Mechanism of CO_2 Retention in Patients With Neuromuscular Disease*

Gianni Misuri, MD; Barbara Lanini, MD; Francesco Gigliotti, MD; Iacopo Iandelli, MD; Assunta Pizzi, MD; Maria Grazia Bertolini, RT; and Giorgio Scano, MD, FCCP

Background: **In many studies of patients with muscle weakness, chronic hypercapnia has appeared to be out of proportion to the severity of muscle disease, indicating that factors other than muscle weakness are involved in CO_2 retention. In patients with COPD, the unbalanced inspiratory muscle loading-to-strength ratio is thought to trigger the signal for the integrated response that leads to rapid and shallow breathing and eventually to chronic hypercapnia. This mechanism, although postulated, has not yet been assessed in patients with muscular dystrophy.**
Subjects: **Twenty consecutive patients (mean age, 47.6 years; range, 23 to 67 years) were studied: 11 patients with limb-girdle dystrophy, 3 with Duchenne muscular dystrophy, 1 with Charcot-Marie-Tooth syndrome, 1 with Becker muscular dystrophy, 1 with myotonic dystrophy, 1 with facioscapulohumeral dystrophy, and 2 with amyotrophic lateral sclerosis, without any respiratory complaints. Seventeen normal subjects matched for age and sex were studied as a control group.**
Methods: **Routine spirometry and arterial blood gases, maximal inspiratory and expiratory muscle pressures (MIP and MEP, respectively), and pleural pressure during maximal sniff test (Pplsn), were measured. Mechanical characteristics of the lung were assessed by evaluating lung resistance (RL) and dynamic elastance (Eldyn). Eldyn was assessed as absolute value and as percent of Pplsn; Eldyn (%Pplsn) indicates the elastic load per unit of inspiratory muscle force. Breathing pattern was assessed in terms of time (inspiratory time [TI]; respiratory frequency [Rf]) and volume (tidal volume [VT]) components of the respiratory cycle.**
Results: **A rapid shallow breathing pattern, as indicated by a greater Rf/VT ratio and a lower TI, was found in study patients compared to control subjects. Eldyn was greater in study patients, while MIP, MEP, and Pplsn were lower. $PaCO_2$ inversely related to VT, TI, and Pplsn ($p = 0.012$, $p = 0.019$, and $p = 0.002$, respectively), whereas it was directly related to Rf, Rf/VT, Eldyn, and Eldyn (%Pplsn) ($p < 0.004$ to $p < 0.0001$). Also Eldyn (%Pplsn) inversely related to TI, and the latter positively related to VT. In other words, increase in Eldyn (%Pplsn) was associated with decrease in TI, and the latter was associated with lower VT and greater $PaCO_2$. Mechanical and breathing pattern variables were introduced in a stepwise multiple regression that selected Eldyn (%Pplsn) ($p < 0.0001$; $r^2 = 0.62$) as a unique independent predictor of $PaCO_2$.**
Conclusions: **The present study shows that in patients with neuromuscular disease, elastic load and respiratory muscle weakness are responsible for a rapid and shallow breathing pattern leading to chronic CO_2 retention.** ***(CHEST 2000; 117:447–453)***

Key words: breathing pattern; hypercapnia; neuromuscular disorders; respiratory muscles

Abbreviations: Eldyn = dynamic lung elastance; Eldyn (%Pplsn) = elastic load per unit of inspiratory muscle force; FRC = functional residual capacity; LGD = limb-girdle dystrophy; MD = myotonic dystrophy; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; NMD = neuromuscular disease; NS = not significant; PI = mean inspiratory driving pressure; $P_{0.1}$ = mouth occlusion pressure; Ppl = pleural pressure; Pplsn = pleural pressure during a sniff maneuver; Rf = respiratory frequency; RL = lung resistance; RSB = rapid and shallow breathing; TE = expiratory time; TI = inspiratory time; TTOT = total time of respiratory cycle; VC = vital capacity; VE = minute ventilation; VT = tidal volume; Zrs = impedance of the respiratory system

*From the Fondazione Don C. Gnocchi, ONLUS, Pozzolatico (Firenze), Italy.
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Correspondence to: Giorgio Scano, MD, FCCP, Section of Respiratory Disease, Fondazione Don C. Gnocchi, ONLUS, Pozzolatico, Via Imprunetana, Pozzolatico (Firenze), CAP 50020 Italy; e-mail: riabrfi@tin.it

In patients with proximal myopathies, chronic hypercapnia may develop in the absence of precipitating factors such as pulmonary infection, oxygen therapy, or sedation.[1] Previous articles[2–5] have shown

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that alveolar hypoventilation was associated with abnormalities in central control. On the other hand, more recently, Gibson et al,[6] in an attempt to identify the role of weakness in the genesis of these findings, found that hypercapnia is related to respiratory muscle weakness in myotonic dystrophies (MDs) in a similar way to other muscle diseases. Gibson et al[6] also believed it not unlikely that in many of the earlier studies the contribution of respiratory muscle weakness itself was unrecognized or underestimated. However, in many studies,[7,8] chronic hypercapnia has appeared to be out of proportion to the severity of muscle diseases in patients with similar pulmonary function parameters and muscle function, indicating that factors other than muscle weakness are involved in CO_2 retention.

Recent observations in a large series of patients with MD indicate that a combination of respiratory muscle weakness and respiratory loading, derived from an increase in mouth occlusion pressure ($P_{0.1}$) help explain part of the variance in $PaCO_2$.[9] However, in patients with neuromuscular disease (NMD), assessment of respiratory neural drive by employing $P_{0.1}$ to extrapolate the inspiratory drive pressure developed by the inspiratory muscles has recently been questioned.[10] Although this does not detract validity to the data of Begin et al[9] in MD, we believe that a more accurate measurement of respiratory mechanics may help define the role of functional alteration of the respiratory system in the development of chronic respiratory insufficiency in patients with NMD.

In patients with NMD, it is not definitely established how the respiratory centers are able to integrate the derangement in respiratory mechanics and eventually elaborate it in ventilatory output. In this connection, a rapid and shallow breathing (RSB) pattern eventually leads to chronic hypercapnia in patients with COPD.[11–13] RSB has also been observed in restrictive lung diseases,[14,15] and in patients with respiratory muscle weakness,[1,14–18] where peripheral afferents, either vagal (pulmonary) or nonvagal (stiffened rib cage, weak respiratory muscles) have been thought[17–19] to act on the central respiratory controller to terminate inspiration and lower tidal volume (VT), thereby leading to chronic hypercapnia. This mechanism, although postulated, has not yet been assessed in patients with NMD. Thus, the present investigation was devised to assess possible factors that, in combination with primary muscle abnormalities, contribute to a qualitatively abnormal ventilatory response leading to chronic hypercapnia.

Materials and Methods

Subjects

Twenty consecutive patients (10 men) with a mean age of 47.6 years (range, 23 to 67 years) were studied: 11 patients with limb-girdle dystrophy (LGD), 3 with Duchenne muscular dystrophy, 2 with amyotrophic lateral sclerosis, 1 with Charcot-Marie-Tooth syndrome, 1 with Becker muscular dystrophy, 1 with MD, 1 with facioscapulohumeral dystrophy, and no respiratory complaints. Nine were ambulatory, and 11 were wheelchair bound. The standard criteria were used to select patients.[20,21]

None of the patients had a scoliosis nor any abnormalities on chest radiograph nor obvious abnormalities in diaphragm placement. Five patients were current mild smokers ($\leq$ 5 pack-years).

Seventeen normal subjects matched for age (range, 26 to 62 years; mean, 41.5 years) and sex (8 men) were studied as a control group. The study was approved by the local ethics committee, and the subjects gave their informed consent.

The anthropometric characteristics of the patients are shown in Table 1.

Functional Evaluation

Routine spirometry, obtained with the patients seated in a comfortable armchair, was measured as previously described.[13,16,22] Functional residual capacity (FRC) was measured by the helium dilution technique. The normal values for lung volumes were those of the European Community for Coal and Steel.[23] Arterial blood gas tensions were measured with a blood gas analyzer (IL-1304; Instrumentation Laboratory; Milan, Italy).

Maximum static inspiratory (MIP) and expiratory (MEP) pressures at FRC, measured against an obstructed mouthpiece with a small leak to minimize oral pressure artifacts, were recorded using a differential pressure transducer (Statham SC 1001; Statham; Hato Rey, Puerto Rico). The subjects were comfortably seated, wearing a noseclip, and performed maximal inspiratory efforts, maintaining maximal pressures for at least 1 s. The maneuvers were repeated until three measurements with $< 5\%$ variability were recorded, and the highest value obtained was taken for analysis. In the presence of respiratory muscle weakness, the measured values of MIP and MEP may be affected by lung volumes as well as by myopathy; we therefore corrected for these effects of lung volumes on MIP and MEP.[24]

For mechanical studies, an esophageal latex balloon (length, 10 cm; air volume, 0.5 mL) was introduced via the nose. A marker was placed on the polyethylene tubing 40 cm from the balloon tip.[25] The catheter was connected to a differential pressure transducer (Validyne; Northridge, CA). Total lung resistance (RL) and dynamic lung elastance (Eldyn) were measured during resting breathing.[13] RL was obtained using the isovolume method[26]; predicted values are those proposed by the European Community for Coal and Steel.[27] Eldyn was determined by dividing the difference in pleural pressure (Ppl) between points of zero flow by VT.

The highest (most negative in sign) Ppl was evaluated at FRC during a sniff maneuver (Pplsn),[13] which was repeated until three measurements with $< 5\%$ variability were recorded. The highest value of Pplsn was used for subsequent analysis.

During room-air breathing, the ventilatory pattern was evaluated with subjects sitting comfortably in an armchair using a Fleisch type-3 pneumotachograph (Beckman Instruments; Schiller Park, IL). The flow signal was integrated into volume. From the spirogram, we derived inspiratory time (TI), expiratory time (TE), total time of the respiratory cycle (TTOT) and VT.

Table 1—*Anthropometric and Clinical Data of the Subjects

Patients	Disease	Sex	Age, yr	Weight, kg	Height, m	BMI, kg/m^2	VC, %pr	TLC, %pr	FEV_1/VC, %	Pa_{O_2}, mm Hg	Pa_{CO_2}, mm Hg
1	Facioscapulohumeral dystrophy	F	65	60	1.56	24.6	51†	103	96	63	52
2	Amyotrophic lateral sclerosis	F	55	53	1.58	21.3	55†	70†	87	81	51
3	Amyotrophic lateral sclerosis	M	63	86	1.83	25.7	43†	60†	89	77	50
4	Duchenne muscular dystrophy	M	23	60	1.70	20.8	12†	46†	85	89	50
5	Charcot-Marie-Tooth syndrome	F	54	50	1.50	22.2	37†	70†	94	88	50
6	LGD	M	45	56	1.65	20.6	37†	50†	92	79	48
7	Duchenne muscular dystrophy	M	25	35	1.70	12.1	26†	48†	98	93	46
8	Duchenne muscular dystrophy	M	24	75	1.75	24.5	47†	60†	97	107	45
9	LGD	F	67	79	1.63	29.7	110	104	78	97	43
10	LGD	M	56	93	1.75	30.4	68†	68†	85	88	42
11	LGD	M	48	80	1.73	26.7	50†	62†	90	86	42
12	Becker muscular dystrophy	M	32	70	1.69	24.5	83	80	88	96	41
13	LGD	F	65	61	1.57	24.7	87	91	78	95	39
14	LGD	M	44	50	1.57	20.3	113	113	79	90	39
15	LGD	F	33	34	1.35	18.7	113	115	100	94	38
16	LGD	F	31	40	1.55	16.6	75†	87	95	92	38
17	LGD	F	64	87	1.65	32.0	121	113	79	84	38
18	MD	M	54	61	1.74	20.1	93	86	77	112	38
19	LGD	F	58	69	1.60	26.9	90	100	82	93	37
20	LGD	F	47	30	1.50	13.3	102	90.2	85	104	37
Mean			47.6	61.5	1.63	22.8	72.6	82.5	87.7	90.3	43.3
SD			14.9	18.5	0.11	5.3	34.6	24.6	7.6	11.6	5.3
Control subjects											
Mean			41.5	67.1	1.68	23.6	105.9	102.24	87.25	—	—
SD			11.7	14.0	0.11	3.4	14.08	8.29	1.5	—	—

*BMI = body mass index; TLC = total lung capacity; M = male; F = female; %pr = percent predicted value.
†Value significantly lower than predicted.[23]

Respiratory frequency (Rf; where Rf 1/T_{TOT} × 60) and minute ventilation ($\dot{V}_E$; where $\dot{V}_E = V_T \times Rf$) were also calculated.

Expired CO_2 was sampled continuously at the mouth by an infrared CO_2 meter (Normocap 200; Datex; Helsinki, Finland).

The output of the CO_2 meter, flow signal, integrated flow signal, and mouth pressure were recorded on a personal computer hard disk using an eight-channel analogical/digital board at 50-Hz sampling rate. After a 10-min adaptation period, evaluation began. Signals were recorded over a 10-min time period. Average values for each subject are presented.

Protocol

All subjects were tested in the morning. Before the experiment, the subjects were well acquainted with the laboratory and equipment. An arterial blood sample and lung function tests were performed, and then changes in volume, flow, and Ppl were recorded. Finally, the respiratory muscle strength tests were performed in each patient.

Data Analysis

Volume and time components of the respiratory cycle, RL, and Eldyn were averaged in each patient over 30 consecutive breaths. Eldyn was expressed both as an actual value and as a percent of Pplsn, an index of the balance between the elastic load of the lung relative to the maximal inspiratory force available. Single and stepwise multiple regression analyses were performed to assess relationships between variables. The statistical analysis we carried out considers the dependency of a variable (*eg*, the level of Pa_{CO_2}) on a series of independent variables. The effect of each variable on Pa_{CO_2} was evaluated independent of the effect of all other variables. In a multivariate analysis, a rule of thumb is to limit the number of variables as a function of the number of patients.[28] Thus, multiple regression analysis with stepwise selection of the independent variables was carried out relating Pa_{CO_2} to functional variables. The proportion of total variance in the dependent variable accounted for by the predicted variables is reported as the square of the correlation coefficient (r^2). Single regression analysis was performed using Pearson's single correlation coefficient. Comparisons between groups were made using the Mann-Whitney *U* test. A value of $p < 0.05$ was considered as the threshold of statistical significance. Data are presented as mean ± SD unless otherwise specified.

Results

Clinical, anthropometric, and respiratory function characteristics of the patients (and control subjects) are shown in Table 1. As shown in Table 1, vital capacity (VC) was reduced in 11 patients, as was total lung capacity in 9. The means of MIP (47.8 ± 28.3 cm H_2O; range, 11 to 127 cm H_2O; $p = 0.00001$) and MEP (49.5 ± 26.2 cm H_2O; range, 15 to 104 cm H_2O; $p = 0.00002$) were significantly lower than in control subjects. In 11 patients and 10 patients, the values of MIP and MEP, respectively, were lower than the mean − 2 SD of the value calculated for the control subjects. Arterial blood gases were normal in all but eight patients in whom Pa_{CO_2} was considered to be high (≥ 45 mm Hg) and in three patients in

Table 2—*Breathing Pattern Parameters and Mechanical Characteristics of the Subjects*

Patients	VT, L	TI, s	TE, s	Rf, cycles/min	$\dot{V}E$, L/min	Rf/VT, cycles/min/L	Pplsn, cm H_2O	Eldyn, cm H_2O/L	RL, cm H_2O/L/s
1	0.50	1.15	1.31	24.5	12.4	49	32*	16.1	2.6
2	0.44	0.96	1.90	21.1	9.4	47.5	12*	18.1	2.9
3	0.61	1.11	1.53	22.9	13.8	37.5	11*	7.3	2.2
4	0.43	0.99	1.20	27.6	11.7	64.2	13*	18.5	3.1
5	0.40	1.21	1.76	20.3	8.1	50.8	13*	15.8	1.9
6	0.45	1.03	1.54	23.6	10.6	52.4	25*	21.1	3.9
7	0.32	1.04	1.21	27.1	8.6	84.7	28*	16.8	3.0
8	0.60	1.54	1.84	17.8	10.7	29.7	58*	10.5	3.0
9	0.69	1.38	2.46	15.7	10.8	22.7	100	8.2	4.3
10	0.63	1.32	1.34	22.7	14.3	36	73	11.3	2.1
11	0.71	2.03	3.05	12.0	8.4	16.9	47*	7.4	1.7
12	0.77	1.25	1.36	23.3	17.9	30.3	127	6.3	1.1
13	0.56	1.64	2.28	15.3	8.5	27.3	58*	5.9	4.4
14	0.85	1.47	1.72	18.8	16.0	22.1	70	4.6	4.4
15	0.64	1.53	2.17	16.2	10.4	25.3	65	10.2	2.7
16	0.35	1.26	2.32	16.9	6.0	48.3	43*	16.3	2.1
17	0.67	1.28	1.88	19.3	12.9	28.8	78	8.8	3.5
18	0.71	1.49	2.08	16.8	12.0	23.7	43*	9.3	3.6
19	0.59	1.30	1.68	20.2	11.9	34.2	66	7.0	2.2
20	0.75	1.96	4.21	10.1	7.6	13.5	57*	11.7	4.9
Mean	0.58	1.35	1.95	19.61	11.1	37.3	50.94	11.56	2.97
SD	0.15	0.29	0.72	4.65	2.96	17.5	30.82	4.93	1.04
Control subjects									
Mean	0.70	1.75	3.19	13.11	9.6	19.62	97.33	4.7	2.7
SD	0.1	0.43	0.93	3.59	2.4	7.9	17.99	1.25	0.65
p Value	NS	0.002	0.0001	0.0002	NS	0.0004	0.00007	0.000002	NS

*Value below mean − 2 SD calculated from control subjects.

whom PaO_2 was low (< 80 mm Hg). In some of the patients, and particularly in patients 12 and 14, in whom $PaCO_2$ was normal, a high level of ventilation was found.

Compared to control subjects, the patients' ventilatory pattern (Table 2 and Fig 1) showed a normal $\dot{V}E$, consistent decrease in TI and TE, and an increase in Rf and Rf/VT; VT tended to be reduced. As shown by the increase in Rf/VT, this pattern depicts RSB.

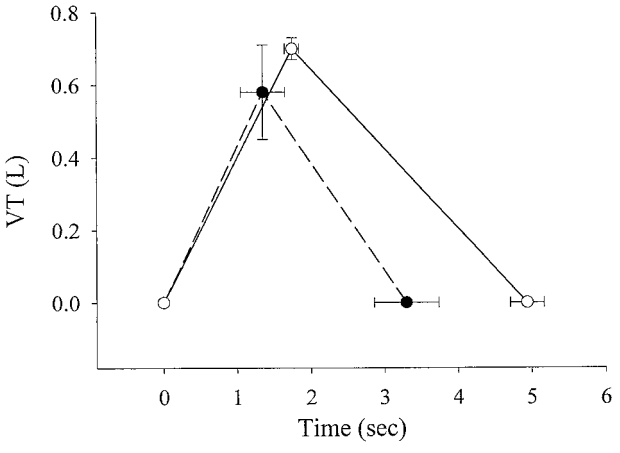

FIGURE 1. Breathing pattern in patients (dotted line and closed circles) and control subjects (continuous line and open circles). Bars are standard error for VT and TTOT.

Mechanical abnormalities were characterized (Table 2) by increased Eldyn, which was greater (greater than mean + 2 SD) in 16 patients than the values calculated for the control subjects; RL was similar in patients as in control subjects.

Individual relationships of $PaCO_2$, as a dependent variable, with mechanical characteristics and breathing pattern of the patients as independent variables, are shown in Table 3 and Figure 2. VT, TI, TE, and Pplsn were inversely related to $PaCO_2$; when Pplsn and $PaCO_2$ were fitted in a curvilinear relationship ($PaCO_2$ = a+b/Pplsn), the explained variance rose to 0.61.

Table 3—*Relationships of $PaCO_2$ with Mechanical Characteristics and Breathing Pattern Variables*

Variables	p Value	r^2
Eldyn (%Pplsn)	0.00001	0.61
Eldyn	0.0036	0.38
Pplsn	0.002	0.42
VT	0.012	0.30
TI	0.019	0.42
TE	0.03	0.24
Rf	0.0029	0.40
Rf/VT	0.0034	0.39

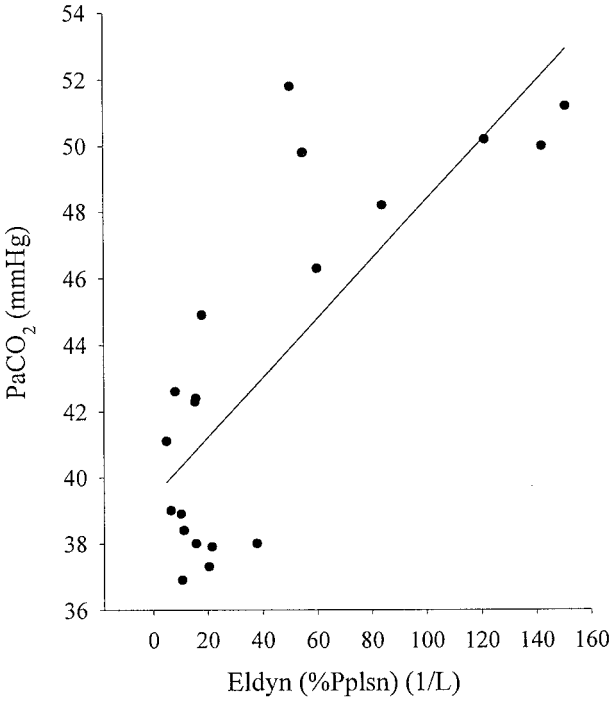

FIGURE 2. Relationships of Eldyn (%Pplsn) with $PaCO_2$ in patients with NMD.

The relationships of TI with Eldyn (%Pplsn) and VT are shown in Figure 3. The selected mechanical and breathing pattern variables were introduced in a stepwise multiple regression that selected Eldyn (%Pplsn) ($p < 0.0001$; $r^2 = 0.62$) as a unique independent predictor of $PaCO_2$, the final regression equation being as follows:

$$PaCO_2 = 39.18 + 0.088 \text{ Eldyn (\%Pplsn)}$$

DISCUSSION

We have found that in patients with NMD, Eldyn (%Pplsn) is the strongest predictor of the variance in $PaCO_2$. Increased Eldyn (%Pplsn) was associated with a decreased TI, which truncates VT, thereby leading to chronic CO_2 retention ($PaCO_2$).

One can argue that this type of study should pertain to patients with more advanced disease. In fact, nine of the patients had $PaCO_2$ values < 42 mm Hg, which does not indicate a definite CO_2 retention. However, a sustained $\dot{V}E$ at a level required to maintain a normal $PaCO_2$ has been reported in patients with neuromuscular disorders.[19] The $PaCO_2$ may initially be low because of the reflex tachypnea, a pattern shown by at least six of our patients with $PaCO_2 \leq 42$ mm Hg. On the standard resting $\dot{V}E/PaCO_2$ relationship, as shown in Figure 1 of the article by Brown et al,[29] almost double than normal (16 L/m) $\dot{V}E$ values are associated with about half of normal (20 mm Hg) $PaCO_2$ levels. Thus, in patients 10, 12, and 14, the $PaCO_2$ values for levels of $\dot{V}E$ between 14.3 and 17.9 L/m are almost double those of normal subjects at the same levels of $\dot{V}E$. Therefore, we believe that the above shortcoming was not such as to influence qualitatively our results.

Chronic hypercapnia characterizes the late stages of many muscular diseases including muscular dystrophies, such as MD and LGD,[2,4,6,7,22] congenital muscle diseases,[3] and metabolic muscle diseases.[8] Although chronic hypercapnia has been thought to be the consequence of muscle weakness,[8,12,13,22] other factors are likely to be involved in chronic hypercapnia.[7,8] In the present study, the strongest predictor of the variance in $PaCO_2$ was Eldyn (%Pplsn), a parameter that reflects elastic load of the lung per unit of maximal inspiratory muscle strength. Increase in elastic load has been reported in NMD to be due to either pulmonary microatelectasis or abnormalities in the rib cage or both.[30] The increase in respiratory muscle loading and the intrinsic decrease in respiratory muscle force have been reported to play a predominant role in the pathogenesis of

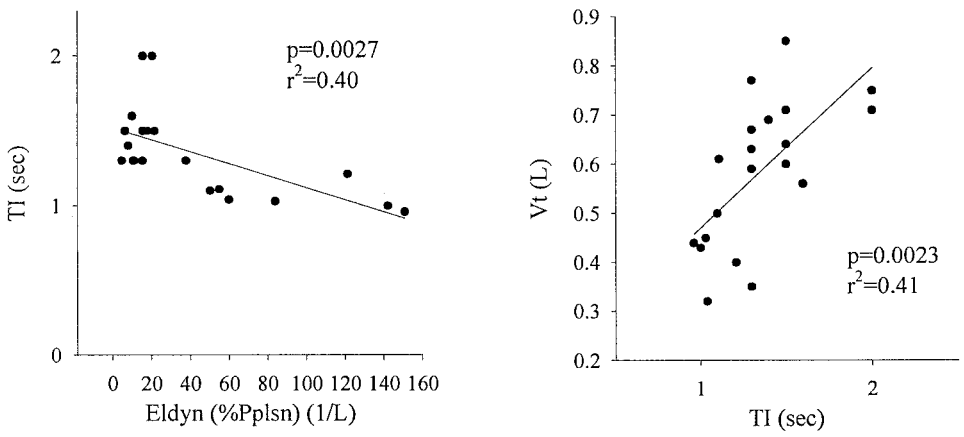

FIGURE 3. Relationships of TI with Eldyn (%Pplsn) (*left panel*) and VT (*right panel*) in patients with NMD.

chronic alveolar hypoventilation both in COPD [12,31] and in peripheral myopathies.[9]

Begin et al[9] have recently expressed the balance between inspiratory muscle loads and strength in MD in a way that includes the loads acting on the entire respiratory system, as assessed in terms of the ratio of total impedance of the respiratory system (Zrs) to MIP. In that study, the greater FEV_1/VC and the lower-than-expected FVC for the degree of respiratory muscle strength suggested an increase in both respiratory system elastance and Zrs. Increased respiratory system elastance was calculated from previous data of Begin et al,[1] by employing $P_{0.1}$ to extrapolate the mean inspiratory driving pressure (PI) developed by the inspiratory muscles. Assuming a linear rate of increased pressure output during inspiration, Begin et al[1,9] equaled PI to $5 \times P_{0.1} \times TI$; by the estimated PI, they also calculated Zrs as follows: Zrs = PI/VT/TI; then, the Zrs/MIP ratio was calculated. Based on the increased respiratory system elastance and Zrs in patients with MD, Begin et al [9] have recently stated that, in agreement with the current working hypothesis based on COPD data,[31] inspiratory muscle fatigue plays no role in the pathogenesis of chronic hypercapnia, whereas inspiratory muscle weakness and loading definitely do.

We agree with Begin et al[9] in that muscle weakness and loading play a role in chronic hypercapnia in NMD. However, we have some concerns about the way of assessing Zrs and its ratio to MIP in diseases other than MD. One clue is the measurement of $P_{0.1}$ as an index of neural respiratory drive; the phase lag between pressure and flow and the shape of the driving pressure are some of the factors that 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 NMD.[32] When ventilation increases, the accessory inspiratory muscles and the expiratory muscles are recruited, and changes in the coordinated action of the respiratory muscles can lead to upper airway obstruction.[33] 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 the inspiration, depending on whether the pressure wave in early inspiration is concave or convex.[10] Thus, a change in shape of the pressure wave is not unexpected in patients with NMD.[10] On this basis, employing $P_{0.1}$ to extrapolate the PI developed by the inspiratory muscles may be questioned. As a matter of fact, when we worked out Zrs from the data of patients with LGD[22] during quiet breathing, we found that $P_{0.1}$ and TI were greater ($p = 0.026$ and $p = 0.0005$, respectively) in normal control subjects ($P_{0.1}$, 1.5 ± 0.5 cm H_2O; TI, 1.97 ± 0.32 s) than in patients ($P_{0.1}$, 1.2 ± 0.18 cm H_2O; TI, 1.46 ± 0.4 s). Thus, PI was lower ($p = 0.0002$) in patients (8.74 ± 2.8 cm H_2O) than in normal subjects (14.7 ± 4.32 cm H_2O) so that, owing the same VT/TI in both groups (0.38 L/s ± 0.06 in patients; 0.40 L/s ± 0.11 in control subjects; p = not significant [NS]), Zrs was unexpectedly smaller ($p = 0.004$) in patients (23.83 ± 9.63 cm H_2O/L/s) than in normal subjects (41.56 ± 21.6 cm H_2O/L/s), while the Zrs/MIP ratio had similar values (p = NS) in patients (0.42 ± 0.18 s/L) as in normal control subjects (0.46 ± 0.26 s/L).

In turn, the use of a noninvasive method to extrapolate data about respiratory mechanics may be simple and widely applied, but may provide misleading conclusions. In the present article, a more invasive but also more accurate method shows that Eldyn and Eldyn (%Pplsn) are greater in patients, indicating a greater inspiratory muscle loading, or better an unbalanced inspiratory muscle loading-to-strength ratio.

Patients with respiratory muscle weakness exhibit RSB.[16–19,22] As weakness progresses, the bellows action of the chest decreases and VT decreases further, eventually resulting in chronic hypercapnia.[1,9,22] Previous data of our patients with COPD[13] and the present results agree with the current hypothesis that an unbalanced inspiratory muscle loading-to-strength ratio triggers the signal for the integrated response that brings about RSB. The latter is aimed at reducing a perceived effort but leads to hypercapnia.[31] An unbalanced inspiratory muscle loading-to-strength ratio was inversely associated with TI in such a way that the greater the former, the smaller the latter. A consequence of a shorter TI was a lower VT, explaining a consistent part of the variance of $PaCO_2$. The present article, in line with the study by Gorini et al[13] and Begin and Grassino[12] in patients with COPD, seems to indicate that different pathologies may lead to the same physiologic abnormalities. Vagal afferents from the lung[18] or nonvagal afferents from chest wall and muscles[34–36] are thought to be involved in shortening TI, truncating VT, and increasing Rf. Either vagal or nonvagal afferents or both are likely to be involved in patients with muscle weakness.[17–19]

In conclusion, the present study shows that in patients with NMD, muscle weakness and elastic load are responsible for the modulation of central respiratory output into a RSB that leads to chronic CO_2 retention.

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