increase in heart rate may lead to an overestimation of both $\bar{X}P$ and $\bar{X}P/Ti$. This seems not to be the case in the present study where a substantial increase in heart rate with histamine was not seen. All of these data corroborate the opinion that surface EMGd may

Table 2. – Comparison between oesophageal EMGd (EMGde) and surface EMGd (EMGds) in two patients with different degrees of histamine-induced bronchoconstriction (variance analysis)

Patient n	EMGds AU		EMGde AU		EMGds/EMGde		FEV_1 *l*	
	C	H	C	H	C	H	C	H
11	2.43* (0.3)	3.14* (0.27)	6.21# (0.75)	8.46# (0.84)	0.39 (0.04)	0.38 (0.03)	3.8	3.0
12	4.7◊ (0.75)	12.57◊ (1.98)	6.96§ (1.3)	18.08§ (2.6)	0.68 (0.13)	0.69 (0.09)	2.0	1.2

*: #: ◊: §: (C *vs* H)=p<0.001; C: before histamine inhalation; H: after histamine inhalation; AU: arbitrary units.

represent a suitable tool in the assessment of inspiratory neural drive for clinical purposes [11, 25].

A second point which needs to be discussed concerns the $P_{0.1}$/EMGd ratio, an index of neuromuscular coupling, showing neuromuscular efficiency. Relating a parameter which evaluates total inspiratory muscle force ($P_{0.1}$) to another which measures the neural drive to only one inspiratory muscle (EMGd) has previously been criticized [26]. However, it has been pointed out that the diaphragm must be the main contributor to the inspiratory muscle output [6]. Furthermore, with the subject in a seated position, the relaxation of the abdominal muscles may take place a few msec before inspiration; if this is so, $P_{0.1}$ may not reflect diaphragmatic EMG activity [8]. In contrast, occlusion pressure measured in the supine position does not seem to include a contribution from the release of elastic recoil of the chest-wall [8]. In no case in the present study did $P_{0.1}$ appear to precede the initial myoelectric potentials of EMGd nor was any expiratory EMGab activity recorded.

In this study, as previously found in experiments on animals [27], histamine increased the neural drive to respiratory muscles, an effect which seems to be linked to changes in airway calibre assessed by FEV_1 (fig. 2). As found in experiments with methylcholine [26, 28], in those patients who had received two or three histamine provocation doses, this increase was graded, *i.e.* a greater degree of bronchoconstriction was associated with a further increase in EMGd. The increase in inspiratory drive during bronchoconstriction is thought to stem either from indirect stimulation and/or from direct stimulation of pulmonary vagal receptors [4, 26–29]; activation of mechanoreceptors of the chest-wall could also be involved [3, 28].

Our data also show an increase in $P_{0.1}$ with histamine. As with EMGd, the $P_{0.1}$ increase was related to the increase in airflow limitation during bronchoconstriction. This result confirms previous findings in normal man [29, 30] and in patients with bronchial asthma [3, 4]. However, the present data seem to indicate that, in conditions of acute bronchospasm, $P_{0.1}$ does not reflect the actual amount of neural drive to the respiratory muscles. This was indicated by the fact that the neuromuscular coupling, assessed by $P_{0.1}$/EMGd ratio, decreased with increasing bronchoconstriction (fig. 3). In individual patients this effect was found to be graded. Two principal reasons could account for such a relationship:

(i) an increase in FRC with a parallel decrease in FEV_1 during moderate bronchoconstriction has been recognized in asthmatics [23, 24]. It is known that increasing lung volume puts the inspiratory muscles at a mechanical and geometrical disadvantage [5, 9] which disrupts the relationship of neural activation to output force of the respiratory muscles [5, 16, 28], thereby causing the increase in $P_{0.1}$ to be less than that of the neural inspiratory drive [7]. Furthermore, with increasing end-expiratory volume, the recoil of the respiratory system is positive. Thus, measurements of $P_{0.1}$ will tend to underestimate the neural drive to breathe [5]. For these reasons, a greater level of hyperinflation could explain the lower neuromuscular coupling noted in patients with greater FEV_1 decreases during histamine challenge. The progressively greater increase in intercostal/accessory inspiratory muscle recruitment with a progressive decrease in FEV_1 is consistent with a hyperinflation condition [24]. In this condition progressive recruitment of these muscles could be necessary to cause effective displacement of the rib cage during inspiration.

(ii) a lack of contribution from abdominal expiratory muscles could also be involved. In an erect position an increase in abdominal muscle recruitment during expiration, putting the diaphragm in a better end-expiratory configuration [6, 8, 23, 24], can contribute to the protection of the diaphragm from the concomitant hyperinflation [23]. Our inability to show any recruitment in abdominal expiratory muscles does not seem to provide evidence for this mechanism in the conditions studied. The supine position in which patients were studied could, however, account for our results. In this position MARTIN and DE TROYER [31] have noticed the absence of abdominal muscle action during loaded breathing, depending on the weight of the abdominal load which displaces the diaphragm upwards thereby contributing to optimization of its operating length [31].

In conclusion, acute airflow limitation increases the neural drive to the respiratory muscles. Progressive increase in bronchospasm causes a progressive increase in respiratory drive with a further decrease in the respiratory neuromuscular coupling. The ratio of transformation of neural activation to, and muscular output from the diaphragm could depend on both histamine-induced changes in lung volume and a lack of abdominal expiratory muscle recruitment.

In severe exacerbations of bronchial obstruction progressive hypoxia and hypercapnia indicate increasing fatigue and exhaustion. The approach we have proposed in order to assess the respiratory control system may be an aid in evaluating the mechanisms underlying these phenomena.

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RÉSUMÉ: Cette étude a été entreprise afin d'évaluer la pulsion neurale vers les muscles respiratoires et le couplage neuromusculaire inspiratoire chez des malades atteints d'asthme bronchique au cours d'une bronchoconstriction induite par histamine. La bronchoconstriction a été provoquée de manière graduée en augmentant des doses d'un aérosol de phosphate histaminique chez douze malades asthmatiques asymptomatiques; elle a été mesurée par FEV_1. La pulsion inspiratoire a été mesurée par activité électromyographique du diaphragme (EGMd) et le couplage de la pulsion neurale aux muscles respiratoires a été évaluée grâce au rapport entre la pression buccale bloquée et l'EMGd. Au cours du test nous avons également mesuré l'activité électromyographique des muscles inspiratoires intercostaux (EMGint), sternomastoïdes (EGMsm), et expiratoires (EGMab). L'histamine a provoqué une diminution significative de l'FEV_1, une augmentation significative de la $P_{0.1}$, de l'EMGd, de l'EMGint, et une augmentation pertinente de l'EMGsm, sans augmentation sensible de l'EMGab. Une relation inverse significative entre le changement de l'FEV_1 et ceux des $P_{0.1}$,

EMGd et EMGint, et une corrélation significative entre le changement de l'FEV_1 et le rapport $P_{0.1}$/EMGd ont été constatées. Nous en concluons que l'augmentation progressive du bronchospasme s'accompagne d'une augmentation progressive de la pulsion neurale respiratoire et une diminution du couplage neuromusculaire. Une augmentation du volume pulmonaire ainsi qu'un manque de recrutement des muscles abdominaux respiratoires pourraient en être la cause.