

Respiratory muscle function and control of breathing in patients with acromegaly

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ABSTRACT: Increase in lung size has been described in acromegalic patients, but data on respiratory muscle function and control of breathing are relatively scarce. Lung volumes, arterial blood gas tensions, and respiratory muscle strength and activation during chemical stimulation were investigated in a group of 10 patients with acromegaly, and compared with age- and sex-matched normal controls.

Inspiratory muscle force was evaluated by measuring pleural ($P_{pl,sn}$) and trans-diaphragmatic ($P_{di,sn}$) pressures during maximal sniffs. Dynamic pleural pressure swing ($P_{pl,sw}$) was expressed both as absolute value and as percentage of $P_{pl,sn}$. Expiratory muscle force was assessed in terms of maximal expiratory pressure (MEP). In 8 of the 10 patients, ventilatory and respiratory muscle responses to hyperoxic progressive hypercapnia and to isocapnic progressive hypoxia were also evaluated.

Large lungs, defined as total lung capacity (TLC) greater than predicted (above 95% confidence limits), were found in five patients. Inspiratory or expiratory muscle force was below normal limits in all but three patients. During unstimulated tidal breathing, respiratory frequency (f_R) and mean inspiratory flow (tidal volume/inspiratory time (VT/t_I)) were greater, while inspiratory time (t_I) was shorter than in controls. Minute ventilation (\dot{V}'_E) and mean inspiratory flow response slopes to hypercapnia were normal. In contrast, four patients had reduced $\Delta(VT/t_I)/\Delta Sa_{O_2}$ and three had reduced $\Delta \dot{V}'_E/\Delta Sa_{O_2}$. $P_{pl,sw}(\%P_{pl,sn})$ response slopes to increasing end-tidal carbon dioxide tension (P_{ET,CO_2}) and decreasing Sa_{O_2} did not differ from the responses of the normal subjects, suggesting normal central chemoresponsiveness. At a P_{ET,CO_2} of 8 kPa or an Sa_{O_2} of 80%, patients had greater f_R and lower t_I compared with controls. $P_{di,sn}$ and $P_{pl,sn}$ related both to $\Delta \dot{V}'_E/\Delta Sa_{O_2}$ ($r=0.729$ and $r=0.776$, respectively) and $\Delta(VT/t_I)/\Delta Sa_{O_2}$ ($r=0.860$ and $r=0.90$, respectively). $P_{di,sn}$ also related both to $\Delta \dot{V}'_E/\Delta P_{ET,CO_2}$ ($r=0.8$) and $\Delta(VT/t_I)/\Delta P_{ET,CO_2}$ ($r=0.76$).

In conclusion, the data suggest the relative independence of pneumomegaly and respiratory muscle strength. Peripheral (muscular) factors appear to modulate a normal central motor output to give a more rapid pattern of breathing.

Eur Respir J 1997; 10: 977–982.

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Keywords: Acromegaly
control of breathing
respiratory muscles

Received: February 23 1996

Accepted after revision January 26 1997

Patients with acromegaly, a disorder of excess growth hormone (GH) secretion [1], may have increased pulmonary volumes [2–7], which have been attributed to an increase in the size [5] or number [8] of alveoli. Surprisingly, although acromegaly results in generalized muscle weakness and wasting [9], respiratory muscle force, a determinant of pulmonary volumes [10], has received little or no attention [5, 7, 8]. Ventilatory responses to chemical stimuli (hypercapnia and hypoxia) have been assessed [11], but the relative contribution of respiratory muscle function to indices of ventilatory control have not been specifically investigated.

To obtain insight in this field, we assessed respiratory muscle function and the control of breathing in a group of patients with acromegaly both during spontaneous and chemically-stimulated breathing.

Subjects and methods

The subjects comprised five males and five females with acromegaly, referred to the section of pneumology of the Department of Internal Medicine at the University of Florence, from the Department of Endocrinology at the same University. They were studied in a clinically stable condition. Acromegaly was diagnosed on the basis of typical history, clinical features (table 1), elevated insulin-like growth factor-I (IGF-1), and lack of suppression of GH after an oral glucose load. Three patients (Nos. 1, 3 and 4) who had previously undergone pituitary surgery, were receiving thyroxine replacement and had stable thyroid function. Patients with major cardiovascular involvement, moderate-to-severe (angles $\geq 40^\circ$) kyphosis, kyphoscoliosis, or radiographic

Table 1. — Anthropometric characteristics and clinical data in 10 patients with acromegaly

Pts No.	Sex	Age yrs	BMI kg·m ⁻²	GH ng·mL ⁻¹	IGF-1 ng·mL ⁻¹	Duration of disease yrs
1	M	42	26.0	10.7	94*	8.5
2	M	43	23.7	50.0	82*	1.0
3	M	23	27.5	0.9	50	3.0
4	M	50	29.9	2.2	43*	3.0
5	M	49	30.1	9.0	NA	5.0
6	F	40	20.3	6.0	80*	2.5
7	F	60	24.3	5.2	78*	13.0
8	F	48	32.5	6.7	64*	NA
9	F	59	25.0	14.0	70*	4.0
10	F	52	32.9	8.0	59*	5.0

Pts: patients; M: male; F: female; BMI: body mass index; GH: growth hormone (normal values <4 ng·mL⁻¹); IGF-1: insulin-like growth factor-I; NA: not available. *: values above the normal range calculated for age and sex.

and echographic findings of pulmonary hypertension were excluded. None of the patients fulfilled diagnostic criteria for chronic obstructive pulmonary disease (COPD) or asthma [12]. Patient No. 4, alone, had a previous history of smoking. A group of normal subjects matched for sex (9 males and 12 females) and age (mean age 43 yrs, range 23–65 yrs) was studied as controls.

Functional evaluation

Spirometric volumes were measured as described previously [13], with subjects in a seated position. The normal values used for lung volumes are those proposed by the European Coal and Steel Community [14]. 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 and adjustment began when the marker was at the external nares. The catheter was connected to a differential pressure transducer (Validyne, Northridge, CA, USA). Maximal (most negative in sign) pleural pressure (P_{pl}) was obtained at functional residual capacity (FRC) during a maximal sniff manoeuvre [15] ($P_{pl,sn}$), which was repeated until three measurements with less than 5% variability were recorded. The highest value of $P_{pl,sn}$ was used for subsequent analysis. Gastric pressure (P_{ga}) was measured simultaneously, using a similar balloon-catheter system connected to a second differential transducer. This balloon was positioned in the stomach with the tip 65–70 cm from the nares and contained 2 mL of air. Transdiaphragmatic pressure ($P_{di,max}$) at FRC during the sniff manoeuvre was obtained by subtracting P_{pl} from P_{ga} [16]. Dynamic P_{pl} was also recorded during tidal breathing, and P_{pl} swings ($P_{pl,sw}$) were calculated as the differences between the P_{pl} measured at end-expiration and end-inspiration. $P_{pl,sw}$ were expressed both as absolute values (cmH₂O) and as percentage of $P_{pl,sn}$. $P_{pl,sw}(\% P_{pl,sn})$ represents the pressure required to breathe relative to the maximal inspiratory pressure (MIP) available. Maximal expiratory pressure (MEP) was recorded from total lung capacity (TLC) as described in detail previously [16, 17]. Predicted values are those proposed by BLACK and HYATT [18].

The ventilatory pattern was evaluated with subjects in a comfortable seated position. In the apparatus used, the inspiratory line was separated from the expiratory line by a one-way valve (Hans-Rudolph, Kansas City, MO, USA) connected to a Fleisch No. 3 pneumotachograph. The flow signal was integrated to give volume. From the spirogram, the following parameters were derived: inspiratory time (t_I), expiratory time (t_E), total time of the respiratory cycle (t_{tot}), tidal volume (V_T), mean inspiratory flow (V_T/t_I), duty cycle (t_I/t_{tot}). Respiratory frequency ($f_R = 1/t_{tot} \times 60$) and minute ventilation ($V'E = V_T \times f_R$) were also calculated.

Expired carbon dioxide tension (P_{CO_2}) was sampled continuously at the mouth by an infrared CO₂ meter. The values for dead space and resistance of the system up to a flow of 4 L·s⁻¹ were 178 mL and 0.92 cmH₂O·L⁻¹·s⁻¹, respectively. Baseline evaluation began after a 10 min adaptation period. The output of the CO₂ meter, the flow signal, integrated flow, mouth pressure and $P_{pl,sw}$ were recorded continuously on a multichannel chart recorder over a 10 min period. Average values for each subject are presented.

Rebreathing tests

Responses to progressive hypercapnia were obtained in eight patients and in eight normal subjects (aged 30–53 yrs), who volunteered to take part in this evaluation. The technique utilized was that proposed by REID [19]. The equipment for measuring ventilation and CO₂ output has been described above. Details of the method have been described previously [17]. The same subjects also underwent progressive isocapnic hypoxia produced by rebreathing air from a 6 L bag. Isocapnic conditions were maintained for 5 min before the onset of hypoxia and throughout the hypoxic period by passing a portion of the expired gas through a CO₂ scrubber before returning it to the rebreathing bag. End-tidal carbon dioxide tension (P_{ET,CO_2}) was kept constant by manually regulating the volume of the expired gas scrubbed. The intensity of the hypoxic stimulus was assessed by continuous recording of the arterial O₂ saturation (S_{a,O_2}) using an ear oximeter (Radiometer, Copenhagen). Rebreathing was terminated when the S_{a,O_2} , displayed digitally, reached 75%. For each run, changes in $V'E$, V_T (both corrected to body temperature atmospheric pressure and saturation with water vapour (BTPS)), time components of the breathing pattern (f_R , t_I , t_E , t_{tot}), and $P_{pl,sw}$ were recorded continuously.

Endocrine data

GH secretion was evaluated as the mean of measurements obtained at hourly intervals over a 12 h period. GH was measured by a radioimmunoassay kit (human growth hormone enzyme-amplified sensitivity immunoassay (HGH-EASIA); Medgenix Diagnostic, Fleurus, Belgium). IGF-1, a GH-dependent growth factor that shows no diurnal variation, was measured by radioimmunoassay kit (Somatomedin-C Radioimmunoassay Competition Test (SM-C-RIA-CT); Medgenix Diagnostic).

The study was approved by the Ethics Committees of our Institutions and informed consent was obtained from the subjects.

Statistical analysis

Values are shown as mean and SD, unless otherwise reported. Results were compared by the Wilcoxon test for paired samples. A p-value less than 0.05 was considered to be significant. Regression analysis was performed by the least squares method.

Results

Table 1 presents the clinical characteristics of the patients. As shown by the elevated levels of IGF-1, most patients were in an active phase of the disease. Body mass index (BMI; weight·height⁻²) ranged 20.3–32.9 kg·m⁻². Patients Nos. 5, 8 and 10 were obese (BMI >30 kg·m⁻²). As shown in table 2, TLC, vital capacity (VC) and forced expiratory volume in one second (FEV₁) were normal or above, irrespective of gender. P_{a,CO_2} was slightly increased in patients Nos. 2 and 3, and P_{a,O_2} was normal in all.

$P_{di,sn}$ was low in patient No. 6, while in patients Nos. 4 and 5 it was just below the lowest normal limits (mean -1.65 SD) for our laboratory (80 cmH₂O in females and 110 cmH₂O in males) (table 2). In patients Nos. 6 and 7, $P_{pl,sn}$ was markedly below the lowest normal limits (mean -1.65 SD) for our laboratory (58 cmH₂O in females and 65 cmH₂O in males). Neither $P_{di,sn}$ nor $P_{pl,sn}$ was related to TLC (% pred). MEP was in the normal range [18] (mean -2 SD) in all but four patients (Nos. 2, 6, 8 and 9), whose values were 39, 38.8, 51 and 52% pred, respectively.

Table 2 also shows the breathing pattern both in patients and in normal subjects. As shown, f_R ($p<0.01$) and V_T/t_I ($p<0.001$) were significantly greater in the patients and $V'E/TLC$ tended to be so ($p=0.055$), with a shorter t_I ($p<0.05$), which was significantly related to $P_{di,sn}$ ($r=0.674$; $p<0.03$).

Hypercapnic responses in terms of $V'E$ and V_T/t_I (fig. 1) were within the normal range (mean values ± 1.65 SD).

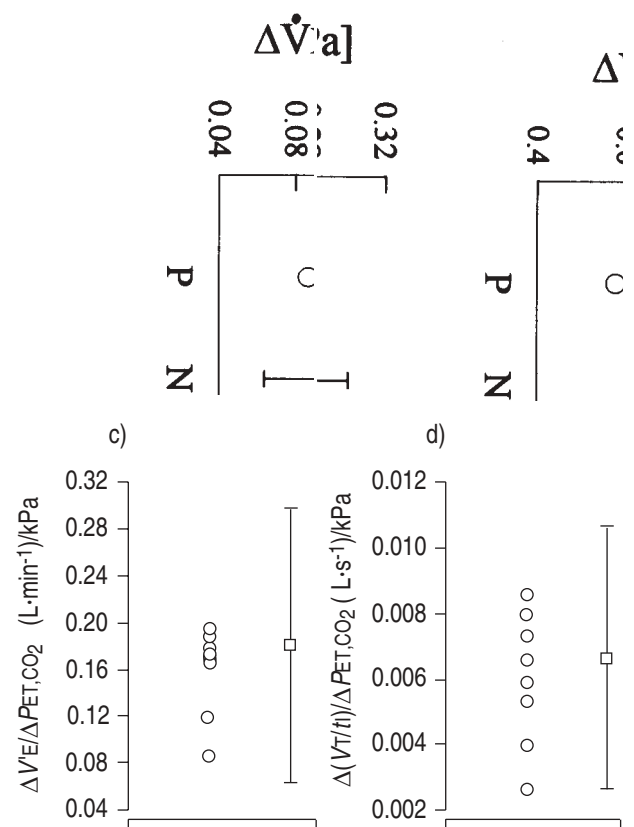


Fig. 1. — a) ventilatory; and b) mean inspiratory flow response slopes to hypoxia in eight patients with acromegaly; c) ventilatory; and d) mean inspiratory flow response slopes to hypercapnia in the same patients. Circles are individual patient's data points. Squares and vertical lines represent the mean and ± 1.65 SD, respectively, of normal values in our laboratory. $V'E$: minute ventilation; V_T/t_I : mean inspiratory flow; S_{a,O_2} : arterial oxygen saturation; P_{ET,CO_2} : end-tidal carbon dioxide tension. See text for further explanation.

Table 2. — Functional data of 10 patients with acromegaly

Pts No.	VC % pred	TLC %pred	FRC % pred	FEV ₁ %pred	P_{a,O_2} kPa	P_{a,CO_2} kPa	$V'E/TLC$ min ⁻¹	f_R breaths·min ⁻¹	V_T/TLC	t_I s	V_T/t_I L·s ⁻¹	$P_{di,sn}$ cmH ₂ O	$P_{pl,sn}$ cmH ₂ O
1	126*	145*	203*	129*	11.4	5.85	0.80	8.9	0.09	2.50	0.44	125	110
2	84	84	99	89	10.6	5.99	2.00	18.2	0.11	1.10	0.55	116	106
3	132*	137*	180*	121*	13.2	5.99	1.36	15.1	0.09	1.53	0.59	142	105
4	112	113	117	80	11.4	5.45	1.83	14.1	0.13	1.64	0.67	106	86
5	197*	186*	189*	167*	10.9	5.45	1.07	11.9	0.09	1.69	0.65	100	83
6	127*	132*	135*	128*	12.1	5.19	2.03	20.3	0.10	1.76	0.34	55	40
7	115	106	100	105	12.0	5.59	2.06	17.2	0.12	1.30	0.46	82	44
8	116	119	95	106	11.4	5.85	2.00	16.7	0.12	1.49	0.47	90	86
9	163*	129*	102	164*	12.5	5.32	1.73	13.3	0.13	1.66	0.42	84	86
10	102	105	109	90	12.8	5.59	1.45	16.1	0.09	1.54	0.52	106	79
Mean	127	126	133	118	11.8	5.64	1.63	15.2	0.11	1.62	0.51	99.5	82.5
SD	32	28	42	30	1.0	0.26	0.45	3.3	0.02	0.37	0.11	26.0	23.9
Normals													
Mean	100	100	101	98	-	-	1.30	12.3	0.106	1.90	0.37	-	-
SD	10	10	10	15	-	-	0.24	3.4	0.017	0.35	0.09	-	-
p-value							0.055	<0.01		<0.05	<0.001		

Pts: patients; VC: vital capacity; TLC: total lung capacity; FRC: functional residual capacity; FEV₁: forced expiratory volume in one second; % pred: percentage of predicted value; P_{a,O_2} : arterial oxygen tension; P_{a,CO_2} : arterial carbon dioxide tension; $V'E$: minute ventilation; f_R : respiratory frequency; V_T : tidal volume; t_I : inspiratory time; V_T/t_I : mean inspiratory flow; $P_{di,sn}$: trans-diaphragmatic pressure during sniff; $P_{pl,sn}$: pleural pressure during sniff. *: values above 95% confidence limits.

By contrast, the V_T/t_I response to hypoxia was below the normal range in four patients and the $V'E$ response was lower in three patients (fig. 1). At a P_{ET,CO_2} of 8 kPa and an S_{a,O_2} of 80%, patients had a greater f_R and shorter t_I compared with controls (table 3).

$P_{di,sn}$ and $P_{pl,sn}$ were related both to $\Delta V'E/\Delta S_{a,O_2}$ ($r=0.729$, $p=0.04$ and $r=0.776$, $p=0.02$, respectively) (fig. 2) and $\Delta(V_T/t_I)/\Delta S_{a,O_2}$ ($r=0.860$, $p=0.006$ and $r=0.90$, $p=0.002$, respectively). $P_{di,sn}$ was also related both to $\Delta V'E/\Delta P_{CO_2}$ ($r=0.8$; $p=0.02$) and $\Delta(V_T/t_I)/\Delta P_{CO_2}$ ($r=0.76$; $p=0.03$). Neither $\Delta P_{pl,sw}/\Delta P_{CO_2}$ (range 0.2–0.8 and 0.5–1.3

$\text{cmH}_2\text{O}\cdot\text{kPa}^{-1}$, for patients and controls respectively) nor $\Delta P_{pl,sw}/\Delta S_{a,O_2}$ (range 0.15–0.56 and 0.3–0.75 $\text{cmH}_2\text{O}/\%$, for patients and controls, respectively) were related to any of the ventilatory response slopes to chemical stimulation. In two of the four patients with low $\Delta V'E/\Delta S_{a,O_2}$, $\Delta P_{pl,sw}/\Delta S_{a,O_2}$ had the lowest value (0.15 $\text{cmH}_2\text{O}/\%$).

Finally, $P_{pl,sw}(\%P_{pl,sn})$ response slopes to increasing P_{ET,CO_2} and decreasing S_{a,O_2} , indices of inspiratory muscle activation (central output) with chemical stimulation, did not differ significantly from the responses of the normal subjects (table 4).

Table 3. – Ventilatory pattern at P_{ET,CO_2} of 8 kPa and S_{a,O_2} of 80% in patients and in normal subjects

	$P_{ET,CO_2} = 8 \text{ kPa}$					$S_{a,O_2} = 80\%$				
	$V'E/\text{TLC}$ min^{-1}	V_T/TLC	f_R $\text{breaths}\cdot\text{min}^{-1}$	t_I s	V_T/t_I $\text{L}\cdot\text{s}^{-1}$	$V'E/\text{TLC}$ min^{-1}	V_T/TLC	f_R $\text{breaths}\cdot\text{min}^{-1}$	t_I s	V_T/t_I $\text{L}\cdot\text{s}^{-1}$
Patients	3.38 (1.25)	0.235 (0.09)	16.5 (4.4)	1.58 (0.32)	0.97 (0.38)	3.84 (1.8)	0.222 (0.093)	19.46 (6.36)	1.4 (0.33)	0.82 (0.3)
Normals	3.05 (1.51)	0.25 (0.087)	13 (2)	1.9 (0.3)	0.7 (0.12)	3.87 (2.05)	0.251 (0.069)	13 (2.1)	1.8 (0.29)	0.8 (0.1)
p-value	NS	NS	<0.05	<0.05	<0.1	NS	NS	<0.05	<0.05	NS

Values are presented as mean, and SD in parenthesis. S_{a,O_2} : arterial oxygen saturation; P_{ET,CO_2} : end-tidal carbon dioxide tension; NS: nonsignificant. For further definitions see legend to table 2.

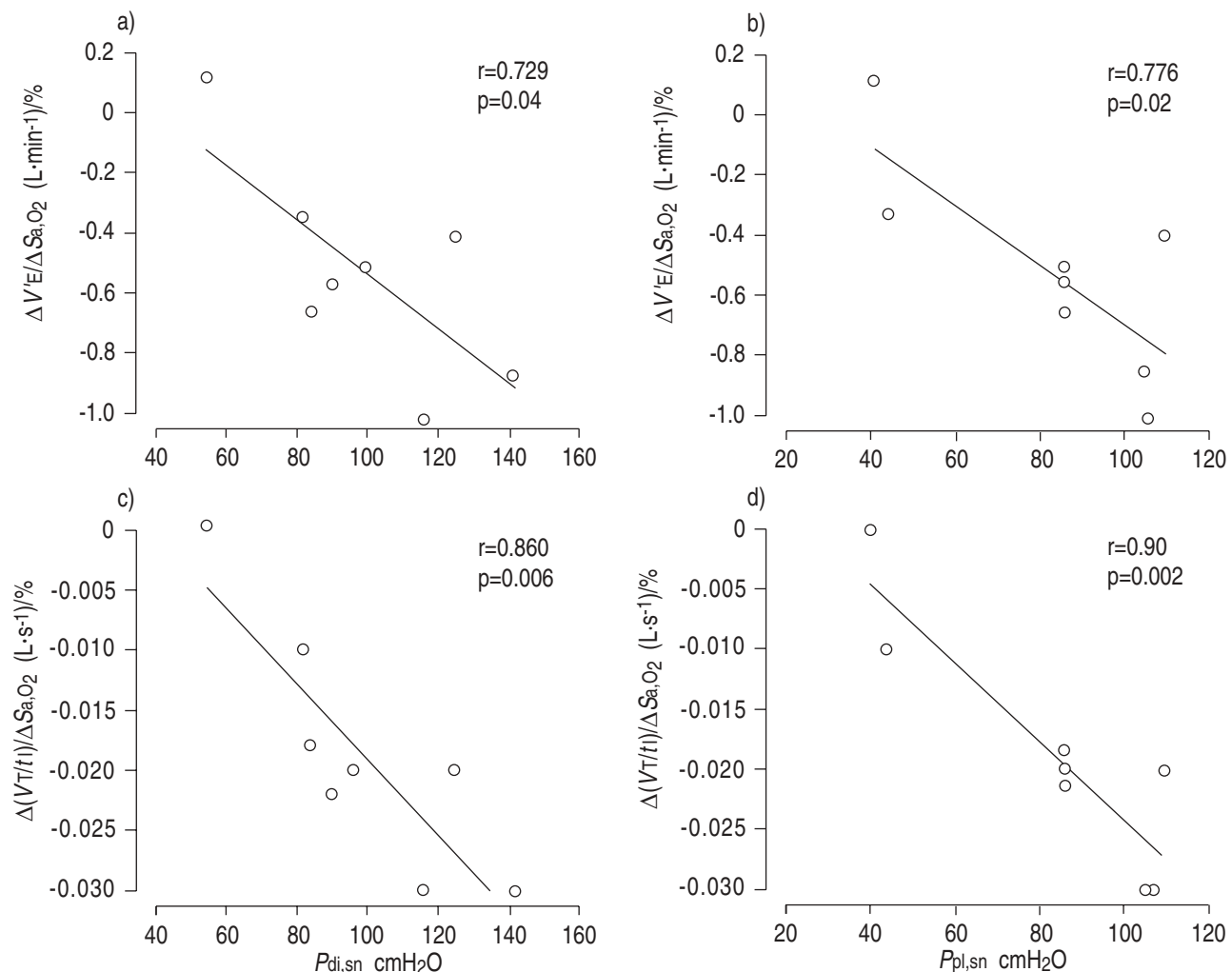


Fig. 2. – Relationships of a) $P_{di,sn}$; and b) $P_{pl,sn}$ to $\Delta V'E/\Delta S_{a,O_2}$ in eight patients with acromegaly. Relationships of c) $P_{di,sn}$; and d) $P_{pl,sn}$ to $\Delta(V_T/t_I)/\Delta S_{a,O_2}$ in eight patients with acromegaly. Individual data points are shown. $P_{di,sn}$: transdiaphragmatic pressure during sniff; $P_{pl,sn}$: pleural pressure during sniff; $V'E$: minute ventilation; V_T/t_I : mean inspiratory flow; S_{a,O_2} : arterial oxygen saturation.

Table 4. – Individual slopes of $P_{pl,sw}(\%P_{pl,sn})$ both to Sa,O_2 and P_{ET,CO_2} in acromegalic patients and normal subjects

	$\Delta P_{pl,sw}/\Delta Sa,O_2$ % $P_{pl,sn}/\%$	$\Delta P_{pl,sw}/\Delta P_{ET,CO_2}$ % $P_{pl,sn}/kPa$
Patients	-0.33 (0.08)	0.512 (0.267)
Normals	-0.39 (0.024)	0.75 (0.43)

Values are presented as mean and SD in parenthesis. $P_{pl,sw}$: pleural pressure swing; $P_{pl,sn}$: pleural pressure during sniff; Sa,O_2 : arterial oxygen saturation; P_{ET,CO_2} : end-tidal carbon dioxide tension.

Discussion

Irrespective of gender, the patients had normal or increased TLC and VC. In seven of the patients, inspiratory or expiratory muscle pressures were abnormal. Compared to the controls, f_R and V_T/t_I were significantly greater, $V'E/TLC$ tended to be so and t_I was shorter in the patients, while CO_2 responsiveness was normal and a blunted hypoxic ventilatory response was found in four out of eight patients. Inspiratory muscle activation or central output to chemical stimulation was normal. t_I was related to $P_{pl,sw}$, and maximal inspiratory muscle strength modulated the ventilatory responses to chemical stimulation.

Inspiratory muscle force

Acromegaly in its earlier stages can cause an increase in muscle bulk and strength. Later it results in generalized muscle weakness and wasting [9]. Muscle biopsy studies have shown segmental fibre degeneration, foci of small cell infiltration, thickening of capillary basement membranes, and variable hypertrophy and atrophy involving either type I or type II fibres [20]. Surprisingly, however, respiratory muscle force, a determinant of pulmonary volumes [10], has not been investigated in detail in acromegaly [5, 7, 8]. In the study by BRODY *et al.* [5] MIP and MEP of 40 cmH₂O, the maximal gauge pressure allowed by an aneroid manometer, were reported as normal. In the study by DONNELLY *et al.* [8], MIP and MEP were normal but no data on the stage of disease were given. In a disease where skeletal abnormalities are often reported [4], suggesting possible change in elastic characteristics of the chest wall, and where skeletal muscle wasting is an ongoing process and death due to respiratory disorders is three times more frequent than would be expected [21], the contribution of the respiratory muscles to breathing needs to be assessed.

In the present study, we have shown that maximal respiratory muscle pressures, either inspiratory (Nos. 4, 5 and 7) or expiratory (Nos. 2, 8 and 9) or both (No. 6) were abnormal in most patients. The observation that a normal or even subnormal respiratory muscle force was accompanied in most cases by a greater than expected TLC suggests the relative independence of pneumomegaly and muscle strength in this condition.

Control of breathing

Control of breathing has been assessed previously in patients with acromegaly [5, 11]. In these patients, V_T

was found to be increased out of proportion to decreased lung elasticity [5], an observation consistent with abnormalities in the control of breathing. Furthermore, increased basal metabolism has been reported in patients with acromegaly [22]. In this context, one has to consider that, according to the equation:

$$P_{a,CO_2} = V'CO_2 \cdot K/V'E (1 - V_D/V_T)$$

where $V'CO_2$ is the CO_2 output, V_D is the dead space and K is a constant, an increased $V'E$ could, in part, account for the normal P_{a,CO_2} found in the present study. An increased $V'E$ may result from increases either in f_R or V_T , or both. In the circumstances of the present study, V_T was normalized by relating it to the lung volume (TLC). The normalized V_T was similar in normal subjects and in patients, in whom a greater f_R maintained the tendency for $V'E$ to be greater, indicating that respiratory central output was modulated, *via* a shorter inspiratory time (t_I), to give a more rapid pattern of breathing. This pattern was also found during stimulated breathing at a given level of chemical drive (table 3).

A possible mechanical linkage between breathing pattern and inspiratory muscle force was shown by the relationship between $P_{pl,sw}$ and t_I . This finding is similar to that observed in patients with several neuromuscular or multisystem disorders [23–25]. Nonvagal afferent information either from weak respiratory muscles [26] or a stiffened rib cage [24] have been thought to act on the central inspiratory controller to terminate inspiration. The contribution of these factors to the shortened t_I and higher f_R was not specifically investigated in the present study.

Normal or increased responsiveness to hypercapnia and normal responsiveness to hypoxia have been reported in patients with acromegaly [11]. In the present study, the ventilatory response slopes to CO_2 were within the normal range, while response slopes to hypoxia were low in four patients. $V'E$ response slopes, either normal or low, were invariably associated with normal $P_{pl,sw}(\%P_{pl,sn})$ response slopes both to hypoxic and hypercapnic stimuli. In clinical terms, a change in the pressure generated by the ventilatory muscles, expressed as a fraction of their maximal pressure generating ability, reflects change in inspiratory muscle activation and, therefore, inspiratory motor output [27, 28]. Hence, the normal $P_{pl,sw}(\%P_{pl,sn})$ response slope, which indicates normal activation of the respiratory muscles during chemically stimulated breathing (central chemoresponsiveness), underlines the normal role of central factors in the control of breathing in these patients. However, the observation that, during chemical stimulation, the lower the $V'E$ (and V_T/t_I) response slopes the lower the inspiratory muscle force, and vice versa (fig. 2), is consistent with respiratory muscle force influencing the responses observed.

In conclusion, respiratory muscle force was not the major determinant of the increased lung volumes in acromegaly. However, peripheral (muscular) factors appear to influence indices of ventilatory control and to modulate a normal central motor output so as to produce a more rapid pattern of breathing.

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