

Control of breathing in patients with limb girdle dystrophy: a controlled study

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Abstract

Background—In patients with limb girdle dystrophy the relative contribution of peripheral factors (respiratory muscle weakness, and lung and/or airway involvement) and central factors (blunted and/or inadequate chemoresponsiveness) in respiratory insufficiency has not yet been established. To resolve this, lung volumes, arterial blood gas tensions, respiratory muscle strength, breathing pattern and neural respiratory drive were investigated in a group of 15 patients with limb girdle dystrophy. An age-matched normal group was studied as a control.

Methods—Respiratory muscle strength was assessed as an arithmetic mean of maximal inspiratory (MIP) and expiratory (MEP) pressures. Breathing pattern was evaluated in terms of volume (ventilation V_E , tidal volume V_T) and time (respiratory frequency R_f , inspiratory time T_I , expiratory time T_E) components of the respiratory cycle. Neural respiratory drive was assessed as the mean inspiratory flow (V_T/T_I), mouth occlusion pressure ($P_{0.1}$) and electromyographic activity (EMG) of the diaphragm (EMGd) and the intercostal parasternal (EMGp) muscles. In 10 of the 15 patients the responses to carbon dioxide (PCO_2) stimulation were also evaluated.

Results—Most patients exhibited a moderate decrease in vital capacity (VC) (range 37–87% of predicted), MIP (range 23–84% of predicted), and/or MEP (range 13–41% of predicted). The arterial carbon dioxide tension ($PaCO_2$) was increased in three patients breathing room air, while PaO_2 was normal in all. Compared with the control group R_f was higher, and V_T , T_I and T_E were lower in the patients. EMGd and EMGp were higher whilst V_T/T_I and $P_{0.1}$ were normal in the patients. Respiratory muscle strength was inversely related to EMGd and EMGp. $PaCO_2$ was found to relate primarily to VC and duration of illness, but not to respiratory muscle strength. During hypercapnic re-breathing $\Delta V_E/\Delta PCO_2$, $\Delta V_T/\Delta PCO_2$, and $\Delta P_{0.1}/\Delta PCO_2$ were lower than normal, whilst $\Delta EMGd/\Delta PCO_2$ and $\Delta EMGp/\Delta PCO_2$ were normal in most patients. A direct relation between respiratory muscle strength and $\Delta V_T/\Delta PCO_2$ was found.

Conclusions—The respiratory muscles, especially expiratory ones, are weak in patients with limb girdle dystrophy. Reductions in respiratory muscle strength

are associated with increased neural drive and decreased ventilatory output ($\Delta V_T/\Delta PCO_2$). The decrease in VC, together with the duration of disease, influence $PaCO_2$. VC is a more useful test than respiratory muscle strength for following the course of limb girdle dystrophy.

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Keywords: neuromuscular diseases, respiratory drive, respiratory muscle strength, breathing pattern.

Patients with limb girdle dystrophy experience chronic cough, dyspnoea on exertion, and recurrent respiratory tract infection.¹ Furthermore, chronic hypercapnia develops in the absence of precipitating factors such as pulmonary infection, oxygen therapy or sedation.^{2,3} Severe diaphragmatic weakness may be a factor contributing to the chronic hypercapnia, a problem which seems much more likely to develop in these patients than in those with Duchenne type dystrophy.⁴ However, no studies have been carried out to establish the relative contribution of peripheral (respiratory muscle weakness, and lung and/or airway involvement) and central (blunted and/or inadequate chemoresponsiveness) factors to respiratory insufficiency in patients with limb girdle dystrophy.

We have examined the relative importance of lung and chest wall mechanics and indices of central respiratory drive by measuring lung volumes, arterial blood gas tensions, overall respiratory muscle strength, breathing pattern, and hypercapnic ventilatory responses in a group of patients with limb girdle dystrophy and age matched controls.

Methods

SUBJECTS

Fifteen patients (seven men) of mean (SD) age 43.3 (15.4) years (range 20–74) with limb girdle dystrophy and no respiratory complaints were studied; 12 were ambulatory and three were wheelchair bound. The following criteria updated from a previous classification⁵ were used to select patients: (1) inheritance pattern: autosomal recessive in six families and nine sporadic cases; (2) phenotype expression: all patients had a symmetrical limb girdle, proximal distribution without facial involvement or contractures. Distal limb muscles were involved only in the severely affected patients; (3) electromyographic findings were compatible with a progressive chronic myopathy; (4) histopathological findings in the muscles

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included dystrophic lesions without an inflammatory cell infiltrate or features of metabolic or congenital myopathies. In addition, in two sporadically affected men the absence of dystrophin abnormalities excluded Duchenne and Becker muscular dystrophies. No patients had a scoliosis or any abnormality on the chest radiograph or obvious abnormalities in diaphragm placement.⁴ Two patients were current smokers. The duration of their disease was 22.2 (9) years (range 8–35).

Twenty normal subjects matched for age (range 20–70 years, 10 men) were studied as a control group.

The study was approved by the local ethics committee and subjects gave their informed consent.

FUNCTIONAL EVALUATION

Routine spirometric tests and arterial blood gas tensions obtained with subjects in a seated position were measured as previously described.⁶ The normal values for lung volumes were those of the European Community for Coal and Steel.⁷ Maximal static inspiratory (MIP) and expiratory (MEP) pressures at residual volume (RV) and total lung capacity (TLC), respectively, measured against an obstructed mouthpiece with a small leak to minimise oral pressure artefacts, were recorded using a differential pressure transducer (Statham SC 1001). The subjects were comfortably seated, wearing a noseclip, and performed maximal inspiratory efforts maintaining maximal pressures for at least one second. The manoeuvres were repeated until three measurements with less than 5% variability were recorded, and the highest value obtained was taken for analysis. The predicted values for maximal respiratory pressures were those proposed by Black and Hyatt.⁸ A value of respiratory muscle strength was calculated as proposed by Braun *et al.*⁹ [(MIP % predicted value + MEP % predicted value)/2]. In the presence of respiratory muscle weakness the measured value of MIP and MEP may be affected by lung volume as well as by myopathy; we therefore corrected for these effects of lung volume on MIP and MEP.¹⁰

After baseline routine testing breathing room air the ventilatory pattern and mouth occlusion pressure were evaluated with subjects in a comfortable supine position. In the apparatus used the inspiratory line was separated from the expiratory line by a one-way valve (Hans-Rudolph) connected to a Fleisch type 3 pneumotachograph. The flow signal was integrated into volume. From the spirogram inspiratory time (Ti), expiratory time (Te), total time of the respiratory cycle (T_{TOT}), tidal volume (VT), mean inspiratory flow (VT/Ti), and duty cycle (Ti/T_{TOT}) were derived. Respiratory frequency ($Rf = 1/T_{TOT} \times 60$) and minute ventilation ($VE = VT \times Rf$) were also calculated. Mouth pressure during VT manoeuvres was measured using a pressure transducer (Statham P23ID). Mouth occlusion pressure 0.1 second after the beginning of inspiration ($P_{0.1}$)¹¹ was recorded as previously described.^{12–14} Expired CO₂ (P_{CO₂})

was sampled continuously at the mouth and measured by an infrared CO₂ meter (Normcap 200, Datex). The values for dead space and resistance of the system up to a flow of 4 l/s were 178 ml and 0.92 cm H₂O/l/s, respectively.

The electromyographic activity (EMG) of the respiratory muscles was recorded as previously described.^{12–14} The EMG of the chest wall muscles was recorded from the second parasternal intercostal muscles (EMGp) and the diaphragm (EMGd) via large surface electrodes. The EMGd was recorded from the lower anterolateral rib cage.¹⁵ Muscle action potentials (“raw”) were differentially amplified and filtered between 100 and 1000 Hz to remove as much ECG as possible without significantly filtering the 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”.¹⁶ Inspiratory activity was quantified both as peak of activity (XP) and as rate of rise of activity (XP/Ti). The former was directly measured in arbitrary units and the latter was obtained by dividing it by the inspiratory time.

Because of 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 total lung capacity (TLC).^{12–14} This was repeated at least three times and in each subject the intensity of the recorded diaphragmatic EMG was closely reproducible (less than 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 checked cardiac artefacts by manually gating the ECG, when necessary, so that it would not contribute to the EMG. EMG data in the text and tables are expressed in terms of rate of rise of activity.

The output of the CO₂ meter, flow signal, integrated flow signal, mouth pressure, and the moving time average were recorded continuously on a multichannel chart recorder. After a 10 minute adaptation period, baseline evaluation began. Respiratory cycles, occlusions, and EMG were continuously recorded for 10 minutes and the cycles following occlusions discarded. Average values for each subject are presented. Subsequently, the subjects underwent a CO₂ rebreathing test.¹⁷ A gas mixture (7% CO₂, 93% O₂) was inhaled for 3–4 minutes and the sampled gas was returned to the rebreathing bag. Rebreathing started after 30–45 seconds which allowed the subject to equilibrate with the circuit, as shown by the plateau on the CO₂ recording and minimal

Table 1 Pulmonary function data in 15 patients with limb girdle dystrophy

Subject	VC (%pred)	FEV ₁ (%pred)	FEV ₁ /VC (%)	FRC (%pred)	RV (%pred)	TLC (%pred)	MIP (%pred)	MEP (%pred)	RMS (%)	PaO ₂ (kPa)	Paco ₂ (kPa)
1	85	83	78	86.4	122.7	96	52.4	27.5	40	13.8	4.65
2	68	69	88	88	102	80	64.1	17.8	41	11.7	5.59
3	55	57	80	84	98	82	92.2	22	57.1	9.7	5.98
4	68	60	70	79	108	88	49.2	12.9	31.1	13.5	4.79
5	99	82	71	97	100	99	68.5	32	50.5	11.9	5.05
6	71	71	81	92	154	100	79.2	30	54.6	13.3	4.52
7	83	83	81	69	152	91	89.2	24.3	56.8	13.3	4.39
8	37	40	81	59	75	62	36.8	14.6	25.7	10.2	6.34
9	57	62	83	72	159	84	84.9	34.2	59.6	13.9	5.47
10	90	79	77	81	130	100	89.6	27.6	58.6	12.7	5.05
11	61	64	81	74	100	73	73.9	42	57.9	10.9	5.68
12	37	41	94	68	135	65	27.5	17.9	22.7	10.1	6.09
13	44	45	82	69	97	70	46.3	22.1	34.2	12.6	5.72
14	57	55	78	95	102	86.9	29	17.2	23.1	10.5	5.88
15	54	52	78	80.5	99	82.3	34.5	32.9	33.7	10.9	5.32
Mean	64.4	62.9	80.2	79.6	115	83.9	61.1	25.0	43.1	11.9	5.37
SD	18.8	14.8	5.9	11.0	25.1	12.4	23.3	8.3	14.0	1.5	0.60

VC=vital capacity; FEV₁=forced expiratory volume in one second; FRC=functional residual capacity; RV=residual volume; TLC=total lung capacity; MIP=maximal inspiratory pressure; MEP=maximal expiratory pressure; RMS=respiratory muscle strength calculated as arithmetical mean of MIP (% predicted) and MEP (% predicted); PaO₂=arterial oxygen tension; Paco₂=arterial carbon dioxide tension.

Pco₂ inspiratory/expiratory swings. The resistance of the circuit used during unoccluded breathing was such that mouth pressure during unoccluded breathing was always within <0.2 kPa of atmospheric pressure. During CO₂ inhalation, when the open loop condition was achieved, occlusions were randomly performed every 10–20 seconds. Both in normal subjects and in patients peak average at TLC remained fairly constant throughout the CO₂ rebreathing run (5–10%). In each subject the test was repeated on the same day with an interval of at least 60 minutes between each test. For each rebreathing run changes in V_E, time, and volume components of breathing pattern, P_{0.1} and EMG were plotted against increasing Pco₂ and subjected to least square linear regression analysis.

Rebreathing data were available for 10 out of the 15 patients (nos 1–5, 11–15), since two of the remaining five did not give their consent to be tested and three patients (nos 6, 8, and 9) sensed such discomfort during inhalation of the CO₂ mixture that it caused early interruption of the test.

DATA ANALYSIS

The results were compared by the Mann-Whitney U test for unpaired samples. The relation between respiratory muscle strength and VC, Paco₂, EMG, and V_E and V_T response slope to increasing CO₂ were assessed by linear regression analysis. The relation between different variables was analysed by multiple regression analysis, a value of p<0.05 being considered to be significant. All statistical analyses were carried out using the Statgraphics 6.0 package (Manugistics Inc, Rockville, MD, USA).

Results

DATA UNDER CONTROL CONDITIONS

Spirometry and arterial blood gas tensions

Lung function, muscle strength, and arterial blood gas tensions for the patients are summarised in table 1. The patients had a decreased vital capacity (VC, 64% of predicted), forced expiratory volume in one second (FEV₁, 62.9%

of predicted), and functional residual capacity (FRC, 79.6% of predicted) with a small increase in residual volume (RV, 115% of predicted). FEV₁/VC% was normal in all patients. A moderate (55% to 40% predicted value) to marked (<40% predicted value) decrease in MIP was observed in seven patients (nos 1, 4, 8, 12–15), and a minimal change (75% to 55% predicted value) was observed in four (nos 2, 5, 6, 11); the decrease in MEP was more marked in all subjects. Arterial oxygen tension (PaO₂) was normal in all but three patients (nos 3, 8, 14) while arterial carbon dioxide tension (Paco₂) was increased in patients 3, 8, and 12.

BREATHING PATTERN

Table 2 shows the breathing pattern in the patient group compared with the normal control group. In the patients V_T (p<0.005), T_I, T_E, and T_{TOT} (p<0.05) were lower, and R_f higher (p<0.05). In particular, in seven patients (nos 6–8, 11–13, and 15) V_T was less than or equal to the mean – 2SD of the value calculated for the control group. No significant difference between the two groups was observed for the V_T/T_I and T_I/T_{TOT} ratios.

Respiratory drive

Mouth occlusion pressure (P_{0.1}) and EMG activity (XP/T_I) during room air breathing are also reported in table 2. Compared with the control group, the P_{0.1} was similar but the EMGd and EMGp were higher in the patients (p<0.05 for both).

Significant relationships were observed between respiratory muscle strength and EMGd (r = –0.7, p<0.005) (fig 1A), EMGp (r = –0.66, p<0.01), and VC (r = 0.55, p<0.03) (fig 1B); VC also related to EMGd (r = –0.69, p<0.01). In addition, stepwise regression analysis showed that VC and disease duration together predicted about 82% of variability in Paco₂ (table 3).

DATA FROM CO₂ REBREATHING

The ventilatory, P_{0.1} and EMG responses to increasing Pco₂ for the two groups are sum-

Table 2 Breathing pattern, mouth occlusion pressure, and electromyographic activity of the diaphragm and intercostal muscles in 15 patients with limb girdle dystrophy

Patients	V_E (l/min)	Rf (cycles/min)	V_T (l)	T_I (s)	T_E (s)	T_{TOT} (s)	V_T/T_I (l/s)	T_I/T_{TOT}	$P_{0.1}$ (cm H ₂ O)	EMGd (%TLC/s)	EMGp (%TLC/s)
1	9.17	14	0.67	1.82	2.6	4.4	0.37	0.41	0.8	2	11.4
2	12.7	22	0.57	1.17	1.6	2.76	0.49	0.43	1.1	14.3	15.6
3	9.7	11	0.85	2.13	3.3	5.4	0.41	0.39	1.5	5.4	6.7
4	7.0	11	0.63	2.1	3.4	5.5	0.29	0.40	1.0	2.1	10
5	8.3	13	0.63	1.65	2.9	4.5	0.38	0.36	1.3	5	10.6
6	9.2	18	0.51	1.24	2.1	3.5	0.40	0.35	1.2	2.5	5
7	7.5	18	0.44	1.62	2.2	3.4	0.27	0.48	1.3	4.8	11.1
8	7.8	26	0.30	0.74	1.5	2.3	0.4	0.32	1.1	59	81
9	7.5	14	0.60	1.5	2.5	4.0	0.4	0.38	1.4	5.1	8.5
10	13.6	20	0.70	1.45	1.6	3.1	0.48	0.46	1.2	6.2	10.2
11	8.8	19	0.46	1.55	1.6	3.2	0.3	0.48	1.2	9	8.8
12	8.1	20	0.47	1.08	2.0	3.1	0.39	0.35	1.1	31.9	18.8
13	9.9	23	0.43	1.14	1.5	2.65	0.38	0.43	1.2	8.6	27.9
14	11.8	22	0.55	1.2	1.58	2.78	0.45	0.43	1.0	40	49
15	7.8	16	0.50	1.47	2.3	3.77	0.34	0.4	1.4	20	25
Mean	9.10	17.8#	0.55†	1.46*	2.20*	3.62*	0.38	0.40	1.20	14.4*	19.9*
SD	2.10	4.5	0.14	0.4	0.65	0.9	0.06	0.042	0.18	16.7	20.0
Control values											
Mean	9.7	12.3#	0.77†	1.97*	3.06*	5.1*	0.4	0.39	1.5	2.43*	2.5*
SD	2.6	2.3	0.15	0.32	0.72	0.90	0.1	0.04	0.5	0.7	1.4

V_E = minute ventilation; Rf = respiratory frequency; V_T = tidal volume; T_I = inspiratory time; T_E = expiratory time; T_{TOT} = total time of the respiratory cycle; $P_{0.1}$ = mouth occlusion pressure; EMGd = electromyographic activity of the diaphragm; EMGp = electromyographic activity of the parasternal muscles. EMG is expressed as ratio of rise of inspiratory activity obtained by dividing peak activity by the relevant inspiratory time (XP/T_I).

* $p < 0.05$; # $p < 0.025$; † $p < 0.005$.

Table 3 Stepwise linear multiple regression analysis for P_{aCO_2}

Variable	Coefficient	Model r^2 (%)	p
Constant	46.8		
VC	-0.18	0.61	0.0001
Duration of disease	0.22	0.82	0.003

VC = vital capacity.

marised in table 4. As a mean, $\Delta(V_T/T_I)/\Delta P_{CO_2}$ was similar in the patients and the controls while $\Delta V_E/\Delta P_{CO_2}$, $\Delta V_T/\Delta P_{CO_2}$ ($p < 0.05$ for both) and $\Delta P_{0.1}/\Delta P_{CO_2}$ ($p < 0.01$) were significantly lower in the patients; $\Delta EMGd/\Delta P_{CO_2}$ and $\Delta EMGp/\Delta P_{CO_2}$ did not differ between the two groups. Also, unlike the normal group, a significant relation between increasing P_{CO_2} and Rf (see table 4) was found in most patients. Table 5 shows V_E , Rf, V_T , V_T/T_I , $P_{0.1}$, and

EMG values during CO_2 rebreathing at 8 kPa of P_{CO_2} . Patients exhibited significantly lower V_T and higher Rf and EMGd ($p < 0.05$ for all comparisons), reflecting the behaviour while they breathed room air. The lower $P_{0.1}$ value ($p < 0.05$) reflected the flat $\Delta P_{0.1}/\Delta P_{CO_2}$.

Respiratory muscle strength related to $\Delta V_T/\Delta P_{CO_2}$ ($r = 0.68$, $p < 0.03$) (fig 2) and tended to be related to $\Delta V_E/\Delta P_{CO_2}$ ($r = 0.62$, $p = NS$). However, neither the relationship of VC with $\Delta V_T/\Delta P_{CO_2}$ nor the relation of respiratory muscle strength to $\Delta(V_T/T_I)/\Delta P_{CO_2}$ or $\Delta P_{0.1}/\Delta P_{CO_2}$ was significant.

Discussion

PULMONARY VOLUMES AND RESPIRATORY MUSCLE STRENGTH

Few studies have addressed the issue of respiratory abnormalities in patients with limb girdle dystrophy. In patients with neuro-

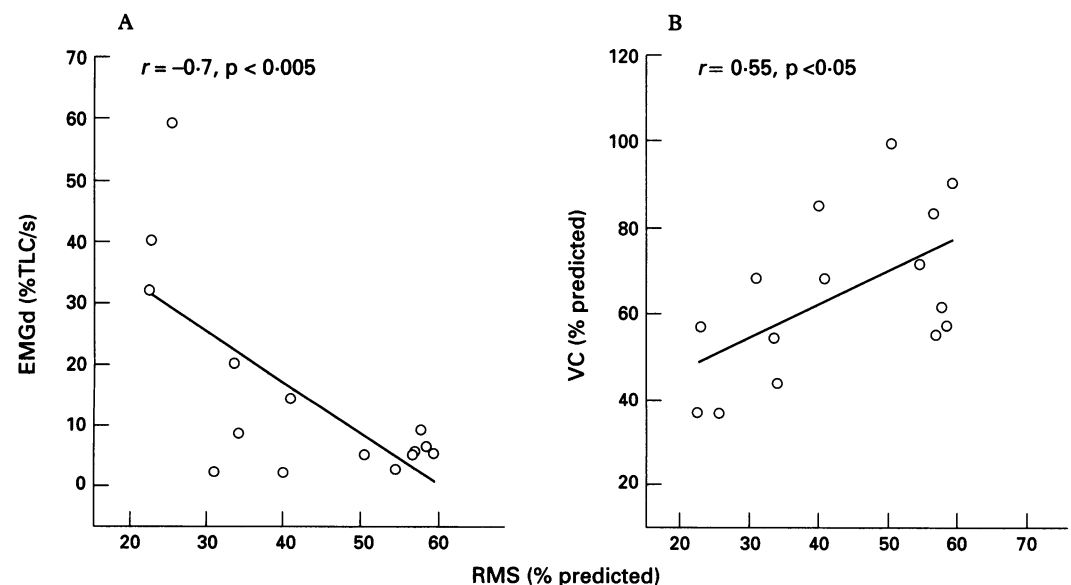


Figure 1 Relation of respiratory muscle strength (RMS) to (A) electromyographic activity of the diaphragm (EMGd) and (B) vital capacity (VC).

Table 4 V_E , R_f , V_T , V_T/T_I , $P_{0.1}$, and EMG response slopes during CO_2 rebreathing in 10 patients with limb girdle dystrophy compared with the control group

Patients	$\Delta V_E/\Delta P_{CO_2}$ (l/min)/kPa	$\Delta V_T/\Delta P_{CO_2}$ (l/kPa)	$\Delta R_f/\Delta P_{CO_2}$ (breaths/min)/ kPa	$\Delta(V_T/T_I)/\Delta P_{CO_2}$ (l/s)/kPa	$\Delta P_{0.1}/\Delta P_{CO_2}$ (cm H ₂ O)/kPa	$\Delta EMG_d/\Delta P_{CO_2}$ (%TLC/s)/kPa	$\Delta EMG_p/\Delta P_{CO_2}$ (%TLC/s)/kPa
1	10.3	0.52	0.31	0.34	1.43	6.77	5.04
2	3.61	0.13	3.01	0.16	1.13	9.10	41.9
3	19.2	0.66	7.51	0.68	2.10	14.3	24.8
4	4.89	0.41	—	0.30	0.45	7.52	—
5	9.10	0.36	1.35	0.23	1.05	5.56	5.04
11	9.77	0.45	—	0.30	1.50	16.4	35.3
12	4.13	0.13	2.76	0.19	0.98	13.3	14.7
13	3.38	0.15	—	0.19	0.53	1.50	6.84
14	9.02	0.19	3.16	0.47	1.43	6.84	13.5
15	7.52	0.29	2.78	0.49	1.05	8.27	21.8
Mean	8.10*	0.33*	2.98	0.33	1.16‡	8.95	18.8
SD	4.74	0.18	2.25	0.16	0.48	4.49	13.3
Control values							
Mean	13.5*	0.64*	—	0.40	2.63‡	10.5	10.6
SD	3.0	0.10	—	0.08	0.60	3.0	3.01

Abbreviations as in table 3. EMG is expressed as ratio of rise of inspiratory activity obtained by dividing peak activity by the relevant inspiratory time (XP/T_I).
* p<0.05; ‡ p<0.01.

Table 5 V_E , R_f , V_T , V_T/T_I , $P_{0.1}$, EMG_d, and EMG_p values during CO_2 rebreathing at a P_{CO_2} of 8 kPa

	V_E (l/min)	R_f (breaths/min)	V_T (l)	V_T/T_I (l/s)	$P_{0.1}$ (cm H ₂ O)	EMG _d (%TLC/s)	EMG _p (%TLC/s)
Limb girdle dystrophy	21.5 (8.8)	21.8* (8.3)	0.98* (0.5)	0.6 (0.19)	2.9* (0.68)	19.7* (11.2)	29.5 (21.0)
Control	24.0 (6.0)	15.0* (4.3)	1.6* (0.41)	0.75 (0.21)	5.40* (2.6)	9.6* (4.8)	11 (5)

Values are mean \pm 1 SD. Abbreviations as in table 3. EMG is expressed as rate of rise of inspiratory activity obtained by dividing peak activity by the relevant inspiratory time (XP/T_I).
* p<0.05.

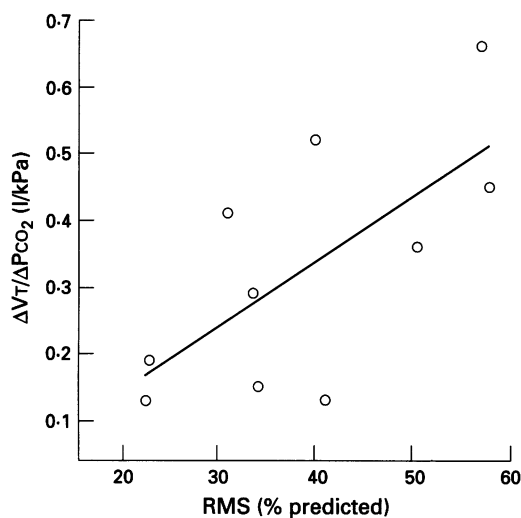


Figure 2 Relation of respiratory muscle strength (RMS) to $\Delta V_T/\Delta P_{CO_2}$. V_T =tidal volume; P_{CO_2} =carbon dioxide tension.

muscular diseases, including 15 patients with limb girdle dystrophy, without respiratory symptoms, the restrictive defect was attributed to a decrease in respiratory muscle strength.¹⁸ The extent of expiratory muscle weakness and the relative contribution of expiratory muscles in that study was similar to our present data. In our study respiratory muscle strength predicted 30.2% of the variance in VC so that the decrease in VC was out of proportion to the decrease in respiratory muscle strength as predicted from theoretical considerations.¹⁹ This confirms that factors other than respiratory muscle weakness itself are implicated in the loss of lung volume.^{20,21}

In our patients the level of P_{ACO_2} at rest was not related to respiratory muscle strength, and

is consistent with the observations by Braun *et al* in patients with metabolic myopathies where respiratory muscle strength was >50% of predicted.⁹ On the other hand, stepwise regression analysis showed that VC and duration of illness accounted for 82% of the variability in P_{ACO_2} . In this sense we agree that VC is a more useful test than respiratory muscle strength to follow the course of the neuromuscular disease.²⁰ No data are available on the histological features of the diaphragm and the other respiratory muscles in limb girdle dystrophy.²² Thus, the mechanism of respiratory muscle weakness remains to be clarified.

BREATHING PATTERN

Compared with the normal control group, patients showed an increase in R_f and a decrease in V_T while breathing room air, a common feature in patients with neuromuscular disease.^{14,23-27} The decrease in V_T was associated with a significant reduction in inspiratory time (T_I). During exogenous CO_2 stimulation $\Delta V_E/\Delta P_{CO_2}$ was lower in the patients as they responded to increasing P_{CO_2} with a similar increase in V_T and a compensatory increase in R_f ($\Delta R_f/\Delta P_{CO_2}$, see table 4). At a P_{CO_2} of 8 kPa the breathing pattern reflected the general behaviour shown during room air breathing. Reduction in lung compliance,²⁶ a stiffer rib cage,²⁰ and respiratory muscle weakness²³ are thought to be important factors which contribute to rapid and shallow breathing. Respiratory muscle weakness might contribute to the perception of respiratory effort in patients with neuromuscular disease and so to the reduction in V_T .²⁸ In contrast, the significant relationship between respiratory muscle strength and $\Delta V_T/\Delta P_{CO_2}$ (fig 2) suggests

that respiratory muscle weakness contributes to the abnormal V_T/T_I response during hypercapnic stimulation in patients with limb girdle dystrophy.

NEURAL RESPIRATORY DRIVE

In addition to traditional measurements for assessing neural respiratory drive (V_T/T_I and $P_{0.1}$), EMG of the respiratory muscles was also employed. We have criticised the use of either surface or oesophageal EMG recordings for assessing neural drive in humans.¹²⁻¹⁴ However, our data support the contention that the rate of rise of the "moving time average" is reliable for assessing neural inspiratory drive to the respiratory muscles both in normal cases and in disease.^{12-14 16 29 30}

Room air breathing

Compared with the normal group, our patients showed a greater fractional electromyographic activity of both the diaphragm (EMGd) and the intercostal parasternal (EMGp) muscles. This activity indicates the extent of its activation per breath relative to its total available activity. We have previously noted higher fractional EMG activity in patients with other respiratory diseases in which the inspiratory drive is expected to increase.¹²⁻¹⁴ In patients with respiratory muscle weakness, a measure of muscle output ($P_{0.1}$)³¹ or its translation into inspiratory flow (V_T/T_I)²⁴ may underestimate the neural respiratory drive. The observation that spontaneously breathing patients with severe respiratory muscle weakness had normal V_T/T_I and $P_{0.1}$ and high levels of EMG activity is therefore likely to reflect, in line with previous studies, an increased neural activation of the inspiratory muscles.^{9 23-25 33} In this connection it has been suggested that, in patients with neuromuscular disorders, neural drive could be increased in response to respiratory muscle weakness or loading.^{3 23 33 34} This is how we interpret the inverse relationships between respiratory muscle strength and both EMGd (fig 1) and EMGp.

Response to CO_2 stimulation

The low $\Delta P_{0.1}/\Delta PCO_2$ is in line with previous studies where respiratory drive was suspected to be either reduced^{35 36} or inadequate,³¹ even when the decrease in respiratory muscle strength was minimal,³⁵ but it is at variance with others^{23 24} where a normal $P_{0.1}$ and low V_T and V_T/T_I responses to carbon dioxide were thought to indicate a normal drive. In the present study the low $\Delta P_{0.1}/\Delta PCO_2$ was in sharp contrast with the normality of $\Delta(V_T/T_I)/\Delta PCO_2$ and both $\Delta EMGd/\Delta PCO_2$ and $\Delta EMGp/\Delta PCO_2$. V_T/T_I is not sensitive to changes in elastic lung properties³⁷ or imposition of elastic loading,³⁰ both conditions resulting in an increased respiratory drive which maintains V_T/T_I constant. Based on those observations, in patients in whom loss of VC disproportionate to the decrease in respiratory muscle strength may suggest abnormalities in elastic properties of the

lung,²⁰ a relatively normal V_T/T_I would suggest an increased neural respiratory drive. It is also possible that the decrease in $\Delta(V_T/T_I)/\Delta PCO_2$ reflects a decrease in respiratory muscle strength rather than a low neural respiratory drive. Although this could not be totally excluded in the present investigation, no significant relation was found between $\Delta(V_T/T_I)/\Delta PCO_2$ and respiratory muscle strength. In fact, in the patients with a low V_T/T_I response, the respiratory muscle strength was similar to that observed in those with a normal V_T/T_I response (34.11 (10.7)% versus 36.9% (12.15)%).

The explanation of a markedly low $\Delta P_{0.1}/\Delta PCO_2$ is not clear. It is unlikely that, in the circumstances of the present study, the decrease in respiratory muscle strength could be the reason for the low $\Delta P_{0.1}/\Delta PCO_2$. In fact, the $P_{0.1}$ response to carbon dioxide did not relate to muscle weakness.

A clue might be the measurement of $P_{0.1}$, the phase lag between pressure and flow and the shape of the driving pressure being some of the factors which should be considered in evaluating $P_{0.1}$ as an index of respiratory drive. Phase lag between pressure and flow may occur as a consequence of resistance just at the end of expiration. This may be due to abnormal function of the upper airway muscles which is common in neuromuscular disease.³⁸ When ventilation increases, as during chemically stimulated breathing, the accessory inspiratory muscles and the expiratory muscles are recruited and changes in the coordinated action of the respiratory muscles can lead to upper airways obstruction.³⁹ As a consequence of phase lag, $P_{0.1}$ may be either higher or lower than the rate of increase in pressure at the beginning of inspiration, depending on whether the pressure wave in early inspiration is concave or convex.⁴⁰ Thus, a change in shape of the pressure wave is not unexpected in patients with neuromuscular disease.⁴⁰

In summary, in patients with limb girdle dystrophy a decrease in VC, together with the duration of disease, seems to influence the P_{aCO_2} . Peripheral factors (respiratory muscle weakness) and, in a few circumstances, blunted or inadequate chemoresponsiveness may account for the reduced V_E and V_T response during high levels of chemical stimulation.

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