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Mechanical loading and control of breathing in patients with severe chronic obstructive pulmonary disease

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Abstract

Background – **High neural drive to the respiratory muscles and rapid and shallow breathing are frequently observed in patients with chronic obstructive pulmonary disease (COPD), and both mechanical and chemical factors are thought to play a part. However, the interrelation between these factors and the modifications in the control of breathing are not clearly defined. The effects of an acute decrease in mechanical load by the administration of a high dose of a β_2 agonist were studied.**

Methods – **Nine spontaneously breathing patients with severe COPD took part in the study. Criteria for entry were FEV_1 of <40% of predicted and an improvement in FEV_1 of <200 ml after inhalation of 400 µg fenoterol. The following parameters were measured: lung volumes, tidal volume (VT), respiratory frequency (Rf), maximal pleural pressure during a sniff manoeuvre (PPLmax), pleural pressure swings (PPLsw), lung resistance (RL), RL/PPLmax ratio, and surface electromyographic activity (EMG) of diaphragm (EDI) and parasternal (EPS) muscles. Arterial oxygen saturation (SaO_2), end tidal carbon dioxide pressure ($PETCO_2$), and the electrocardiogram were also monitored. Each variable was measured under control conditions and 20 and 40 minutes after the inhalation of 800 µg fenoterol. In five patients the effects of placebo were also studied.**

Results – **Fenoterol resulted in an increase in FEV_1 and decrease in FRC. SaO_2 did not change, while $PETCO_2$ fell and heart rate increased. The VT increased, and Rf decreased, PPLsw fell and PPLmax increased, thus the PPLsw/PPLmax ratio fell. Both RL and RL/PPLmax also fell, and a substantial decrease in EDI and EPS was observed. Changes in PPLsw were related to changes in FEV_1 and RL. Changes in VT and Rf, and EDI/TI and EPS/TI were also related to changes in PPLsw and RL/PPLmax ratio, but not to changes in FEV_1. No variation was observed with placebo.**

Conclusions – **In patients with severe COPD a decrease in inspiratory muscle loading relative to the maximal available strength, as expressed by the RL/PPLmax and PPLsw/PPLmax ratios, appears to be the major determinant of changes in breathing pattern and inspiratory muscle activity (decrease in EMG).**

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Keywords: chronic obstructive pulmonary disease, mechanical load, breathing pattern, respiratory muscles.

Patients with severe chronic obstructive pulmonary disease (COPD) have both a high neural drive to the respiratory muscles[1–4] and a more rapid and more shallow pattern of breathing.[4–6] Both mechanical[1 6–8] and chemical[1 9] factors are thought to be involved in determining these functions. Among the mechanical factors, an increase in airways resistance plays an important part in increasing neural inspiratory drive in both normal subjects[10 11] and in asthmatic patients.[11 12] On the other hand, the relationship between an acute increase in airways resistance and neural inspiratory drive appears to be more complex in patients with COPD. Altose *et al*[7] reported that adding external inspiratory resistance produced no augmentation in mouth occlusion pressure ($P_{0 \cdot 1}$). Furthermore, the $P_{0 \cdot 1}$ response seen with progressive hypercapnia did not occur during methacholine-induced bronchoconstriction.[13] Pardy *et al*[14] observed rapid shallow breathing with no change in mean inspiratory flow during histamine-induced airways resistance in patients with COPD, suggesting that an increase in airways resistance enhances central respiratory activity and modifies the pattern of breathing. An increase in airways resistance and a decrease in respiratory muscle strength may trigger the signal for the integrated response that controls the pattern of breathing.[8] However, the interrelation of increased mechanical load relative to respiratory muscle strength and changes in neural inspiratory drive and breathing pattern has not yet been established.

We have investigated the effects of a large and rapid decrease in mechanical load following the administration of a large dose of a bronchodilator in a small group of patients with severe COPD.

Methods

SUBJECTS

Nine men with chronic obstructive pulmonary disease, as defined by the criteria of the American Thoracic Society,[15] gave informed consent to the experimental procedures. Criteria for entry were: a forced expiratory volume in one second (FEV_1) of less than 40% of the predicted value; an improvement in FEV_1 of less than 200 ml after inhalation of 400 μg fenoterol; a peripheral blood eosinophil count of less than 400/mm^3; and no treatment with inhaled or oral corticosteroids. Inhaled bronchodilators were withdrawn 24 hours before the study.

MEASUREMENTS

Age, height and weight (expressed both as absolute value and as percentage predicted) were recorded. All respiratory measurements were performed with the patients seated. Routine spirometry was obtained by a water sealed spirometer (Godart); functional residual capacity (FRC) was measured by the helium dilution technique. Arterial blood gases were also measured with the subjects breathing room air. The normal values for lung volumes were those of the European Community for Coal and Steel.[16]

For ventilation measurements patients breathed through a Fleisch no. 3 pneumotachograph connected to a flow transducer. Volume was obtained from electrical integration of the flow signal. From the spirogram we derived: inspiratory time (TI), expiratory time (TE), total time of the respiratory cycle (TTOT), and tidal volume (VT). Mean inspiratory flow (VT/TI), duty cycle (TI/TTOT), respiratory frequency ($Rf = 1/TTOT \times 60$), and instantaneous ventilation ($VE = VT \times Rf$) were also calculated. End tidal carbon dioxide pressure ($PETCO_2$) was sampled continuously at the mouth by an infrared carbon dioxide meter (Datex Normocap); arterial oxygen saturation (SaO_2) was monitored by an ear oximeter (Radiometer).

For mechanical studies an oesophageal latex balloon (length 10 cm; air volume 0·5 ml) was introduced via the nose. A marker was placed on the polyethylene tubing exactly 45 cm from the balloon tip[17] and adjustment began when this marker appeared at the external nares. The catheter was connected to a differential pressure transducer (Validyne). The maximal pleural pressure (PPLmax) was evaluated during the maximal sniff manoeuvre[18] which was repeated until three measurements with less than 5% variability were recorded. The highest value of PPLmax obtained was used for subsequent analysis. Pleural pressure was also recorded during tidal breathing and PPL swings (PPLsw) were calculated as the difference between the pleural pressure measured at end expiration and end inspiration. PPL swings were expressed both as absolute values (cm H_2O) and as percentage of the maximal pleural pressure (PPLsw/PPLmax ratio), which represents the force required to breathe relative to the maximal inspiratory force available. Total lung resistance (RL) was calculated by an isovolume method[19]; RL/PPLmax ratio was also calculated and represented the balance between the mechanical impediment to breathing and the ability of inspiratory muscles to develop force. The tension time index of the inspiratory muscles was calculated as the product of TI/TTOT × PPLsw/PPLmax. Mouth pressure during tidal breathing was measured using a pressure transducer (Statham P23ID).

The electromyographic activity (EMG) of the inspiratory muscles was recorded using a method previously described.[20,21] Electromyographic activity of parasternal muscles (EPS) was recorded from the second to third intercostal spaces parasternally and that of the diaphragm (EDI) from the lower anterolateral rib cage, from the sixth to seventh intercostal space on the midclavicular line, via large surface electrodes. Muscle action potentials ("raw") were differentially amplified, filtered between 100 and 1000 Hz. 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".[22-24] Inspiratory activity was quantified both as peak activity and as rate of rise (slope). The former was directly measured in arbitrary units and the latter obtained by dividing this value by the relevant inspiratory time. Because of the variability of the impedance between inspiratory muscles and electrodes, absolute values (mV) are not comparable between different subjects. To overcome this problem and to obtain a reference value, EMG activity was measured whilst the subject performed an inspiratory capacity (IC) manoeuvre up to TLC connected to the pneumotachograph.[25] This manoeuvre was repeated at least three times and in each subject both IC and the intensity of the recorded parasternal and diaphragmatic EMG was reproducible (less than 5% variability). The maximal level of this EMG activity was taken as a reference and the successive measurements have been expressed as a percentage of this value at TLC. As the inhalation of β_2 agonists could induce changes in lung volumes and in chest wall configuration, each patient performed TLC manoeuvres twice – first under control conditions and second after the inhalation of fenoterol. Thus, for each phase of the experiment EMG measurements were expressed as a percentage of the relevant value recorded at TLC. As EMG activity of an inspiratory muscle may include cardiac muscle activity, we checked cardiac artifacts to a manually gated ECG, when necessary, so that it would not contribute to the EMG.

The output of the carbon dioxide meter, flow signal, integrated flow signal, mouth pressure, oesophageal pressure, and the moving time average of both diaphragm and parasternal muscles were recorded continuously on a multichannel chart recorder (Gould TA4000).

PROTOCOL

On a pre-intervention day subjects underwent blood eosinophil count and baseline spirometric testing and the response to 400 μg fenoterol was measured. Patients fulfilling the

Table 1 Anthropometric characteristics, lung volumes, and arterial blood gas tensions of the nine patients with COPD

Subject	Age (years)	Height (cm)	Weight (kg)	FEV$_1$		VC		FRC		RV (l)	TLC (l)	Pao_2 (kPa)	$Paco_2$ (kPa)
				l	%pred	l	%pred	l	%pred				
1	61	172	72	0·40	12·7	3·87	93·6	5·69	163·3	4·42	8·29	9·18	5·85
2	70	170	68	0·73	26·2	2·56	68·1	4·04	114·8	3·38	5·94	9·59	5·98
3	69	165	84	0·53	20·3	2·51	72·1	4·79	141·2	4·02	6·52	11·33	5·60
4	69	169	95	0·83	29·9	3·25	87·2	5·89	168·2	3·99	7·24	9·99	5·80
5	67	168	45	0·70	25·1	3·49	93·8	5·35	155·3	4·19	7·68	10·55	5·98
6	71	162	64	0·60	24·8	4·04	124·5	5·33	160·0	3·60	7·65	10·11	5·76
7	63	177	89	0·64	19·4	2·19	49·9	6·09	168·3	5·42	7·61	8·22	7·65
8	63	163	55	0·43	16·0	2·22	62·9	4·84	147·9	3·65	5·86	9·48	5·71
9	58	162	63	0·32	11·4	2·36	65·4	6·69	207·5	5·82	8·19	10·23	6·69
Mean	65·7	168	70·3	0·57	20·6	2·9	79·7	5·4	158·5	4·3	7·2	9·85	6·11
SE	1·51	1·69	5·28	0·06	2·12	0·24	7·47	0·26	8·3	0·28	0·30	0·29	0·22

FEV$_1$ = forced expiratory volume in one second; VC = vital capacity; FRC = functional residual capacity; RV = residual volume; TLC = total lung capacity; Pao_2 = arterial partial pressure of oxygen; $Paco_2$ = arterial partial pressure of carbon dioxide.

entry criteria were enrolled. On the study day FEV$_1$, VC, FRC, and PPLmax were measured. Patients then breathed quietly through the pneumotachograph and, after a 10 minute acclimatisation period, PPLsw, breathing pattern, and electromyographic activity of inspiratory muscles were recorded. On completion of baseline measurements each patient inhaled 800 μg fenoterol from a metered dose inhaler via a space device. Twenty and 40 minutes after inhalation we recorded PPLsw, breathing pattern, EPS and EDI during quiet breathing and, finally, the FEV$_1$. After completion of the 40 minutes recording, VC and FRC were remeasured. In five patients we also studied the effects of placebo administration (single blind design) following the same experimental protocol.

DATA ANALYSIS

Mean values and standard errors of mean have been calculated for all variables. Data obtained in control conditions and at 20 and 40 minutes after inhalation of fenoterol were compared by two way analysis of variance. Subsequent comparisons were performed by the Bonferroni test. Changes in VC and FRC were analysed by the Student's *t* test for paired samples. All statistical analyses were carried out using the Statgraphics 6.0 package (Manugistics Inc, Rockville, Maryland, USA).

Results

Anthropometric details, lung volumes, and arterial blood gas tensions are summarised in table 1. Patients exhibited severe airway obstruction (<40% FEV$_1$), moderate hyperinflation (FRC), and a reduction of VC. Pao_2 was slightly reduced and patients nos 7 and 9 were hypercapnic. After inhalation of 800 μg fenoterol FEV$_1$ increased significantly and FRC decreased significantly; changes in VC were not significant (table 2).

BREATHING PATTERN MEASUREMENTS

Mean breathing pattern, minute ventilation, and $PETCO_2$ under control conditions and 20 and 40 minutes after inhalation of fenoterol are shown in fig 1. After fenoterol TI and TE lengthened, decreasing respiratory frequency (from 17·6 (1·7) to 14·6 (1·4) breaths/min under control conditions and at 40 minutes respectively, $p<0·005$), and VT increased ($p<0·01$). VE did not change, and VT/TI exhibited a small but significant decrease ($p<0·05$) (fig 1). No significant change was observed in TI/TTOT. Following the increase in VT, $PETCO_2$ decreased significantly (fig 1) but arterial oxygen saturation did not change (from 92·5 (0·81)% to 92·2 (0·70)%). A small but significant increase in heart rate was noted (from 84·1 (5·6) to 90·6 (6·4) beats/min, $p<0·01$) without any arrhythmias.

INSPIRATORY MUSCLE STRENGTH MEASUREMENTS

The patients had reduced inspiratory muscle strength with a low value of PPLmax, and a small but significant increase was observed both

Table 2 Mean (SE) lung volumes of the patients with COPD before and after inhalation of 800 μg fenoterol (nine patients) and of placebo (five patients)

	FEV$_1$		VC		FRC	
	l	%pred	l	%pred	l	%pred
Before fenoterol	0·57	20·6	2·9	79·7	5·41	158·5
	(0·06)	(2·12)	(0·24)	(7·47)	(0·26)	(8·29)
After fenoterol	0·71	25·7	3·1	84·3	5·17	152·1
	(0·04)	(1·77)	(0·27)	(9·20)	(0·33)	(10·14)
t	5·64	5·44	1·49	1·45	4·00	3·70
p	<0·0005	<0·0005	NS	NS	<0·01	<0·01
Before placebo	0·54	18·38	2·8	72·1	5·33	158·7
	(0·09)	(2·52)	(0·23)	(3·48)	(0·38)	(12·8)
After placebo	0·6	20·34	3·0	78·64	5·10	151·7
	(0·10)	(2·72)	(0·33)	(5·45)	(0·43)	(14·71)
t	1·18	1·05	1·87	1·81	1·78	1·78
p	NS	NS	NS	NS	NS	NS

For abbreviations see footnote to table 1.

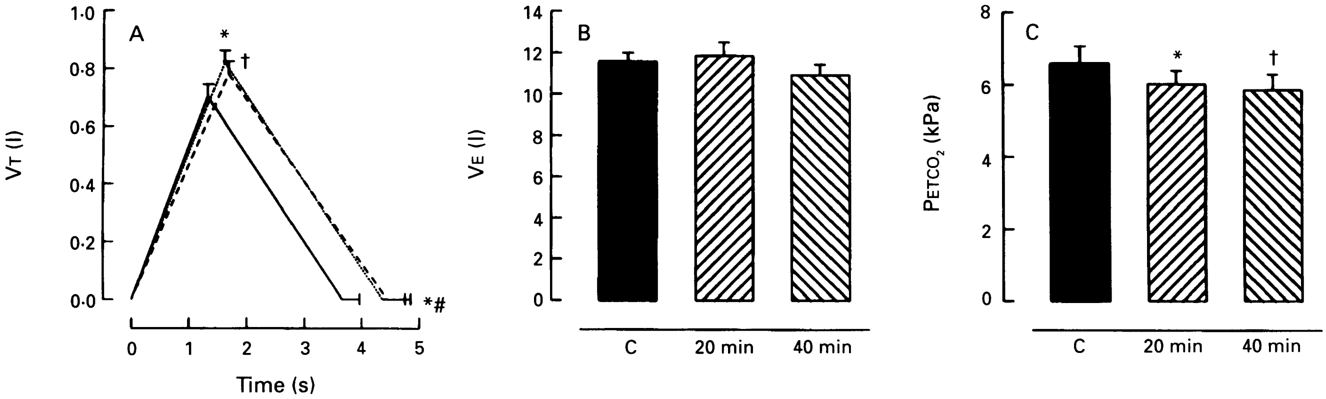

*Figure 1 (A) Schematic representation of breathing pattern under control conditions (continuous line), and 20 (dotted line) and 40 (broken line) minutes after the inhalation of 800 μg fenoterol. (B) and (C) Minute ventilation (VE) and end tidal P_{CO_2} under control conditions (C), and 20 and 40 minutes after the inhalation of 800 μg fenoterol, respectively. *C versus 20 min, $p<0\cdot05$; †C versus 40 min, $p<0\cdot05$. VT = tidal volume, VE = minute ventilation, P_{ETCO_2} = end tidal partial pressure of carbon dioxide.*

20 and 40 minutes after fenoterol inhalation ($p<0\cdot05$) (fig 2).

MECHANICAL MEASUREMENTS

Swings of pleural pressure during tidal breathing, expressed either in absolute values or as percentage PPLmax, were increased under control conditions and this value fell significantly after fenoterol (table 3 and fig 2). All patients had raised values of RL and RL/PPLmax ratio; both variables exhibited significant reductions after fenoterol (table 3). Tension time index (TTI) of inspiratory muscles decreased significantly after fenoterol (table 3); since no variation in TI/TTOT was observed after fenoterol, the change in TTI appeared to be due mainly to a decrease in the PPLsw/PPLmax ratio.

ELECTROMYOGRAPHIC MEASUREMENTS

Under control conditions patients showed high levels of both EDI and EPS, expressed either as peak or slope (normal values of our laboratory for age-matched and sex-matched subjects are: EDI 4·1% TLC, EDI/TI 1·93% TLC/s; EPS 3·43% TLC, and EPS/TI 1·85% TLC/s). With fenoterol a marked and significant reduction in both peak and slope were observed (table 3).

RELATIONSHIPS BETWEEN CHANGES IN VARIABLES

For each variable, values recorded at 20 and 40 minutes after fenoterol inhalation were similar. We therefore plotted the different variables in terms of changes recorded between control and 40 minutes after fenoterol. The results of these plots are summarised in table 4. In particular, changes in VT and R*f* were significantly related to changes in both PPLsw (% PPLmax) and the RL/PPLmax ratio (table 4 and fig 3) but not to changes in RL or FEV_1; similarly, changes in EDI/TI and EPS/TI were related to changes in PPLsw (% PPLmax) and RL/PPLmax ratio (table 4). Finally, changes in PPLmax did not relate to changes in FRC.

PLACEBO EFFECTS

With placebo no significant change was observed in the studied variables (tables 2 and 3). Only heart rate exhibited small but significant changes (from 80·6 to 84·1 and 82·9 under control conditions and at 20 and 40 minutes after fenoterol inhalation, respectively).

Discussion

Our results suggest that patients with COPD and severe obstruction of the airways have reduced inspiratory muscle strength, a rapid and shallow pattern of breathing, high pleural

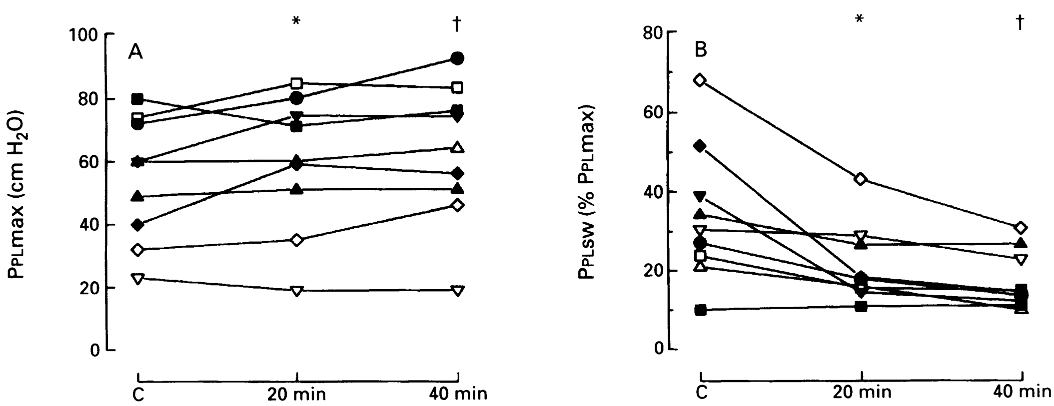

*Figure 2 (A) Maximal pleural pressure (PPLmax) during sniff manoeuvre and (B) pleural pressure swings (PPLSW) expressed as % of PPLmax during tidal breathing under control conditions (C) and 20 and 40 minutes after the inhalation of 800 μg fenoterol. *C versus 20 min, $p<0\cdot05$; †C versus 40 min, $p<0\cdot05$.*

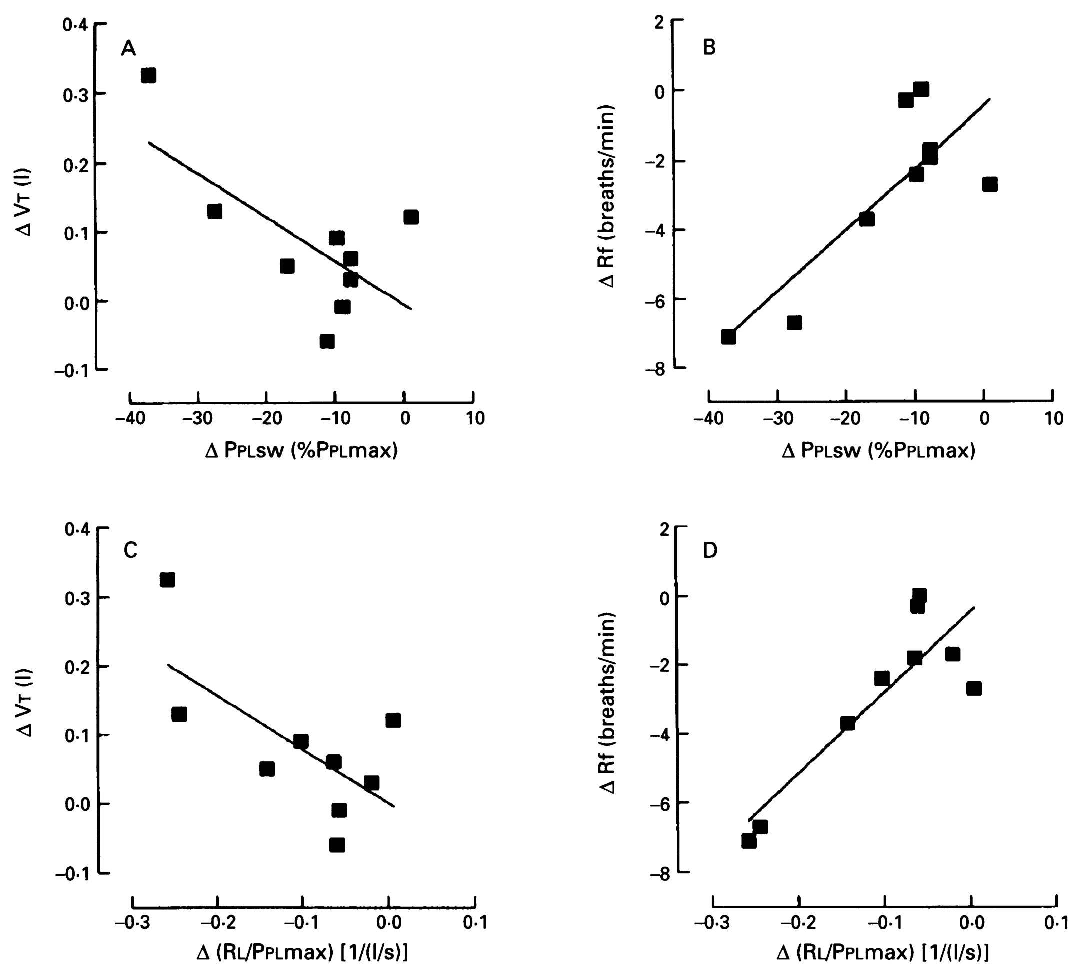

Figure 3 Relationships between changes in tidal volume (VT) and respiratory frequency (Rf) with (A,B) changes in PPLSW (% PPLmax) and (C,D) RL/PPLmax. Abbreviations as in table 3. For explanation see text.

pressure swings during tidal breathing, and high activity of inspiratory muscles as assessed by electromyographic activity of both parasternal and diaphragm muscles. Airflow obstruction plays an important part in determining these alterations, as significant changes were measured after inhalation of a large dose of fenoterol.

Decreased inspiratory muscle strength is common in patients with COPD, particularly when there is accompanying hyperinflation. The reduction in maximal inspiratory pressure

Table 3 Mean (SE) pleural pressure swings, total lung resistance, electromyographic activity of diaphragm and parasternal muscles under control conditions, and 20 and 40 minutes after the inhalation of fenoterol (nine patients) and placebo (five patients)

	PPLsw (cm H_2O)	*RL* (cm H_2O)/(l/s)	*RL/PPLmax* 1(l/s)	*TTI*	*EDI* (%TLC)	*EDI/TI* (%TLC/s)	*EPS* (%TLC)	*EPS/TI* (%TLC/s)
Fenoterol (n = 9)								
Control	16·42	12·85	0·27	0·121	29·5	26·8	31·1	27·3
	(1·99)	(0·99)	(0·04)	(0·020)	(5·8)	(6·3)	(7·9)	(7·6)
20 min	11·19	9·04	0·18	0·080	18·7	13·5	19·0	13·3
	(1·06)	(0·43)	(0·09)	(0·013)	(4·1)	(3·3)	(2·9)	(2·3)
40 min	9·95	8·85	0·167	0·066	14·9	9·9	16·6	10·9
	(1·13)	(0·39)	(0·03)	(0·029)	(3·8)	(2·7)	(2·1)	(1·8)
Analysis of variance								
F	16·01	21·156	10·44	12·356	9·84	9·04	4·29	4·80
p	<0·001	<0·001	<0·005	<0·001	<0·005	<0·005	<0·05	<0·05
Bonferroni test								
p (C *v* 20′)	<0·05	<0·05	<0·05	<0·05	<0·05	<0·05	NS	NS
p (C *v* 40′)	<0·05	<0·05	<0·05	<0·05	<0·05	<0·05	<0·05	<0·05
p (20′ *v* 40′)	NS	NS	NS	NS	NS	NS	NS	NS
Placebo (n = 5)								
Control	16·52	14·07	0·29	0·120	28·98	25·37	29·18	24·45
	(1·97)	(1·21)	(0·06)	(0·024)	(3·0)	(4·9)	(5·88)	(3·63)
20 min	17·4	14·00	0·29	0·115	29·86	27·37	31·67	28·79
	(1·77)	(1·14)	(0·06)	(0·020)	(2·3)	(3·7)	(6·7)	(5·6)
40 min	18·3	14·26	0·30	0·126	29·44	27·30	31·28	27·80
	(2·1)	(1·10)	(0·06)	(0·023)	(4·3)	(4·6)	(7·6)	(4·7)
Analysis of variance								
F	1·555	0·018	0·006	0·817	0·065	0·188	0·542	0·977
p	NS	NS	NS	NS	NS	NS	NS	NS

PPLSW = swings of pleural pressure during tidal breathing; RL = total lung resistance; PPLmax = maximal pleural pressure during maximal sniff manoeuvre; TTI = tension time index of inspiratory muscles calculated as the product of TI/TTOT × PPLSW/PPLmax; EDI = peak of electromyographic activity of diaphragm; EDI/TI = rate of rise of electromyographic activity of diaphragm; EPS = peak of electromyographic activity of parasternal muscles; EPS/TI = rate of rise of electromyographic activity of parasternal muscles.

Table 4 Regression equations between changes in studied variables

Independent variable	*Dependent variable*	*Regression equation*	*Correlation coefficient (r)*	*p*
ΔFEV_1	ΔPPLsw	$y=0{\cdot}65-51{\cdot}20x$	−0·83	<0·01
ΔRL	ΔPPLsw	$y=-0{\cdot}14+1{\cdot}6x$	0·95	<0·002
ΔPPLsw	ΔVT	$y=-0{\cdot}006-0{\cdot}006x$	−0·68	<0·05
ΔPPLsw	ΔRf	$y=-0{\cdot}47+0{\cdot}18x$	0·82	<0·01
ΔRL/PPLmax	ΔVT	$y=0{\cdot}0002-0{\cdot}78x$	−0·67	<0·05
ΔRL/PPLmax	ΔRf	$y=-0{\cdot}51-23{\cdot}3x$	0·86	<0·005
ΔPPLsw	ΔEDI/TI	$y=0{\cdot}87+1{\cdot}28x$	0·91	<0·001
ΔPPLsw	ΔEPS/TI	$y=6{\cdot}96+1{\cdot}68x$	0·90	<0·001
ΔRL/PPLmax	ΔEDI/TI	$y=0{\cdot}75+169x$	0·96	<0·0001
ΔRL/PPLmax	ΔEPS/TI	$y=4{\cdot}04+196x$	0·84	<0·005
$\Delta PETCO_2$	ΔEDI/TI	$y=-3{\cdot}54+3{\cdot}32x$	0·81	<0·01
$\Delta PETCO_2$	ΔEPS/TI	$y=2{\cdot}26+4{\cdot}65x$	0·86	<0·005

VT = tidal volume; Rf = respiratory frequency; $PETCO_2$ = end tidal partial pressure of carbon dioxide. For other abbreviations see footnotes to tables 1 and 3.

is mainly dependent on increased lung volume, which places the inspiratory muscles at a mechanical disadvantage.[4 26 27] However, an increase in the maximal strength of the inspiratory muscles following a β_2 agonist has been reported,[28–30] with an increase in inspiratory muscle fibre length following a fall in end expiratory lung volume[29 30]; a direct effect of β_2 agonists on the respiratory muscles[28] may also have a role. In the present study fenoterol caused a small but significant increase in PPLmax and a decrease in FRC, but no significant relationship between these changes was found. The present data confirm the ability of β_2 agonists to increase inspiratory muscle strength, but the small changes cast doubt on the clinical significance of these increases.

Change in pleural pressure during tidal breathing – that is, PPL swing – is an expression of the mechanical load that inspiratory muscles have to sustain to maintain ventilation, as shown by the close relationship between changes in PPLsw and RL or FEV_1 with fenoterol. The balance between the mechanical impediment to breathing and the ability of inspiratory muscles to develop force – that is, the ratio of RL or PPLsw to PPLmax – reflects the relative force required for inspiration.[8] The high values of PPLsw/PPLmax and RL/PPLmax we obtained indicate that at each breath patients had to use a high proportion of their maximal strength in order to achieve airflow. Fenoterol caused a dramatic decrease in both RL and PPLsw and a small increase in PPLmax; the consequent decrease in RL/PPLmax indicated a decrease in inspiratory muscle loading relative to the maximal available force. The high TTI values in control conditions and their significant decrease after fenoterol confirm this interpretation.

Fenoterol induced small but significant changes in the breathing pattern (increase in VT and reduction in Rf). In order to achieve the increased mechanical load a higher pressure must be developed with each breath and, in the presence of the reduced inspiratory muscle strength (increased RL/PPLmax ratio), a high proportion of the available force will be used at each breath (high PPLsw/PPLmax ratio). In these conditions central respiratory activity is directed towards a shallower pattern of breathing and an increase in respiratory frequency, the latter offsetting the reduction in VT and allowing VE to remain in the normal range.[8] Fenoterol induced significant changes in both VT (increase) and Rf (decrease), which related to changes in PPLsw (%PPLmax) and RL/PPLmax ratio but not to changes in either RL or FEV_1. Consistent with the hypothesis of Rochester,[8] these findings indicate that it is the ratio between the mechanical load and the available strength rather than the mechanical load itself which determines the pattern of breathing.

Patients with COPD have a high neural inspiratory drive compared with normal subjects.[1–4] Our patients showed high values of EMG activity of both diaphragm and intercostal muscles and this suggests that a high neural inspiratory drive was present. This conclusion may be correct if one considers the EMG activity of the inspiratory muscles to be a reliable index of neural inspiratory drive. We have criticised the use of either surface or oesophageal EMG recordings for assessing neural drive in humans.[4 20 31] However, a close correlation between changes in electrical activity of the phrenic nerve and the diaphragm has been reported in dogs, during both normal breathing and obstructed breathing,[32] and data are available to support the contention that the slope of the "moving time average" is a reliable measure for assessing neural inspiratory drive to the respiratory muscles both in normal and in disease states.[4 20 21 24 31] The close relationship between EMG and PPLsw further supports the hypothesis that surface EMG of inspiratory muscles may be a useful tool for evaluating inspiratory muscle activation for clinical purposes. Both mechanical (pulmonary and chest wall)[1 6 7] and chemical afferents[1 9] may be involved in the increased neural inspiratory drive observed in our patients. Fenoterol induced a marked decrease in EDI and EPS in terms of both peak (49·5% and 46·62%, respectively) and slope (63·05% and 60·02%, respectively) activity. The close relationship between decrease in either PPLsw or RL/PPLmax ratio and decrease in EMG activity of both diaphragm and parasternal muscles (table 4) supports the hypothesis that mechanical impairment has an important role in determining the increase in inspiratory neural drive. Chemical factors may also play a part, as shown by the significant relationship between changes in $PETCO_2$ and changes in EDI/TI and EPS/TI.

In conclusion, in patients with severe COPD high doses of fenoterol induce a significant decrease in total lung resistance and a concomitant decrease in PPLsw and in PPLsw/

PPLmax. Decrease in inspiratory muscle loading relative to the maximal available strength, as expressed by the RL/PPLmax and PPLsw/PPLmax ratios, appears to be the major determinant of both changes in breathing pattern and decrease in inspiratory muscle activation. These findings may be of clinical relevance since β_2 agonists at high doses may induce a significant improvement in respiratory mechanics with minor cardiac side effects.

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