Eur Respir J, 1993, 6, 371–377
Printed in UK - all rights reserved

European Respiratory Journal
ISSN 0903 - 1936

Effects of intravenous broxaterol on respiratory drive and neuromuscular coupling in COPD patients

F. Gigliotti*†, G. Gurrieri**, R. Duranti*, M. Gorini*†, G. Scano*

Effects of intravenous broxaterol on respiratory drive and neuromuscular coupling in COPD patients. F. Gigliotti, G. Gurrieri, R. Duranti, M. Gorini, G. Scano. ©ERS Journals Ltd 1993.

ABSTRACT: Broxaterol, a new selective β_2-agonist, has been shown to exert inotropic effects on both fresh and fatigued canine diaphragm. We evaluated the effect of broxaterol on the activation and force output of the respiratory muscles in patients with chronic obstructive pulmonary disease (COPD).

We studied 9 patients with moderate to severe COPD. Each patient was infused with saline and Broxaterol (200 μg) in saline alternately. We measured lung volumes, maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), breathing pattern, $P_{0.1}$, respiratory muscle EMG (diaphragm, EMGd, and parasternal, EMGp) and $P_{0.1}$/EMGd ratio. Measurements were made under control conditions and at 15, 30, 60, and 120 min after each infusion.

Broxaterol, but not saline, resulted in a slight but significant increase in vital capacity (VC), forced expiratory volume in one second (FEV_1) and MIP, and a decrease in functional residual capacity (FRC). Breathing pattern did not change, while EMG significantly decreased, and $P_{0.1}$/EMGd significantly increased in 5 of the 9 patients after broxaterol.

These data seem to indicate that by partially unloading the respiratory muscles, broxaterol results in decreased muscle activation (EMG). Increase in chest wall neuromuscular coupling ($P_{0.1}$/EMGd) may also be observed.
Eur Respir J, 1993, 6, 371–377.

* Istituto di Clinica Medica III, Università degli Studi, Florence, Italy. † Fondazione Pro Juventute Don C. Gnocchi, Pozzolatico, Florence, Italy. ** Zambon research Group, Bresso, Italy.

Correspondence: G. Scano
Istituto di Clinica Medica III
Università degli Studi
V. le Morgagni 85
50134 Florence
Italy

Keywords: Broxaterol
chronic obstructive pulmonary disease
electromyography
mouth occlusion pressure
respiratory muscles

Received: March 9 1992
Accepted after revision September 17 1992

The effects of β_2-agonists on the contractile performance of the respiratory muscles remain controversial [1–5]. Terbutaline [4] and fenoterol [2], but not salbutamol [1, 3], have been shown to increase the contractility of canine fatigued diaphragm, with no effect on the non-fatigued muscle. In normal man, salbutamol has no effect on the strength of non-fatigued diaphragm [1]. In normocapnic patients with chronic obstructive pulmonary disease (COPD) terbutaline has no significant effect on respiratory muscle contractility [5]. Broxaterol (1-(3-bromo-5-isoxazoiyl)-2-(tert-butil amino) ethanol hydrochloride), (synthetized and developed by Zambon Research Spa, Bresso, Italy), a new selective β_2-agonist, has been proved to exert inotropic effects on fresh canine diaphragm strips [6] and to increase both the force output of the fatigued muscle [7] and diaphragmatic blood flow, at a given transdiaphragmatic pressure (Pdi) [8].

In man, broxaterol has similar bronchodilator activity to that of salbutamol [9, 10]. However, the effects of broxaterol on the respiratory muscles are scarcely known, particularly in patients with COPD, in whom broxaterol has recently been reported to improve respiratory muscle endurance [11].

Contributing to this field, the present investigation was carried out in order to evaluate the effects of broxaterol on the activation and force output of the respiratory muscles in patients with stable COPD.

Materials and methods

Subjects

The study was performed on nine male eucapnic patients (mean±SD age 64±7 yrs) with COPD, according to the American Thoracic Society criteria [12]. At the time of the study, all patients were in a clinically stable state. Therapy (aerosolized β_2-agonists and ipratropium bromide) was withheld 12 h before the study. No patient exhibited a >10% increase in forced expiratory volume in one second (FEV_1) after inhalation of a β_2-agonist bronchodilator agent (400 μg of fenoterol). Functional data of an age-matched normal control group represent the standard of our laboratory. This control group did not receive any treatment. Informed consent was obtained from each subject before the start of the study. All subjects were accustomed to the equipment and procedure and we were confident about their volitional participation.

Functional evaluation

Routine spirometry, obtained with subjects in a seated position, and arterial blood gas values were measured as described previously [13]. The normal values for lung

volumes are those proposed by the European Community for Coal and Steel [14]. Maximal static inspiratory and expiratory pressures (MIP and MEP) at functional residual capacity (FRC) and total lung capacity (TLC), respectively, against an obstructed mouthpiece, with a small leak to minimize oral pressure artifacts, were measured using a differential pressure transducer (Statham SC 1001). Subjects performed maximal inspiratory and expiratory efforts and were instructed to maintain maximal pressures for at least 1 s. The mean of three reproducible and satisfactory measurements was calculated, the variability among the three measurements being <3%.

After baseline routine testing during room-air breathing, the ventilatory pattern, respiratory drive, and mouth occlusion pressure were evaluated with subjects in a comfortable supine position. In the apparatus we used, the inspiratory line was separated from the expiratory one by a one-way valve (Hans-Rudolph) connected to a Fleisch No.3 pneumotachograph. The flow signal was integrated into volume. From the spirogram we derived: inspiratory time (T_I), expiratory time (T_E), total time of the respiratory cycle (Ttot), tidal volume (V_T). Mean inspiratory flow (V_T/T_I), duty cycle (T_I/T_{tot}), respiratory frequency ($Rf=1/T_{tot}\times 60$) and instantaneous ventilation ($\dot{V}_E=V_T\times Rf$) were also calculated. Mouth pressure during V_T manoeuvres was measured using a pressure transducer (Statham P23ID). Mouth occlusion pressure 0.1 s after the beginning of inspiration ($P_{0.1}$) [15] was recorded as described previously [16–19]. Expired end-tidal CO_2 (P_{ETCO_2}) was sampled continuously at the mouth by an infra-red CO_2 meter. The values for dead space and resistance of the system up to a flow of 4 *l* were 178 ml and 0.09 kPa·l^{-1}·s), respectively.

The electromyographic activity (EMG) of the respiratory muscles was recorded as described previously [16–19]. The EMG of the chest wall muscles was recorded from the second parasternal intercostal (EMGp), and diaphragm (EMGd) muscles *via* large surface electrodes. The EMGd was recorded from the lower anterolateral rib cage as described by GROSS *et al.* [20].

Muscle action potentials ("raw") were differentially amplified, filtered between 100 and 1,000 Hz, to remove as much electrocardiographic activity (ECG) as possible, without significantly filtering EMG. The filtered EMG signal, along with mouth pressure recording, were displayed on a single-beam storage oscilloscope (Tektronix 5115). EMG activity was full-wave rectified and integrated over time (time constant 100 ms) using a third-order, low-pass filter to provide a measurement of change in average electrical activity as a function of time, referred to as "moving time average" (X) [21, 22]. Inspiratory activity was quantified both as peak of activity and as rate of rise of activity (slope). The former (Xp) was directly measured in arbitrary units and the latter (Xp/T_I) was obtained by dividing Xp by the inspiratory time.

Owing to the variability of the impedance between diaphragm and electrodes, absolute values (mV) are not comparable among different subjects. To overcome this problem and to obtain a reference value, EMG activity was measured while the subject connected to the pneumotachograph, performed an inspiratory capacity (IC) manoeuvre, breathing in up to the TLC [19]. This manoeuvre was repeated at least three times, and in each subject both IC and the intensity of the recorded diaphragmatic EMG was closely reproducible (<5% variability). The mean level of this EMG activity was taken as a reference; all successive measurements have been expressed as a percentage of this reference value obtained at TLC. As EMG activity of an inspiratory muscle may include cardiac muscle activity, we studied cardiac artifacts to manually gate ECG, when necessary, so that it would not contribute to the EMG.

The output of the CO_2 meter, the flow signal, the integrated flow signal, the mouth pressure, and the moving time average were recorded continuously on a multichannel chart recorder. After a 10 min adaptation period, baseline evaluation began. Respiratory cycles, occlusions and EMG were continuously recorded over a 10 min time period and the cycles following occlusions discarded. Average values for each subject are presented. To assess the coupling of the inspiratory neural drive to force output of the inspiratory muscles, $P_{0.1}$ value was plotted against the rate of rise of EMG (Xp/T_I) [16, 17, 22].

Data are presented as the mean±standard deviation (SD). Results were compared by the Mann Whitney U-test for unpaired samples and Wilcoxon test for paired samples; analysis of the variance (ANOVA) was also employed. A value of $p<0.05$ was considered to be significant.

Protocol

A randomized, double-blind, cross-over, placebo-controlled study was performed. After baseline functional evaluation, breathing pattern, $P_{0.1}$ and EMG assessment were performed. Patients were then randomly allocated to either saline, or 200 µg of broxaterol in 100 ml of 0.9% NaCl solution, both infused in 10 min. With intravenous administration, the mean apparent elimination half-life is 1.5 h (Ferrandes B., "Pharmacokinetics of broxaterol in man". Data on file Zambon Research, 1991). Thus, at 15, 30, 60 and 120 min after infusion, breathing pattern, $P_{0.1}$ and EMG were repeated. Spirometry, MIP and MEP were also reassessed at 120 min after infusion, as described previously. After 48 h the same protocol was repeated with alternate infusion.

No adverse effects were recorded after either infusion.

Results

Table 1 summarizes pulmonary function data of the patients before and at 120 min after broxaterol infusion. Under control conditions, patients exhibited definite airway obstruction, decreased forced expiratory volume in one second (FEV_1) and FEV_1/ vital capacity (VC), hyperinflation increased (FRC) as well as mild hypoxia (arterial oxygen tension (Pa_{O_2}) 9.2±0.86 kPa) and normocapnia (arterial carbon dioxide tension (Pa_{CO_2}) 5.4±0.4 kPa). Respiratory muscle strength (MIP, MEP)

was reduced ($p<0.001$ for both) compared with the normal control group (mean age 62±9 yrs, MIP 9.8±0.8 kPa MEP 16.6±0.84 kPa). At 120 min after the infusion, significant increase in MIP (0.9±0.6 kPa, $p<0.02$) and slight, but consistent, increase in VC ($p<0.005$), and FEV_1 ($p<0.02$), and decrease in FRC ($p<0.05$) were observed.

Heart rate (HR), P_{ETCO_2}, ventilatory pattern, EMG activity and $P_{0.1}$/EMGd ratio, an index of neuromuscular coupling [16–19, 22] under control conditions (C) and at 15, 30, 60 and 120 min after broxaterol infusion, are shown in Table 2. In C, patients exhibited EMGd and EMGp values markedly greater ($p<0.01$ for both), and $P_{0.1}$/EMGd ratio lower ($p<0.001$), than that of the normal control group EMGd 3.6±2.3 $\%TLC \cdot s^{-1}$; EMGp 0.9±0.2 $\%TLC \cdot s^{-1}$, $P_{0.1}$ /EMGd 0.05±0.01 $kPa \cdot \%TLC^{-1} \cdot s$). EMGd (ANOVA, $F=7.24$; $p<0.005$) and EMGp (ANOVA, $F=4.2$; $p<0.01$) (table 2) was found. Figure 1 is a schematic representation of percentage changes in EMGd at the various measurement times. Changes in $P_{0.1}$/EMGd ratio did not attain statistical significance after broxaterol administration. However, in five of the nine subjects, increase in $P_{0.1}$/EMGd ratio, expressed as percentage of the control value, was observed at each time after the infusion (fig. 2); in each of these five cases, variance was found to be significant, with p ranging from <0.01 to <0.0001, in terms of the studied variables. In these five patients, increase in MIP was found to significantly relate to the increase in $P_{0.1}$/EMGd ratio ($p<0.05$); in the same five patients, FRC was found to decrease consistently, while changes in FRC were trivial in the remaining four patients.

Table 1. – Baseline pulmonary function data under control conditions and 120 min after broxaterol infusion in nine patients with COPD

Conditions	Age yrs	VC % pred	RV % pred	FRC % pred	TLC % pred	FEV_1 % pred	FEV_1/VC %	MIP kPa	MEP kPa
Control	65 (6)	77.7 (19)	153 (51.9)	144.1 (26.3)	106.2 (11.2)	38.9 (19.2)	37.3 (14)	5.4 (1.7)	12.4 (1.4)
Broxaterol		80.4# (15.5)	148 (50.8)	134.3* (25.1)	106 (15.3)	40.4§ (19.9)	38.0 (14.6)	6.3§ (1.8)	13.1 (1.6)

Values are mean±1SD. VC: vital capacity; FRC: functional residual capacity; RV: residual volume; FEV_1: forced expiratory volume in one second; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure. *: $p<0.05$; §: $p<0.02$; #: $p<0.005$.

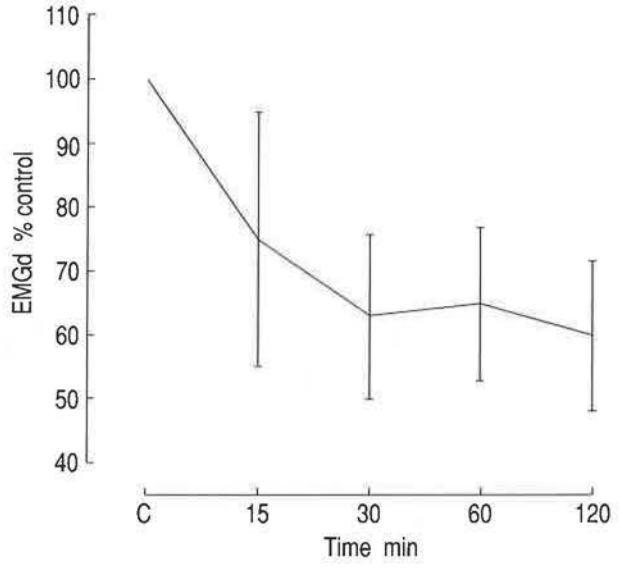

Fig. 1. – Average change in EMGd, expressed as percentage of control (C), at 15, 30, 60 and 120 min after broxaterol infusion. EMGd: electromyographic activity of the diaphragm.

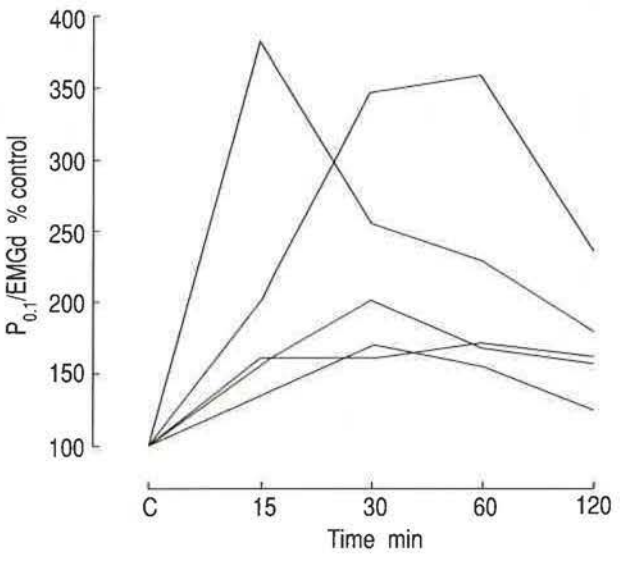

Fig. 2. – Individual changes in $P_{0.1}$/EMGd ratio, expressed as percentage of control (C), at 15, 30, 60, and 120 min after broxaterol infusion in 5 cases showing an increase. $P_{0.1}$: mouth occlusion pressure; EMGd: electromyographic activity of the diaphragm.

Broxaterol resulted in a slight, but significant, (ANOVA, $F=10.88$; $p<0.001$) increase in HR which reached a maximum at 15 min after infusion, then progressively decreased. No significant changes were observed in P_{ETCO_2}, ventilatory pattern ($\dot{V}_E$, Rf, V_T, T_I, T_E, Ttot, V_T/T_I, T_I/Ttot) and $P_{0.1}$. Conversely, a significant decrease in both

No significant differences were observed between pre-broxaterol and pre-saline control conditions. At 120 min after saline, spirometric values and MIP and MEP did not significantly differ from baseline values, neither did ventilatory parameters, $P_{0.1}$ and EMG at each time after the infusion (table 3).

Table 2 – Heart rate, P_{ETCO_2}, ventilatory pattern, $P_{0.1}$ and electromyographic activity of the diaphragm (EMGd) and parasternal intercostals (EMGp) under control conditions (C) and after broxaterol infusion (B)

	HR b·min^{-1}	P_{ETCO_2} kPa	$\dot{V}_E$ l·min^{-1}	Rf br·min^{-1}	V_T l	T_I s	T_E s	Ttot s	V_T/T_I l·s^{-1}	T_I/Ttot	$P_{0.1}$ kPa	Xp/Tid %TLC·s^{-1}	Xp/Tip %TLC·s^{-1}	$P_{0.1}$/(Xp/Tid) kPa/(%TLC·s^{-1})
C	70.3 (10.3)	5.7 (0.9)	10.8 (2.7)	15.6 (2.1)	0.69 (0.15)	1.43 (0.22)	2.48 (0.41)	3.9 (0.6)	0.49 (0.13)	0.37 (0.02)	0.19 (0.07)	19.2 (12.7)	14.0 (9.6)	0.015 (0.011)
B 15'	79.8 (12.9)	5.6 (0.94)	11.2 (2.8)	16.2 (3.0)	0.70 (0.16)	1.43 (0.18)	2.4 (0.48)	3.8 (0.67)	0.49 (0.09)	0.38 (0.03)	0.23 (0.08)	14.4 (11.3)	9.7 (5.0)	0.024 (0.021)
B 30'	76.9 (13.6)	5.6 (0.9)	11.4 (3.4)	15.9 (2.6)	0.73 (0.18)	1.44 (0.25)	2.45 (0.47)	3.88 (0.71)	0.50 (0.11)	0.37 (0.05)	0.20 (0.06)	12.1 (7.6)	9.2 (3.6)	0.020 (0.007)
B 60'	74.7 (10.1)	5.65 (0.86)	10.5 (2.1)	15.0 (3.2)	0.72 (0.18)	1.55 (0.33)	2.59 (0.77)	4.18 (1.06)	0.47 (0.09)	0.38 (0.03)	0.182 (0.056)	12.5 (7.1)	7.2 (3.1)	0.016 (0.005)
B 120'	73.4 (11.3)	5.7 (0.94)	10.4 (2.9)	16.0 (3.6)	0.67 (0.19)	1.47 (0.29)	2.46 (0.63)	3.92 (0.9)	0.46 (0.11)	0.38 (0.02)	0.15 (0.05)	11.6 (6.8)	10.3 (6.1)	0.016 (0.007)

Values are mean±SD. C: control; B15', 30', 60', 120': at 15, 30, 60 and 120 min after broxaterol infusion; HR: heart rate; P_{ETCO_2}: end-tidal tension of CO_2; $\dot{V}_E$: minute ventilation; Rf: respiratory frequency; V_T: tidal volume; T_I: inspiratory time; T_E: expiratory time; Ttot: total time of the respiratory cycle; V_T/T_I mean inspiratory flow; T_I/Ttot: duty cycle; $P_{0.1}$: mouth occlusion pressure. EMG was quantified as slope (Xp/Ti) obtained by dividing peak of inspiratory activity (Xp) by Ti.

Table 3. – Heart rate, P_{ETCO_2}, ventilatory pattern, $P_{0.1}$ and electromyographic activity of the diaphragm (EMGd) and parasternal intercostals (EMGp) under control conditions and after saline infusion (S)

	HR b·min^{-1}	P_{ETCO_2} kPa	$\dot{V}_E$ l·min^{-1}	Rf br·min^{-1}	V_T l	T_I s	T_E s	Ttot s	V_T/T_I l·s^{-1}	T_I/Ttot	$P_{0.1}$ kPa	Xp/Tid %TLC·s^{-1}	Xp/Tip %TLC·s^{-1}	$P_{0.1}$/(Xp/Tid) kPa/(%TLC·s^{-1})
C	75.3 (10.1)	6.0 (0.73)	9.8 (1.9)	16.3 (1.2)	0.60 (0.15)	1.43 (0.07)	2.30 (0.20)	3.71 (0.3)	0.42 (0.10)	0.39 (0.01)	0.18 (0.06)	18.9 (6.6)	14.2 (7.6)	0.01 (0.009)
S 15'	76.1 (9.8)	6.05 (0.83)	10.0 (2.1)	16.0 (1.2)	0.64 (0.14)	1.47 (0.10)	2.37 (0.17)	3.8 (0.30)	0.43 (0.10)	0.38 (0.01)	0.19 (0.02)	16.5 (5.3)	12.2 (3.5)	0.013 (0.003)
S 30'	74.9 (11.1)	6.1 (0.88)	10.0 (2.5)	14.7 (1.6)	0.67 (0.14)	1.50 (0.15)	2.37 (0.21)	4.1 (0.70)	0.44 (0.10)	0.37 (0.03)	0.18 (0.03)	15.9 (5.6)	12.3 (2.8)	0.013 (0.004)
S 60'	75.7 (10.2)	6.1 (0.98)	9.7 (1.9)	15.6 (1.5)	0.62 (0.16)	1.44 (0.09)	2.42 (0.27)	3.85 (0.34)	0.43 (0.10)	0.38 (0.02)	0.18 (0.02)	18.1 (4.4)	13.1 (5.0)	0.013 (0.004)
S 120'	75.4 (10.0)	6.1 (0.9)	9.6 (1.7)	15.7 (1.2)	0.61 (0.12)	1.47 (0.10)	2.35 (0.21)	3.84 (0.3)	0.42 (0.08)	0.39 (0.01)	0.18 (0.02)	17.7 (4.5)	12.9 (4.6)	0.014 (0.005)

Values are mean±1SD. For abbreviations see legend to table 2.

Discussion

Our data show that broxaterol slightly, but significantly, modifies pulmonary volumes and maximal inspiratory pressure (MIP), and decreases respiratory drive, assessed in terms of EMG activity of the respiratory muscles. Chest wall neuromuscular coupling, assessed by $P_{0.1}$/EMGd ratio, did not consistently change. However, in 5 patients $P_{0.1}$/EMGd ratio was significantly increased. These patients showed the greatest improvement in FRC and a significant relationship between MIP and $P_{0.1}$/EMGd ratio.

The small, but significant, increase in MIP ($p<0.02$) observed after broxaterol administration is not consistent with previous observations [5, 11]; therefore, the present results deserve some comments. In COPD patients changes in static maximal inspiratory pressure may depend on changes in length-tension and geometric characteristics (P=T/r) of the respiratory muscles. Increase in inspiratory muscle fibre length, by a reduction in end-expiratory lung volume (FRC), improves diaphragmatic ability to generate pressure (increase in MIP) in response to a given neural input from the respiratory centre [23, 24]. In the conditions of the present study, measurement of MIP was performed at FRC, which did slightly but significantly decrease. On the other hand, mouth pressure generated during static MIP is a voluntary manoeuvre, and factors, such as individual motivation and experience with tests of respiratory muscle performance, could explain the increase in MIP that we noted after broxaterol. However, all subjects were accustomed to the equipment and procedure; in addition, if increase in MIP were due to learning effect a similar increase would have been noticed after saline infusion.

Before broxaterol, patients exhibited a greater neural respiratory drive, assessed in terms of electromyographic activity (EMG) compared to the normal control group. EMG of the respiratory muscles (diaphragm and parasternal intercostals) is considered a useful tool in assessing spinal respiratory output [16–25]. However, this method warrants some criticism.

i) Several studies have demonstrated that the slope of the moving time average of the EMGd (Xp/Ti) allows the assessment of neural inspiratory drive [16–18, 21, 22, 26, 27]. However, the employment of surface electrodes for studying the electrical activity of the diaphragm may be criticized, since other chest wall muscles (external intercostal and/or abdominal) may interfere with the recorded signal. We cannot exclude the possibility of an external intercostal component on surface EMGd signal. In this regard, however, two of the nine patients had participated in a previous study [28] where EMGd was recorded simultaneously by means of surface (EMGds) and bipolar oesophageal (EMGdoes) electrodes; these patients had shown a good agreement between EMGds and EMGdoes [28].

Although abdominal EMG activity is well explored by needle electrodes, this procedure was not accepted by the patients. Nevertheless, the supine position, which is associated with absence of abdominal muscle action [29], and our inability to record any surface EMG activity during expiration, may suggest that abdominal muscle activity did not substantially interfere with the recorded EMGd. Finally, in the conditions of the present study, one could ask whether changes in mechanical and breathing characteristics during broxaterol infusion were such as to modify the EMGd signal *per se*. However, the decrease in FRC with broxaterol would increase EMG amplitude, by shortening the distance between muscle and electrodes thereby underestimating the decrease in EMGd activity that we noticed. These observations seem to indicate that, in particular circumstances, the amount of EMG does not depend mainly on the proximity of the electrodes to the contracting muscles.

ii) In filtering EMG, a low cut-off at 100 Hz was used. However this may be a rather high frequency cut-off, since spectral analysis has shown diaphragmatic power to be down to 25–30 Hz and, thereby, a part of EMGd is probably being lost. Nevertheless, our previous results [17] showed that the integrated peak EMGd signal was not substantially altered by a similar low cut-off.

iii) The method of normalization of the EMG at TLC was proposed years ago [30], and has been utilized subsequently in clinical settings [31] but so far it has not been validated. If one uses maximal EMG activity generated at TLC as reference activity, its validity depends on the subject truly generating maximal effort. Differences in motivation and volitional participation between the two control conditions, preceding either placebo or broxaterol infusion, are possible but we are reasonably confident about our patient's co-operation and familiarity with the techniques.

iv) In hyperinflated patients who exhibit higher EMG activity an important question arises with regard to the reliability of EMG in assessing an increased neural respiratory drive: increase in EMG has been thought of as a simple result of change in the orientation of diaphragm from hyperinflation. This possibility, however, has recently been excluded by Begle *et al.* [26].

For all these reasons, we think that the greater EMG recorded in our patients is likely to reflect an increased neural drive to the respiratory muscles.

The reasons for the increase in respiratory drive in patients with COPD have been considered previously by ourselves and others [16, 18, 19, 23–25, 32, 33]. Basically, nervous outflow from chemoreceptors and from lung and/or chest wall mechanoreceptors could be involved in the observed increase in neural inspiratory drive [32–35]. The mechanical disadvantage due to the shortening of muscle fibre length could contribute to this increased drive [26, 36].

In this connection, decrease in mechanical loading (decreased FRC, increased VC and FEV_1) and possibly a better configuration of the inspiratory muscles might explain, at least in part, the reduction in EMG with broxaterol. One has also to consider that improvement in respiratory muscle force has been proved to be associated with a decrease in respiratory centre output [25]. Similar patterns, increase in MIP and decrease in EMG with minimal changes in lung volume, have also been observed with ventilatory muscle rest [18]. In addition,

intravenous broxaterol has been proved to slightly, but significantly, increase Pao_2 in COPD patients [37]; if this applies to our study increase in Pao_2 could have played a role in decreasing EMG.

Nevertheless, we feel that none of these factors is unique in explaining the decrease in EMG, but a combination of them could account for it.

Simultaneous recording of EMG activity and $P_{0.1}$ has been proposed in patients with COPD as a simple and suitable, even if rather generic, measurement of inspiratory neuromuscular coupling, *i.e.* the ratio of transformation of neural output from the respiratory centres (EMG) into total inspiratory muscle output ($P_{0.1}$) [16, 18, 19, 22]. At least two major reasons could account for a low $P_{0.1}$ relative to EMGd in patients with COPD. Firstly, increase in end-expiratory lung volume impairs ventilatory muscle efficiency, and limits the production of $P_{0.1}$ in conditions of increased neural inspiratory drive [16, 18, 19, 38], thereby decreasing $P_{0.1}$/EMGd ratio [16, 19]. Secondly, the inability of $P_{0.1}$ to reflect the total amount of respiratory neural drive (EMGd) could depend on intrinsic positive end-expiratory pressure (PEEPi). PEEPi represents an extra burden for respiratory muscles, which they must offset before inflating the lung [39].

The effects of β_2-agonists on the diaphragm contractility remains controversial [1–4]. Terbutaline and fenoterol [2, 4], but not salbutamol [1, 3], have both been proved to increase contractility of the fatigued canine diaphragm, without any effect on the non-fatigued muscle. On the other hand, broxaterol is known to improve skeletal muscle contractility by several mechanisms. *In vitro* studies on fresh isolated diaphragm strips from dogs demonstrated an inotropic effect of broxaterol [6]. A further *in vivo* study in a dog showed that the drug significantly increased both the strength of fatigued diaphragm, as assessed by Pdi [7], and the diaphragmatic blood flow at a given Pdi [8]. Also, broxaterol seems to enhance the endurance time of the respiratory muscles and Pao_2 in non-hypercapnic COPD patients during fatiguing respiratory load; a better muscle perfusion has been thought to play a role in these observations [11]. Increase in cardiac output and Pao_2 and decrease in vascular resistance after infusion of broxaterol in spontaneously breathing COPD patients [37] may substantiate an increased muscle perfusion. Thus one could speculate that a better O_2 supply to the respiratory muscles might have played a role in the increased $P_{0.1}$/EMGd ratio found in 5/9 patients after broxaterol injection. However, the effect of a decrease in FRC and increase in MIP on $P_{0.1}$/EMGd ratio have mostly to be considered (see Results).

In conclusion, broxaterol seems to partially unload the respiratory muscles, and this results in decreased EMG activity in obstructed normoxic COPD patients. Increase in chest wall neuromuscular coupling ($P_{0.1}$/EMGd) was found to be inconsistent, even if significant in half of the patients.

Further studies are warranted in order to control the effects of broxaterol in hypercapnic, hypoxic COPD patients with respiratory muscle pump failure.

References

1. Javaheri S, Smith JT, Thomas JP, Guilfoile TD, Donovan EF. – Albuterol has no effect on diaphragmatic contractility in humans. *Am Rev Respir Dis* 1988; 137: 197–201.
2. Suzuki S, Numata H, Sano F, *et al.* – Effect and mechanism of fenoterol on fatigued canine diaphragm. *Am Rev Respir Dis* 1988; 137: 1048–1054.
3. Howell S, Fitzgerald RS, Roussos C. – Effects of neostigmine and salbutamol on diaphragmatic fatigue. *Respir Physiol* 1985; 62: 15–29.
4. Aubier M, Viires N, Murciano D, *et al.* – Effects and mechanisms of action of terbutaline on diaphragmatic contractility and fatigue. *J Appl Physiol: Respirat Environ Exercise Physiol* 1984; 56: 922–929.
5. Stoller JK, Wiedemann HP, Loke J, *et al.* – Terbutaline and diaphragm function in chronic obstructive pulmonary disease: a double-blind, randomized clinical trial. *Br J Dis Chest* 1988; 82: 242–249.
6. Derom E, Jansen S, Gurrieri G, Decramer M. – Broxaterol increases force production of fresh and fatigued canine diaphragm *in vitro* but decreases endurance. *FASEB J* 1990; 4: A1069.
7. Decramer M, Derom E, Jansen S, Gurrieri G. – Effect of broxaterol and theophylline on low frequency fatigue in canine diaphragm. *FASEB J* 1990; 4: A1069.
8. Decramer M. – Role of β_2-agonists in respiratory muscle pharmacotherapy. International Meeting on Bronchial Asthma, Florence, 7th–9th March, 1991, Book of abstracts, p. 35.
9. Perruchoud AP, Brundles M, Godly R, Inhof E, Herzog H. – Broxaterol, a new oral β_2-agonist compared with salbutamol. *Respiration* 1987; 51: 113–118.
10. Al-Jeboory AA, Marshall RJ. – Correlation between the effects of salbutamol on contractions and cyclic AMP content of isolated fast and slow contracting muscles of the guinea-pig. *Naunyn-Schmiedeberg's Arch Pharmacol* 1978; 305: 201–206.
11. Nava S, Crotti P, Gurrieri G, Fracchia C, Rampulla C. – Effect of a β_2-agonist (broxaterol) on respiratory muscle strength and endurance in COPD patients with irreversible airway obstruction (personal communication) *Chest* (in press).
12. American Thoracic Society. – Chronic bronchitis, asthma and pulmonary emphysema. A statement by the committee on diagnostic standards for non-tuberculous respiratory disease. *Am Rev Respir Dis* 1962; 85: 762–768.
13. Scano G, Garcia Herreros P, Stendardi D, *et al.* – Cardiopulmonary adaptation to exercise in coal miners. *Arch Environ Health* 1980; 35: 360–366.
14. European Community for Coal and Steel. – Standardization of lung function tests. *Bull Eur Physiopathol Respir* 1983; 19: 1–95.
15. Whitelaw WA, Derenne JP, Milic-Emili J. – Occlusion pressure as a measure of respiratory center output in conscious man. *Respir Physiol* 1975; 23: 181–199.
16. Scano G, Duranti R, Spinelli A, *et al.* – Control of breathing in normal subjects and in patients with chronic airflow obstruction. *Bull Eur Physiopathol Respir* 1987; 23: 209–216.
17. Gorini M, Ginanni R, Spinelli A, Duranti R, Scano G. – Inspiratory muscle strength and respiratory drive in patients with rheumatoid arthritis. *Am Rev Respir Dis* 1990; 142: 289–294.
18. Scano G, Gigliotti F, Duranti R, *et al.* – Changes in ventilatory muscle function with negative pressure ventilation in patients with severe COPD. *Chest* 1990; 97: 322–327.

19. Gorini M, Spinelli A, Ginanni R, *et al.* – Neural respiratory drive and neuromuscular coupling in patients with chronic obstructive pulmonary disease (COPD). *Chest* 1990; 98: 1179–1186.
20. Gross D, Grassino AE, Ross WR, Macklem PT. – Electromyogram pattern of diaphragmatic fatigue. *J Appl Physiol: Respirat Environ Exercise Physiol* 1979; 46:1–7.
21. Evanich MJ, Lopata M, Lourenço RV. – Analytical methods for the study of electrical activity in respiratory nerves and muscles. *Chest* 1976; 70 (Suppl.): 158–162.
22. Lopata M, Zubillaga G, Evanich MJ, Lourenço RV. – Diaphragmatic EMG response to isocapnic hypoxia and hyperoxic hypercapnia in humans. *J Lab Clin Med* 1978; 91: 698–709.
23. Sharp JT. – The respiratory muscles in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 134: 1089–1091.
24. Sharp JT, Druz W, Danon J, Mi Ja Kim. – Use of respiratory muscle electromyography in the evaluation of respiratory regulation. *Chest* 1976; 70: 150–153.
25. Druz WS, Sharp JT. – Electrical and mechanical activity of the diaphragm accompanying body position in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1982; 125: 275–280.
26. Begle RL, Skatrud JB, Dempsey JA. – Ventilatory compensation for changes in functional residual capacity during sleep. *J Appl Physiol* 1987; 62: 1299–1306.
27. Belman MJ, Sieck GC. – The ventilatory muscles; fatigue, endurance and training. *Chest* 1982; 82: 761–766.
28. Gigliotti F, Duranti R, Fabiani A, Schiavina M, Scano G. – Suppression of ventilatory muscle activity in healthy subjects and COPD patients with negative pressure ventilation. *Chest* 1991; 99: 1186–1192.
29. Martin JG, De Troyer A. – The behaviour of the abdominal muscles during inspiratory mechanical loading. *Respir Physiol* 1982; 50: 63–73.
30. Evanich MJ, Bruce E, Eldridge FL, *et al.* – Conference report. Workshop on assessment of respiratory control in humans. IV. Measurement of the electrical activity in respiratory muscles. *Am Rev Respir Dis* 1977; 115: 541–548.
31. Grassino A, Goldman MD, Mead J, Sears TA. – Mechanics of the human diaphragm during voluntary contraction: statics. J *Appl Physiol: Respirat Environ Exercise Physiol* 1978; 44: 829–839.
32. Roussos C, Macklem PT. – The respiratory muscles. *N Engl J Med* 1982; 23: 786–797.
33. Roussos C. – Ventilatory muscle fatigue governs breathing frequency. *Bull Eur Physiopathol Respir* 1984; 20: 445–451.
34. Sorli J, Grassino A, Lorange G, Milic Emili J. – Control of breathing in patients with chronic obstructive lung disease. *Clin Sci Mol Med* 1978; 54: 295–305.
35. Cherniack NS, Kelsen S, Altose MD. – Prolonged alveolar hypoventilation in patients with lung disease. *Bull Eur Physiopathol Respir* 1979; 15: 31–41.
36. Green M, Mead J, Sears TA. – Muscle activity during chest wall restriction and positive pressure breathing in man. *Respir Physiol* 1978; 35: 283–300.
37. Mori G, Marchioni CF, Cacciani GC, *et al.* – Hemodynamic effects of a new β_2-agonist: broxaterol. Data on file. Zambon Research, 1991.
38. Gribbin HR, Gardiner IT, Heinz III GJ, Gibson GJ, Pride NB. – Role of impaired inspiratory muscle function in limiting the ventilatory response to carbon dioxide in chronic airflow obstruction. *Clin Sci* 1983; 64: 487–495.
39. Dal Vecchio L, Polese G, Poggi R, Rossi A. – "Intrinsic" positive end-expiratory pressure in stable patients with chronic obstructive pulmonary disease. *Eur Respir J* 1990, 3: 74–80.