Neural Respiratory Drive and Neuromuscular Coupling During CO₂ Rebreathing in Patients with Chronic Interstitial Lung Disease

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In 12 patients with CILD and 18 age-matched normal subjects we assessed the ventilatory control system at three levels: (a) neural, as assessed by EMGd (ΔP/ΔP0CO2) and EMGint muscles via surface electrodes; (b) muscular, as assessed by mouth occlusion pressure (P0,1); and (c) ventilatory, as assessed by both ventilation (Ve) and the related parameters, tidal volume (Vr) and respiratory frequency (f). Compared with a normal control group, patients exhibited a significant decrease in lung volumes and in MIP; Vr and inspiratory time (Ti) were significantly lower, while Vr/Ti, P0,1, and both EMGd and EMGint were significantly greater in patients. During a CO₂ rebreathing test, patients exhibited significantly greater EMGd, EMGint, and P0,1 responses to increasing PextCO2 than the control group. Vt response slopes were similar in the two groups. For a given EMGd response slope (ΔP/ΔP0CO2), the average P0,1 response slope (ΔP/ΔP0CO2) was found to be significantly lower in patients than in the normal control group. Compared with normal subjects, CILD patients have a normal or increased neural component of respiratory activity and relatively low neuromuscular coupling (ΔP/ΔP0CO2). The decreased neuromuscular coupling could be explained in these patients by a reduced inspiratory muscle strength.

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| CILD = chronic interstitial lung disease; EMGd = EMG activity of diaphragm muscle; EMGint = EMG activity of intercostal muscles; MIP = maximal inspiratory pressure; EMGd = EMG activity recorded by esophageal electrodes; EMGd = EMG activity recorded by surface electrodes |

In normal man during progressive exercise, the increase in mouth occlusion pressure (P0,1), a measure of neuromuscular inspiratory drive, is mostly due to augmented transdiaphragmatic pressure and coincident with EMGd during this initial part of inspiration. A similar effect has been observed in supine man during application of external elastic load to breathing. The effect of exercise and elastic loading on the P0,1/EMGd relationship has suggested that in the studied conditions the increase in P0,1 is secondary to increased diaphragmatic drive. This has also been hypothesized in patients with CILD, in whom an increase in P0,1 has been reported. In these patients, however, the coupling of neural to muscular events may be changed by the reported abnormalities in chest wall and lung mechanics. Thus, simultaneous assessment of inspiratory neural drive (EMGd) and P0,1 should be carried out in patients with CILD to evaluate the rate of transformation of inspiratory neural drive (EMGd) into inspiratory muscle output (P0,1).

The present investigation was undertaken in patients with CILD to evaluate both the amount of neural output to the respiratory muscles as assessed by EMG of both diaphragm and intercostal muscles and the neuromuscular coupling, assessed by relating change in P0,1 to change in EMGd, during both room air and chemically stimulated breathing.

MATERIAL AND METHODS

We studied 12 patients with biopsy-proved interstitial lung disease (seven men and five women, mean age 57.3 years ± 12, SD) and 18 normal subjects (eight men and ten women, mean age 50 years ± 16.9, SD; range, 25 to 78 years) who served as controls. Informed consent was obtained from each subject. Anthropometric and clinical data of the patients are shown in Table 1. Patients 6, 9, and 12 had progressive systemic sclerosis, and patient 10 had rheumatoid arthritis. In the remaining cases idiopathic pulmonary fibrosis was diagnosed. No patient was considered undernourished, the average body weight expressed as percentage of the ideal weight being 117 ± 19 (SD). Ten patients had been receiving steroid treatment for many years and four for more than ten years (cases 4, 9, 10, and 11).

Routine spirometric values obtained with subjects seated, single-breath diffusion capacity (Dsb), and arterial blood gas values were measured as previously described. The normal values for lung volumes are those proposed by the European Community for Coal

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824 Neural Respiratory Drive in Interstitial Lung Disease (Gorini et al)
and Steel. The MIP at RV against an obstructed mouthpiece, with a small leak to minimize oral pressure artifacts, was measured using a differential pressure transducer (Statham SC 1001). Subjects performed maximal inspiratory effort at RV and were instructed to maintain maximal pressure for at least 1 s. The mean of three reproducible and satisfactory measurements was calculated.

After baseline routine testing during room air breathing, the ventilatory pattern, respiratory drive, and mouth occlusion pressure were evaluated with subjects in a comfortable supine position. In the apparatus we used, the inspiratory line was separated from the expiratory one by a one-way valve (Hans-Rudolph) connected to a Fleisch type 3 pneumotachograph. The flow signal was integrated into the volume. From the spirogram we derived breath-by-breath time and volume components of the respiratory cycle: inspiratory time (TI), expiratory time (TE), total time of the respiratory cycle (Ttot), and tidal volume (Vt). Mean inspiratory flow (Vt/TI), duty cycle (Vt/Ttot), respiratory frequency (f = 1/Ttot x 60), and instantaneous ventilation (V = Vt x f) were also calculated. Mouth pressure during RV maneuvers was measured using a pressure transducer (Statham P23ID). Mouth occlusion pressure 0.1 s after the beginning of inspiration (P0.1) was recorded as previously described. Expired CO2 (PETCO2) 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 were 178 ml and 0.92 cm H2O-L-1·s-1, respectively.

The EMG activity of the chest wall muscles was recorded from the second parasternal intercostal (EMGint) and diaphragm (EMGd) muscles via large surface electrodes. The EMGd was recorded from the lower anterolateral rib cage as described by Gross et al. Muscle action potentials (“raw”) were differentially amplified, filtered between 80 and 1,000 Hz, to remove as much ECG signal as possible without significantly filtering EMG. Although a significant proportion of EMG content is found below 100 Hz, a stable enough baseline is difficult to achieve if lower frequencies are not filtered. Moreover, at low frequencies, if not adequately gated, the ECG signal may significantly modify the EMG signal. Preliminary measurements of filtered signals between 20 and 1,000 Hz and 80 and 1,000 Hz, respectively, showed that the integrated peak EMGd signal was not substantially altered by a low cutoff at 80 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, 200 ms) using a third-order, low-pass filter to provide a measurement of change in average electric activity as a function of time, referred to as “moving time average” (XT). This method of analysis allows the description of the time course of inspiratory muscle activity, which shows a definable rate of increase, reaching a peak of amplitude and then rapidly decreasing. Inspiratory activity was quantified both as peak of activity and as rate of rise of activity (slope). The former was directly measured in arbitrary units (XP), and the latter was obtained by dividing XP by the inspiratory time (XP/TI).

In a complementary study, carried out in three normal subjects and three patients, the EMGd was simultaneously recorded by means of a bipolar esophageal electrode (Disa 13K63) passed through the nose. The esophageal electrode was positioned to obtain optimal and reproducible signal-to-noise ratio at VT and MIP and then fixed at the nose with tape.

Owing to the variability of the impedance between diaphragm and electrodes, absolute values (mV) are not comparable among different subjects. To overcome this problem in our subjects we obtained a reference value, measuring the EMG activity (XP) with the subject in a supine position at maximal inflation (TLC). This XP reference value was the average of at least three measurements. All successive XP measurements have been expressed as a percentage of this reference value obtained at TLC and then divided by the inspiratory time. As EMG activity of an inspiratory muscle may include cardiac muscle activity, we checked cardiac artifacts to manually gate ECG, when necessary, so that it would not contribute to the progressive increase of EMG.

The output of CO2 meter, the flow signal, the integrated flow signal, the mouth pressure, and the moving time average were recorded continuously on a multichannel chart recorder. After a 10-min adaptation period, baseline evaluation began. Successively, the subjects underwent a CO2 rebreathing test following the procedure recommended by Read. A gas mixture (7 percent CO2, 93 percent O2) was inhaled for 3 to 5 min from a 5- to 8-L bag, the largest bag being reserved for normal subjects. In each normal subject, the rebreathing test was repeated on two to three different days, while in patients it was duplicated on the same day with an interval of 60 min between each test. The resistance of the circuit used during the CO2 rebreathing test was such that mouth pressure during unoccluded breathing was always ≤2 cm H2O greater or less than atmospheric pressure. During CO2 inhalation, when the open-loop condition was achieved, occlusions were randomly performed every 10 to 20 s.

Ventricular parameters Ppeak, and EMG were calculated from the data averaged from three breaths preceding each occlusion.

For each rebreathing run, change in VE, time, and volume components of breathing pattern, Ppeak, and EMG were plotted against increasing Ppeak and subjected to least squares linear regression analysis. To assess the coupling of the inspiratory neural drive to force output of the inspiratory muscles during rebreathing, the change in Ppeak per unit change in Ppeak was plotted against the change in the rate of rise of EMGd (XP/TI) per unit change in Ppeak of the same sitting.

To obtain a normal reference range, an average slope value of the runs carried out by each normal subject was considered. In no case was the response exhibited on one day twofold greater or less than the response obtained on each of the other days. For each patient the mean slope for the two runs was calculated. Results were compared by the Mann-Whitney U test for unpaired samples. Comparisons between interindividual slopes were made by covariance analysis.

RESULTS

Functional data of the 12 patients are shown in Table 2. All but two patients (3 and 12) exhibited a significant decrease in static pulmonary volumes (predicted –
Table 2—Routine Pulmonary Function Data and Maximal Static Inspiratory Pressure for 12 Patients with CILD and 16 Normal Subjects

<table>
<thead>
<tr>
<th>Case</th>
<th>VC, % pred</th>
<th>RV, % pred</th>
<th>FRC, % pred</th>
<th>TLC, % pred</th>
<th>FEV₁, % pred</th>
<th>FEV₁/VC, %</th>
<th>MIP*, % pred</th>
<th>Dsb, mm Hg</th>
<th>PaO₂, mm Hg</th>
<th>PaCO₂, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>65</td>
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<td>54</td>
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<td>82</td>
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<td>46.7</td>
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<td>68</td>
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<td>7</td>
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<td>72</td>
<td>69</td>
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<td>54</td>
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<td>65</td>
<td>58</td>
<td>71.1</td>
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<td>70</td>
<td>70</td>
<td>79</td>
<td>75</td>
<td>72</td>
<td>39</td>
<td>72</td>
<td>82.9</td>
<td>31.8</td>
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<tr>
<td>11</td>
<td>62</td>
<td>80</td>
<td>68</td>
<td>68</td>
<td>64</td>
<td>103</td>
<td>39</td>
<td>65</td>
<td>52</td>
<td>43.7</td>
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<td>12</td>
<td>79</td>
<td>85</td>
<td>80</td>
<td>80</td>
<td>74</td>
<td>93</td>
<td>74</td>
<td>71</td>
<td>73.5</td>
<td>41.3</td>
</tr>
<tr>
<td>Mean</td>
<td>68.9</td>
<td>62.1</td>
<td>67.1</td>
<td>67.3</td>
<td>66.2</td>
<td>82.85</td>
<td>69</td>
<td>62.7</td>
<td>68.6</td>
<td>39.6</td>
</tr>
<tr>
<td>SD</td>
<td>16.2</td>
<td>24.4</td>
<td>19.6</td>
<td>17.2</td>
<td>18.4</td>
<td>12.6</td>
<td>20.7</td>
<td>10.2</td>
<td>11.4</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Normal subjects

| Mean | 106 | 108 | 102 | 106 | 101 | 82 | 103.9 |
| SD | 7.4 | 12 | 10 | 28 | 8 | 8.5 | 14.6 |

*MIP = maximal static inspiratory pressure against an occluded airway at RV.

1SD × 1.64: on average, the VC was 68.9 percent; RV, 62.1 percent; FRC, 67.1 percent; and TLC, 67.3 percent of the predicted values; the FEV₁, was significantly decreased in all patients but two (3 and 8) (mean = 66.2 percent of predicted), and the FEV₁/VC ratio was normal in all patients but one (9) (mean = 82.85 percent). Diffusing lung capacity (Dsb) was significantly decreased in 11 of the 12 patients (mean = 62.7 percent of predicted). Mean PaO₂ for the group, 68.6 mm Hg, was noticeably reduced in three patients (1, 4, and 11); in all but one (subject 5) the PaCO₂ was <45 mm Hg. The MIP in percentage of the predicted value was significantly decreased in all patients but five (5 to 8 and 12); the mean value (69 percent ± 20.7) was significantly reduced compared with the mean value of the normal control group (103.9 ± 14.6; SD; p<0.001).

Breathing pattern Pₐ₁, and EMG during room air breathing are shown for the two groups in Table 3. As shown, compared with the normal control group, patients exhibited lower Vₚ (p<0.01), Ti (p<0.001), and Ti/Ttot ratio (p<0.05) and a greater Vₚ/Ti (p<0.001) and f (p<0.01); the Pₐ₁ and EMGd (p<0.001 for both) and EMGint (p<0.01) were also greater in patients, while the Pₐ₁/EMGd ratio was significantly lower (p<0.05).

Ventilatory, occlusion pressure (Pₐ₁), and EMG responses to hypercapnia for the two studied groups (mean ± 1SD) are shown in Table 4. The average X/Pₜi response slopes to PETCO₂ for the diaphragm (p<0.001) and intercostal muscles (p<0.01) were significantly greater in patients than in the normal control group, as was the Pₐ₁ response slope to PETCO₂ (p<0.05); in contrast, the Vₚ response slope was lower in patients than in normal subjects (p<0.01). The relationship of EMGd change per PETCO₂ change among individual patients compared with the mean normal response slope (±1SD) is shown in Figure 1. In all but three patients (1, 8, and 12) the X/Pₜi response slope was higher than the mean normal slope ±1SD.

Matching the two groups for a given level of PETCO₂

Table 3—Breathing Pattern, Pₐ₁, and EMG Activity During Room Air Breathing

*Mean ± 1SD. Vₜ = minute ventilation; Vₚ = tidal volume; Ti = inspiratory time; Ti/Ttot = duty cycle; Vₚ/Ti = mean inspiratory flow; f = respiratory frequency; Pₐ₁ = mouth occlusion pressure; EMGd = electromyographic activity (moving time average) of the diaphragm; EMGint = EMG activity of the intercostal muscles. EMG was quantified as slope (X/Pₜi) obtained by dividing peak of inspiratory activity (X) by inspiratory time (Ti); X is expressed in % of the activity recorded at TLC while the subjects were breathing room air.

<table>
<thead>
<tr>
<th>Group</th>
<th>Vₜ, L/min</th>
<th>Vₚ, L</th>
<th>Ti, s</th>
<th>Ti/Ttot</th>
<th>Vₚ/Ti, L/s</th>
<th>f, cycles/s</th>
<th>Pₐ₁, cm H₂O</th>
<th>EMGd, %TLC/s</th>
<th>EMGint, %TLC/s</th>
<th>Pₐ₁/EMGd, cm H₂O/°TLC/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>9.88</td>
<td>0.75</td>
<td>1.92</td>
<td>0.40</td>
<td>0.39</td>
<td>13.5</td>
<td>1.9</td>
<td>2.4</td>
<td>2.45</td>
<td>0.76</td>
</tr>
<tr>
<td>(2.8)</td>
<td>(0.18)</td>
<td>(0.46)</td>
<td>(0.03)</td>
<td>(0.10)</td>
<td>(3.4)</td>
<td>(0.67)</td>
<td>(0.93)</td>
<td>(1.56)</td>
<td>(0.25)</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>12.80</td>
<td>0.56</td>
<td>1.10</td>
<td>0.34</td>
<td>0.64</td>
<td>22.17</td>
<td>5.26</td>
<td>25.3</td>
<td>16.0</td>
<td>0.45</td>
</tr>
<tr>
<td>(4.7)</td>
<td>(0.09)</td>
<td>(0.30)</td>
<td>(0.07)</td>
<td>(0.20)</td>
<td>(8.3)</td>
<td>(1.4)</td>
<td>(16.0)</td>
<td>(11.0)</td>
<td>(0.27)</td>
<td></td>
</tr>
</tbody>
</table>

*Mean ± 1SD. Vₜ = minute ventilation; Vₚ = tidal volume; Ti = inspiratory time; Ti/Ttot = duty cycle; Vₚ/Ti = mean inspiratory flow; f = respiratory frequency; Pₐ₁ = mouth occlusion pressure; EMGd = electromyographic activity (moving time average) of the diaphragm; EMGint = EMG activity of the intercostal muscles. EMG was quantified as slope (X/Pₜi) obtained by dividing peak of inspiratory activity (X) by inspiratory time (Ti); X is expressed in % of the activity recorded at TLC while the subjects were breathing room air.

tp<0.01.

*tp<0.001.

*¡p<0.05.
Table 4—Slopes of VE, VT, P1, EMGd, and EMGint vs PexCO\textsubscript{2} and of P1 vs EMGd During CO\textsubscript{2} Rebreathing in the Two Groups of Subjects\*  

<table>
<thead>
<tr>
<th>Group</th>
<th>(\Delta V E/\Delta P e x C O_2), L/min/%TLC\textsuperscript{s}\textsubscript{-1} Hg</th>
<th>(\Delta V T/\Delta P e x C O_2), L/mm Hg</th>
<th>(\Delta P_{1}/\Delta P e x C O_2), cm H\textsubscript{2}O/mm Hg</th>
<th>(\Delta E M G d/\Delta P e x C O_2), % TLC/s/mm Hg</th>
<th>(\Delta E M G i n t/\Delta P e x C O_2), % TLC/s/mm Hg</th>
<th>(\Delta P_{1}/\Delta E M G d), cm H\textsubscript{2}O/%TLC/s\textsuperscript{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1.36 (0.57)</td>
<td>0.073 (0.020)</td>
<td>0.35 (0.17)</td>
<td>1.10 (0.59)</td>
<td>1.06 (0.50)</td>
<td>0.33 (0.09)</td>
</tr>
<tr>
<td>Patients</td>
<td>1.39 (0.73)</td>
<td>0.039 (0.031)</td>
<td>0.539 (0.263)</td>
<td>2.98 (1.77)</td>
<td>3.20 (2.07)</td>
<td>0.21 (0.059)</td>
</tr>
</tbody>
</table>

\*Mean ± 1 SD. EMG was quantified as slope (XP/Ti) obtained by dividing peak of inspiratory activity (XP) by inspiratory time (Ti); change in XP during rebreathing was expressed in % of the activity recorded at TLC while the subjects were breathing room air; PexCO\textsubscript{2} = end-tidal tension of carbon dioxide. Other abbreviations as in Table 3.  

65 mm Hg (Table 5) showed in patients a greater absolute value of both P\textsubscript{0.1} (p<0.01) and diaphragmatic \(\bar{X}P/Ti\) (p<0.01). The VT (p<0.05) and Ti (p<0.01) were lower in patients, while VT/Ti (p<0.05) and f (p<0.01) were greater than in the normal control group; in contrast, VE and Ti/Ttot were similar in the two groups.

To assess neuromuscular inspiratory coupling, both in individual normal subjects and in patients (Fig 2), the P\textsubscript{0.1} response slope was plotted against EMGd response slope to PetCO\textsubscript{2}. In the normal subjects but not in patients, this relationship was significant (\(Y = 0.065 + 0.25 P e x C O_2\), \(r = 0.862\), and p<0.001). Figure 2 shows that in eight of the 12 patients, for a given EMGd response slope, the P\textsubscript{0.1} response slope fell below the normal regression line, and in six patients it was below the 95 percent confidence interval. As a mean \(\Delta P_{0.1}/\Delta E M G d\) was 0.33 cm H\textsubscript{2}O/\%TLC/s\textsuperscript{-1} ± 0.09 SD in normal subjects and 0.21 cm H\textsubscript{2}O/\%TLC/s\textsuperscript{-1} ± 0.09 SD in patients, with p<0.01 (Table 4). For a PetCO\textsubscript{2} of 65 mm Hg (Table 5), the P\textsubscript{0.1}/EMGd ratio was (0.31 cm H\textsubscript{2}O/\%TLC/s\textsuperscript{-1} ± 0.15 SD) significantly lower in patients (p<0.05) than in normal subjects (0.50 cm H\textsubscript{2}O/\%TLC/s\textsuperscript{-1} ± 0.22 SD). Plotting the P\textsubscript{0.1}/EMGd response slopes of patients with hypercapnia against the estimated duration of the disease showed no significant relationship.

In three normal subjects and in three patients, we compared EMGd activity as recorded by surface electrodes (EMGds) and EMGd activity as recorded by esophageal electrodes (EMGd) during CO\textsubscript{2} rebreathing. Comparison between intraindividual slopes (by covariance analysis) is shown in Table 6. In both normal subjects and in patients there were no significant differences between the EMGds and EMGd response slopes to increasing PetCO\textsubscript{2}.

No substantial change in heart rate during CO\textsubscript{2} rebreathing was observed in any patient. While breathing room air, the average heart rate was 78 ± 20 beats/min, and during rebreathing, the average maximal heart rate was 82 ± 20 beats/min (p = NS).

**Discussion**

Our data show a shallower and faster breathing in patients than in normal subjects. In fact, a lower VT and Ti and a greater f were observed in patients during room air breathing and chemically stimulated breathing. These data are consistent with those of Di Marco et al\textsuperscript{a} and Savoy et al\textsuperscript{a} in patients with CILD. As in other studies,\textsuperscript{4,5} the VT/Ti was greater in patients, and the value of this increase was slightly greater than that calculated by Di Marco et al\textsuperscript{a} and Renzi et al.\textsuperscript{5} The reasons for the abnormalities in time components of the breathing pattern in patients have previously been provided; basically, afferents arising from the lung and rib cage are expected to be involved in shortening Ti and increasing respiratory frequency.\textsuperscript{4,6,9}

Before considering our data on neural drive to the respiratory muscles, we will deal with the method we used in assessing this drive: (1) Processing the EMG "raw" signal, as proposed by Lopata et al.\textsuperscript{7,11} It allows the assessment of neural drive to the respiratory muscles.\textsuperscript{2,3,7,8,11,15,18} However, the employment of sur-
Table 5—Breathing Pattern, $P_{a1}$, EMGd, and $P_{a1}/$EMGd at 65 mm Hg of PetCO$_2$ in the Two Groups of Subjects$^*$

<table>
<thead>
<tr>
<th>Group</th>
<th>$V_e$, L/s$^1$</th>
<th>$f$, cycles$^1$</th>
<th>$V_t$, L</th>
<th>$T_i$, s</th>
<th>Ti/Tot, Ls$^1$</th>
<th>$V_r/T_i$, Ls$^1$</th>
<th>$P_{a1}$, cm H$_2$O</th>
<th>EMGd, % TLC$^3$</th>
<th>$P_{a1}$/EMGd, cm H$_2$O/% TLC$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>23.6</td>
<td>15.7</td>
<td>1.59</td>
<td>1.76</td>
<td>0.43</td>
<td>0.86</td>
<td>4.9</td>
<td>13.6</td>
<td>0.50</td>
</tr>
<tr>
<td>Patients</td>
<td>30.10</td>
<td>28.30</td>
<td>1.20</td>
<td>1.03</td>
<td>0.40</td>
<td>1.24</td>
<td>10.80</td>
<td>42.28</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*Mean ± 1SD. Abbreviations as in Table 3.
† = p<0.01.
‡ = p<0.05.

Contemporary, EMGd for studying the electric activity of the diaphragm may be criticized, since chest wall muscles (intercostal and/or abdominal) can interfere with EMGd values recorded by means of surface electrodes. Nevertheless, previous studies either in normal man$^{10,12-14}$ or in patients with chronic airflow obstruction$^{15-17}$ seem to indicate that when EMGd activity is recorded by surface electrodes, there is only a minimal contamination from the activity of other chest wall muscles during either spontaneous breathing or presentation of fatiguing resistive respiratory loads.$^{18,19}$ Consistently, our data show a good agreement between EMGd activity as recorded by surface electrodes (EMGds) and EMGd activity as recorded by esophageal electrodes (EMGde). However, in a recent article, Bellemare and Grassino$^{20}$ could not confirm the agreement between EMGds and EMGde previously noticed.$^{13}$ The authors explained this EMGds/EMGde disagreement as due to contamination of EMGds signal by voluntary inspiratory recruitment of abdominal muscles, which did not occur in the previous study by Gross and Grassino.$^{13}$ On the other hand, with patients in a supine position, Martin and De Troyer$^{21}$ noticed the absence of abdominal muscle action during loaded breathing. In this connection, abdominal muscles were suspected not to be involved in patients during the condition of the present study. (2) In filtering EMG, a low cutoff at 80 Hz was used. However, this may be a rather high frequency cutoff, since spectral analysis has shown diaphragm power to be down to 25 to 30 Hz, and thereby a part of the EMGd is probably being lost. Nevertheless, our preliminary measurements (see Material and Methods) showed that the integrated peak EMGd signal was not substantially altered by a low cutoff at 80 Hz, a datum consistent with a previous report.$^{22}$ (3) The ECG represents an artifact on an EMG signal, and any increase in heart rate may cause an overestimation of both $X_P$ and $X_P/T_i$. This seems not to be the case in the present study, where no substantial increase in heart rate during chemical stimulation occurred. In turn, all of these data corroborate the opinion that surface EMGd may represent a suitable tool in the assessment of inspiratory neural drive for clinical purposes.$^{8,13,18-20}$

Compared with the normal control group, our patients exhibited a normal or significantly greater increase in neural drive to the respiratory muscles as assessed by EMGd and EMGint. In two patients (2 and 5), those without systemic disease and who had not had steroid therapy, respiratory drive was markedly increased as well. The average greater absolute EMGd value during control conditions and for a given PetCO$_2$ (65 mm Hg) seems to indicate that nonchimerical, presumably mechanical, compensatory influences were involved in this increased respiratory drive. In patients with CILD pulmonary abnormalities may increase the firing of intrapulmonary vagal receptors$^{24,25}$ and increase the $P_{0.1}$. Further, patients also exhibited a lower $V_t$ along with a greater $f$ (Tables 3 to 5); since the rib cage contribution to $V_r$ depends on the size of the breath (eg, the smaller the latter, the less the former$^{25}$), owing to their smaller $V_r$, the patients with CILD are expected to have a decrease in rib cage expansion.$^4$ Any restriction of rib cage

Figure 2. Representation of neuromuscular coupling assessed by plotting $P_{a1}$ change per change in PetCO$_2$ against EMGd change per change in PetCO$_2$ of the same sitting. Solid and broken lines, the mean slope and 95% confidence intervals, respectively, of this relationship in 21 normal subjects. Individual data points for normal subjects (+) and patients (X).
expansion may alter the activity of mechanoreceptors in chest wall, which may increase respiratory drive both in normal subjects\textsuperscript{3,7,8} and in patients with CILD.\textsuperscript{4,5} Hence, in agreement with others,\textsuperscript{4,6} we argue that either vagal afferents from the lung or a reduction in rib cage expansion might contribute to the observed responses.

A second point deals with the method of assessing inspiratory neuromuscular coupling, ie, the $P_{0.1}$/EMGd relationship.\textsuperscript{2,3,7,8} Relating a parameter that evaluates total inspiratory muscle force ($P_{0.1}$) with one that measures neural drive to only one inspiratory muscle, the diaphragm (EMGd), has previously been criticized.\textsuperscript{29} However, it has been pointed out that the diaphragm is the main contributor to the inspiratory muscle output, both during quiet breathing and at high levels of ventilatory effort.\textsuperscript{29} A further criticism deals with the possibility that in some instances the relaxation of the abdominal muscles may take place a few ms before inspiration starts, preventing the $P_{0.1}$ from reflecting diaphragmatic EMG activity.\textsuperscript{31} In contrast, with the supine posture, occlusion pressure does not seem to include contributions from release of elastic recoil of chest wall.\textsuperscript{31} More recently, Hussain et al\textsuperscript{30} have shown that in normal man during progressive exercise, the increased $P_{0.1}$ is mostly due to augmented transdiaphragmatic pressure and coincident with increased EMGd during this initial part of inspiration. On this basis, we thought that in the studied conditions the $P_{0.1}$/EMGd relationship may also be considered a suitable index in assessing the transfer of neural output from the respiratory centers into total respiratory muscle output.

As was the case of EMG response slope, the average $P_{0.1}$ response slope was significantly greater in patients than in the normal control group, the greater $P_{0.1}$ and EMGd values observed in patients for a given $\text{PETCO}_2$ also reflecting their baseline situation. Nevertheless, compared with normal subjects, the average $P_{0.1}$/EMGd response slope was significantly lower in patients, indicating a decreased neuromuscular coupling (Fig 2 and Tables 4 and 5); ie, the inability of $P_{0.1}$ to reflect the actual amount of neural inspiratory drive. Di Marco et al\textsuperscript{4} hypothesized that in patients with CILD, neural drive to the respiratory muscles is increased. Compared with a normal control group, in their patients, the MIP was found to be lower, while $P_{0.1}$, the product of both neural drive to and the resulting force output of the inspiratory muscles,\textsuperscript{1} was found to be greater. Di Marco et al\textsuperscript{4} reasoned that the increased $P_{0.1}$ in patients could reflect an increased neural drive to the respiratory muscles. Our results confirm their hypothesis of an increased inspiratory drive, but seem to show that the $P_{0.1}$ does not reflect the actual amount of neural output to the inspiratory muscles in patients with CILD (Fig 2).

The factors underlying change in neuromuscular coupling are likely to be complex: (1) $P_{0.1}$ represents the total output of the activated inspiratory muscles; although the diaphragm is the main contributor in generating $P_{0.1}$, other inspiratory muscles, particularly the intercostal inspiratory muscles, assist the diaphragm function.\textsuperscript{32,33} Our data showing a progressive increase in EMGint activity indicate that there is no apparent reason to suspect in patients a low contribution of intercostal inspiratory muscles to aid the diaphragm to generate pleural pressure more efficiently. (2) It has been shown that poor nutrition impairs respiratory muscle function.\textsuperscript{34} Since our patients were not considered to be undernourished (Table 1), this factor is not thought to be involved in the low muscle output force they generated. (3) As is the case for other ventilatory parameters, one factor could be linked to aging, but difference in age was not observed between the two studied groups. (4) A decrease in pulmonary volume places the inspiratory muscles in a more efficient pressure-generating configuration.\textsuperscript{35} In contrast, in the present study, as in another,\textsuperscript{1} in spite of the reduction in pulmonary volumes, MIP was found to be decreased in patients. A poor inspiratory muscle strength could explain the low neuromuscular coupling and prevent $P_{0.1}$ from reflecting the actual amount of neural inspiratory drive (EMGd) in patients. For these reasons, we suspect that a poor respiratory muscle function was playing an important role in the abnormalities we observed. In agreement with Di Marco et al,\textsuperscript{4} we can only speculate that the advanced stage of the disease, the prolonged

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**Table 6—Intraindividual Comparisons Between EMGd Response to Increasing $\text{PETCO}_2$ as Recorded by Esophageal and Surface Electrodes (Covariance Analysis) in 3 Patients with CILD and in 3 Normal Subjects**

<table>
<thead>
<tr>
<th>Group</th>
<th>Case</th>
<th>ΔEMGd/ΔPETCO(_2)</th>
<th>f</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1</td>
<td>1.24</td>
<td>0.80</td>
<td>3.035</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.36</td>
<td>1.30</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.15</td>
<td>1.24</td>
<td>0.080</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>3.24</td>
<td>2.19</td>
<td>1.15</td>
</tr>
<tr>
<td>Patients</td>
<td>7</td>
<td>9.35</td>
<td>7.20</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>1.38</td>
<td>1.30</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*Abbreviations as in Table 3.*
steroid treatment, \cite{36,37} and the multisystem nature of the interstitial disorders\cite{38} we noted in some cases (Table 1) could account for this possibility, as well as the interindividual differences observed in patients.

Patients with CILD show a normal or increased neural inspiratory drive. Mouth occlusion pressure (P_{01}) does not seem to reflect accurately the actual amount of this drive. This could be explained by a poor inspiratory muscle function.

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Neural Respiratory Drive in Interstitial Lung Disease (Gorini et al)