Long-term Nasal Intermittent Positive Pressure Ventilation in Advanced Duchenne’s Muscular Dystrophy*

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The aim of our study was to evaluate the long-term effect of nasal ventilation in patients with advanced Duchenne’s muscular dystrophy (DMD). To this end, we compared the clinical and pulmonary function course of five subjects affected with chronic ventilatory failure due to DMD and treated with nasal intermittent positive pressure ventilation (NIPPV) with that of an unventilated comparison group; the latter consisted of another five patients with DMD, with a similar degree of clinical and respiratory functional impairment, who refused long-term mechanical ventilation. The duration of the follow-up was 24 months. At the conclusion of the trial, all patients treated with NIPPV were still alive; in contrast, four of five patients who underwent simple conservative treatment had already died (mean survival, 9.7 ± 5.8 months). After 6 months of follow-up, mean loss of FVC and maximal voluntary ventilation was considerably higher in nonventilated subjects (respectively: −0.23 L vs + 0.03 L and −5 L/min vs −1.5 L/min). These are the first comparative results confirming that long-term NIPPV helps to stabilize pulmonary function and to prolong the expectancy of life of patients with DMD. (Chest 1994; 105: 445-48)

DMD=Duchenne’s muscular dystrophy; NIPPV = nasal intermittent positive pressure ventilation; tcPCO2 = transcutaneous carbon dioxide tension; tcPO2 = transcutaneous oxygen tension

Several studies have reported that chronic ventilatory failure, sometimes with a superimposed acute respiratory insufficiency due to pneumonia or atelectasis, is the major cause of death in Duchenne’s muscular dystrophy (DMD).1-3

In recent years, with the appearance of nasal ventilation, there has been a rapid increase in the application of noninvasive long-term mechanical ventilation for the treatment of chronic hypoventilation in patients with neuromuscular disorders.4-6

There is general agreement about the efficacy of long-term nasal intermittent positive pressure ventilation (NIPPV) in determining a sustained reversal of chronic hyperventilation in patients with DMD, with normalization of PaCO2, alleviation of symptoms related to CO2 retention, and prolongation of life.7-10

Nevertheless, as controlled studies concerning the role of NIPPV in DMD have not yet been performed, the real effectiveness of mechanical ventilation via nasal mask on pulmonary function and the life expectancy of patients with DMD could not be completely evaluated.

In our article, we analyze the clinical and pulmonary function course of ten patients with advanced DMD affected with chronic respiratory failure; five were administered long-term NIPPV, while the other five refused this treatment. The two groups of patients had similar features from a clinical and respiratory functional point of view, which made it possible to consider the comparison group (not ventilated subjects), though not randomly selected, as a control group, and enabled us to assess the efficacy of long-term NIPPV in patients with DMD in conditions similar to those of a controlled trial.

MATERIAL AND METHODS

Between January 1987 and June 1990, ten unselected young male patients affected with advanced DMD were referred to the Respiratory Pathophysiology Department of the City Hospital of Padua, because of symptoms consistent with chronic hypercapnia (i.e., hypersonolence, insomnia, morning headaches, fatigue, enuresis).

The diagnosis of DMD was based on standard clinical, enzymatic, electromyographic, and biopsy criteria.

At the beginning of the study, the mean age was 20.1 ± 5.2 years (range, 12 to 27 years) and all the patients belonged to the IX functional class of Inkley’s classification (wheelchair-bound).3 Moreover, they were free from respiratory tract infections. Prior to referral, severe cardiomyopathy had been excluded by a two-dimensional echocardiography in eight patients and by clinical and radiographic findings in the remaining two.

All the subjects were administered the following examinations: clinical evaluation; chest radiograph; the posteroanterior radiograph of the chest was taken for calculating the degree of scoliotic deformity, according to the method of Cobb;11; and pulmonary function tests, including the following: (1) conventional spirometry, performed following standard criteria;12 in seated position, with a 10-L closed-circuit automated spirometer (Baires 80, Biomedin, Padua); static lung volumes were measured by the closed-circuit helium dilution technique; and (2) measurement of maximal voluntary ventilation (MVV).13

Reference values are those of the European Community14 or of

For editorial comment see page 337

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Table 1—Anthropometric, Radiographic, and Pulmonary Function Data at Detection of Daytime Hypercapnia

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Loss of Ambulation, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>Degree of Scoliosis (Cobb's Angle)</th>
<th>FVC, L</th>
<th>FVC, %</th>
<th>FEV1, %</th>
<th>FEV1/FVC</th>
<th>MVV, L/min</th>
<th>PaO2, mm Hg</th>
<th>PaCO2, mm Hg</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>15</td>
<td>9</td>
<td>160</td>
<td>26</td>
<td>90</td>
<td>0.32</td>
<td>9</td>
<td>0.27</td>
<td>9</td>
<td>10.0</td>
<td>55</td>
<td>48</td>
<td>7.40</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>24</td>
<td>11</td>
<td>155</td>
<td>56</td>
<td>20</td>
<td>0.56</td>
<td>13</td>
<td>0.52</td>
<td>15</td>
<td>21.7</td>
<td>79</td>
<td>47</td>
<td>7.42</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>26</td>
<td>13</td>
<td>165</td>
<td>62</td>
<td>30</td>
<td>0.34</td>
<td>7</td>
<td>0.30</td>
<td>8</td>
<td>13.6</td>
<td>87</td>
<td>50</td>
<td>7.42</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>21</td>
<td>10</td>
<td>160</td>
<td>46</td>
<td>20</td>
<td>0.31</td>
<td>6</td>
<td>0.30</td>
<td>8</td>
<td>15.0</td>
<td>73</td>
<td>54</td>
<td>7.39</td>
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<tr>
<td>Mean</td>
<td>21</td>
<td>19.8</td>
<td>9.8</td>
<td>158.0</td>
<td>54.6</td>
<td>38.0</td>
<td>0.67</td>
<td>19</td>
<td>0.57</td>
<td>19.8</td>
<td>17.9</td>
<td>74.8</td>
<td>48.8</td>
<td>7.40</td>
</tr>
<tr>
<td>± SD</td>
<td>5.8</td>
<td>2.5</td>
<td>5.7</td>
<td>13.8</td>
<td>29.4</td>
<td>0.6</td>
<td>23</td>
<td>0.5</td>
<td>22.1</td>
<td>7.5</td>
<td>12.1</td>
<td>3.4</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>6</td>
<td>27</td>
<td>8</td>
<td>165</td>
<td>55</td>
<td>90</td>
<td>0.23</td>
<td>6</td>
<td>0.22</td>
<td>7</td>
<td>12.0</td>
<td>50</td>
<td>79</td>
<td>7.36</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>16</td>
<td>12</td>
<td>152</td>
<td>45</td>
<td>60</td>
<td>0.80</td>
<td>26</td>
<td>0.79</td>
<td>31</td>
<td>24.0</td>
<td>76</td>
<td>47</td>
<td>7.41</td>
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<tr>
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<td>19</td>
<td>13</td>
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<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>10.6</td>
<td>11.2</td>
<td>165.2</td>
<td>60.8</td>
<td>66.7</td>
<td>0.74</td>
<td>19.1</td>
<td>0.70</td>
<td>20.2</td>
<td>19.1</td>
<td>66.8</td>
<td>53.6</td>
<td>7.40</td>
<td></td>
</tr>
<tr>
<td>± SD</td>
<td>5.6</td>
<td>1.9</td>
<td>8.4</td>
<td>12.7</td>
<td>20.1</td>
<td>0.4</td>
<td>6.7</td>
<td>0.5</td>
<td>12.5</td>
<td>6.7</td>
<td>14.8</td>
<td>14.2</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Polgar and Promadhar,13 for subjects older or younger than 18 years, respectively. Arm span was used for determining percent predicted values in patients with severe scoliosis.

Pulmonary function tests were not performed in one patient because of lack of cooperation.

All subjects also underwent arterial blood gas analysis during spontaneous breathing on air room (AB 30, Radiometer, Copenhagen, Denmark).

Since all the patients evidenced stable daytime hypercapnia (PaCO2 >45 mm Hg), they were advised to undergo long-term mechanical ventilation via nasal mask, in agreement with other authors.10,13

Five subjects accepted long-term ventilatory therapy, whereas the other five rejected this option, since they were convinced that home mechanical ventilation would have further decreased their quality of life. When younger than 18 years, they took this decision in accordance with their families.

As a consequence, the patients were included respectively in group A (treated with NIPPV) and group B (not ventilated).

Before starting long-term NIPPV, group A underwent three consecutive overnight transcutaneous monitorings of oxygen tension and carbon dioxide tension (TCM3 Radiometer, Copenhagen, Denmark), during a brief hospitalization period.

Nocturnal transcutaneous oxygen tension (tcPO2) and transcutaneous carbon dioxide tension (tcPaCO2) recordings during mechanical ventilation guided the adjustments of tidal volume and respiratory rate, with the goal of maintaining tcPO2 over 70 mm Hg and tcPaCO2 below 45 mm Hg, while the patients were sleeping and using the ventilator. NIPPV was administered by a volume-cycled, portable ventilator (PB2800, Portable Volume Ventilator, Puritan-Bennett, Carlsbad, Calif.), blowing room air in the nose through two armed cannulas (Willy Rusch AG, Waiblingen Germany). These were sustained by a custom-made nasal interface, light and elastic, well-fitted to the face of the patient (Coltene, Altstatten, Switzerland).

Following discharge from the hospital, the patients continued to use their ventilator each night at home, at least 7 h per night. The proper use of the ventilator was checked on frequently by a physician of our department, who visited the patients at home, at least once a week.

After the detection of chronic ventilatory failure, subjects belonging both to group A and B were reevaluated, at 6-month intervals, over a period of 2 years, following the same series of examinations performed at the beginning of the study.

Table 2—Clinical and Pulmonary Function Data at Conclusion of the Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient No.</th>
<th>Clinical Outcome</th>
<th>Hospitalization</th>
<th>FVC, L</th>
<th>FVC, %</th>
<th>MVV, L/min</th>
<th>PaO2, mm Hg</th>
<th>PaCO2, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>Living at home</td>
<td>1 for pneumonia</td>
<td>0.32</td>
<td>7</td>
<td>7.7</td>
<td>85</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Living at home</td>
<td>1 for pneumonia</td>
<td>0.90</td>
<td>19</td>
<td>19.5</td>
<td>86</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Living at home</td>
<td>1 for severe CO2 retention</td>
<td>0.42</td>
<td>9</td>
<td>16.8</td>
<td>88</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Living at home</td>
<td>—</td>
<td>0.23</td>
<td>5</td>
<td>9.0</td>
<td>65</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Living at home</td>
<td>—</td>
<td>1.59</td>
<td>38</td>
<td>30.0</td>
<td>85</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Death at 2nd mo</td>
<td>1 for carbocorticoma</td>
<td>—</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Death at 11th mo</td>
<td>1 for carbocorticoma</td>
<td>—</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Death at 16th mo</td>
<td>1 for pneumonia at 14th mo, tracheostomy</td>
<td>—</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>B</td>
<td>9</td>
<td>Sudden death at home at 10th mo</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>Living at home</td>
<td>1 for nocturnal ventilatory failure with seizure</td>
<td>1.08</td>
<td>20</td>
<td>20.3</td>
<td>82</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

Long-term NIPPV in Advanced Duchenne's Dystrophy (Vianello et al)
At the conclusion of the trial (June 1992), we analyzed the clinical data and serial values of FVC, MVV, PaO\textsubscript{2}, and PaCO\textsubscript{2} for each patient.

For statistical comparison, we used Pearson’s correlation method for correlations between pulmonary function data and survival time. A p value of less than 0.05 was considered significant.

RESULTS

Anthropometric, radiographic, pulmonary function, and blood gas data at detection of stable hypercapnia are reported in Table 1.

With regard to these parameters, there are no significant differences between the two groups.

As in other studies,\textsuperscript{10} in our group of patients, FVC and MVV values showed a great variation at the onset of daytime hypercapnia.

Clinical, pulmonary function, and blood gas data collected at the end of the study are summarized in Table 2.

At the end of the trial, all the patients of group A were still alive and reported a good tolerance of NIPPV.

During long-term NIPPV, subjects 1 and 2 needed to be hospitalized because of acute pneumonia, complicated by inability to cough; in this phase, they became dependent on NIPPV almost 24 h/d and were submitted to cricothyroid “minitracheotomy” that was closed at discharge from hospital. This is a procedure of percutaneous tracheal cannulation with a small-bore tube that provides constant tracheal access for sputum suction.\textsuperscript{17} Patient 4 needed to be hospitalized because of the onset of progressive, marked hypercapnia, despite mechanical ventilation; this was due to a severe nasal insufflation leak, with ineffective pulmonary ventilation. By remodeling nasal interface, the leak was eliminated, effective ventilation was restored, and arterial blood gas values rapidly improved.

Among patients not receiving NIPPV, patients 6 and 7 died because of the progression of chronic respiratory insufficiency, with carbonarotic coma, respectively, 2 and 11 months after the detection of stable ventilatory failure. Patient 8 was hospitalized after acute respiratory failure due to pneumonia; he underwent tracheostomy and died 16 months after the onset of chronic hypercapnia. Subject 9 experienced a sudden death at home, 10 months after the beginning of the study.

From the onset of daytime hypercapnia, the mean survival of these four patients was 9.7 ± 5.8 months.

Patient 10 was still alive at the conclusion of our study; during the follow-up, he needed to be hospitalized due to severe nocturnal ventilatory failure with seizure.

In the first 6 months of receiving NIPPV, FVC plateaued in the treated group (in the mean: + 0.03 L), while a further sudden decline was recorded (in the mean: − 0.23 L) in the untreated patients.

The progression of FVC is described in Figure 1.

In the same period, MVV declined slowly in group A (− 1.5 L/min), whereas in group B, the mean loss of MVV was considerably higher (−5 L/min) (Fig 1).

At the conclusion of the follow-up period, a moderate improvement in PaO\textsubscript{2} and PaCO\textsubscript{2} was found in group A, compared with the initial values (mean PaO\textsubscript{2}, 81.6 ± .9 vs 74.8 ± 12.1 mm Hg; mean PaCO\textsubscript{2}, 46 ± 8.8 vs 48.8 ± 3.4 mm Hg).

DISCUSSION

The success of NIPPV in the long-term treatment of chronic ventilatory failure due to neuromuscular
effectiveness of this technique in prolonging survival of the patients and slowing the loss of FVC could not be demonstrated definitively.

In our experience, five subjects with DMD refused to undergo long-term mechanical ventilation, in spite of a severe respiratory impairment. Since the severity of their clinical status and the degree of their respiratory function disability were in the mean the same as those of another five patients who elected to undergo NIPPV, it was possible to evaluate the efficacy of long-term NIPPV in patients with DMD in conditions similar to those of a controlled trial, though the comparison group was not precisely a control group, as it was not randomly selected.

The first major finding of our study is the evidence that the application of NIPPV decreases mortality in patients with DMD: 24 months after the detection of chronic ventilatory failure, all the subjects treated with nocturnal NIPPV were still alive; in contrast, four of five patients who underwent simple conservative treatment had already died (mean survival, 9.7 ± 5.8 months).

During the follow-up, two patients in group A, affected with an acute respiratory tract infection, had cricothyroid "minitracheotomy:" this procedure provided an effective suctioning of bronchial secretions, making tracheotomy unnecessary.

In the comparison group not receiving ventilation, a close inverse relationship was observed between the severity of \( CO_2 \) retention at the beginning of follow-up and the patient’s expectancy of life \( (r: -0.84) \): these data confirm that the main explanation for the effectiveness of NIPPV in prolonging survival of patients with DMD may be the stabilization and improvement in pulmonary gas exchanges and the reversal of chronic hyperventilation.

The mechanism by which long-term NIPPV may correct stable hypoventilation in DMD has not been clearly demonstrated.

In our experience, we found a substantial stabilization of MVV after the first 6 months of receiving mechanical ventilation in group A; in contrast, a further marked decline was recorded \( (-5 \text{ L/min}) \) in the subjects not receiving ventilation. Since the magnitude of MVV is considered to be a function of respiratory muscle strength, the different development of this parameter in the two groups of patients enables us to advance the hypothesis that the improvement induced by NIPPV on pulmonary ventilation and gas exchanges may stem from a reduction of the functional deterioration of respiratory muscles. Nevertheless, more extended follow-ups showed that mechanical ventilation failed to prevent the decline in respiratory muscle function over a longer period of time.\(^9,10\)

In conclusion, this is the first time, to our knowledge, that the efficacy of long-term NIPPV in the treatment of respiratory failure caused by DMD has been evaluated in a comparative study. Our follow-up data confirm previous observations that nasal ventilation helps to stabilize pulmonary function, probably by slowing the deterioration of respiratory muscles, and prolongs the life expectancy in patients with DMD.

REFERENCES

8 Bach JR, Alba AS. Management of chronic alveolar hypoventilation by nasal ventilation. Chest 1990; 97:52-7
11 Cobb JR. Outline for the studies of scoliosis. American Academy of Orthopaedic Surgeons Instructional Course Lectures 1948; 5:261
13 Arora NS, Rochester DF. Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. Am Rev Respir Dis 1982; 126:5-8
18 Braun NMT, Arora NS, Rochester DF. Respiratory muscle and pulmonary function in polymyositis and other proximal myopathies. Thorax 1983; 38:616-23