Noninvasive Mechanical Ventilation Improves Endurance Performance in Patients With Chronic Respiratory Failure Due to Thoracic Restriction*

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Objective: Treatment with noninvasive mechanical ventilation (NMV) alleviates hypoventilation and improves gas exchange in patients with chronic respiratory failure (CRF) due to thoracic restriction. However, little is known about the effects of NMV on respiratory and peripheral muscle endurance.

Design: Prospective case-control study.

Subjects: Ten patients in clinically stable condition (age, 53.5 ± 8.2 years [mean ± SD]) with mild-to-moderate CRF due to thoracic restriction (Pco₂ between 45 mm Hg and 55 mm Hg) were treated with NMV during the night for 3 months. Ten matched patients (age, 52.2 ± 9.5 years) receiving 3 months of normal care without NMV served as a control group.

Intervention and measurements: After a 3-day period of familiarization with the endurance tests, all patients performed a baseline preintervention inspiratory threshold loading test, cycle ergometer test, and shuttle walking test on the same day. The endurance tests were then repeated following the 3-month intervention period.

Results: NMV was used on average for 7.1 ± 0.9 h/d during the 3-month period. There was a significant improvement in endurance time (p < 0.0001) in all three endurance tests in the NMV group compared with the control group. In the NMV group, endurance time increased by 278 ± 269% during the inspiratory threshold loading test, by 176 ± 159% during the cycle ergometer test, and by 32 ± 22% during the shuttle walking test. Significant improvements (p < 0.01) in both PO₂ and PCO₂ were also observed in the NMV group but not in the control group.

Conclusions: Three months of treatment with NMV increases both respiratory and peripheral muscle endurance in patients with CRF due to thoracic restriction.

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Key words: chronic respiratory failure; cycle ergometer; inspiratory threshold loading; noninvasive mechanical ventilation; respiratory muscle endurance; shuttle walk

Abbreviations: CRF = chronic respiratory failure; fresp = breathing frequency; NMV = noninvasive mechanical ventilation; PCV = pressure-controlled ventilation; Pmax = peak static inspiratory mouth pressure; VCO₂ = carbon dioxide elimination; VC = vital capacity; VCV = volume-controlled ventilation; VO₂ = oxygen consumption; VT = tidal volume

Many patients with chronic lung disease have a reduced exercise capacity and an associated decline in activities of daily living. Using a movement detector (pedometer) as a measure of daily activity levels, we have observed1 a correlation between FEV₁ and daily physical activity levels in patients with COPD. Furthermore, a relationship between the severity of chronic respiratory failure (CRF), in terms of hypercapnia, and daily activity was also demonstrated in this study.

Treatment with noninvasive mechanical ventilation (NMV) relieves hypventilation and improves blood gas levels in patients with CRF due to restrictive thoracic disease.2–4 We have observed an impressive increase in daily movement count in patients with CRF following 3 months of NMV.1 One hypothesis that could account for this improvement is an increase in the endurance capacity of peripheral
limb and/or respiratory muscles. Therefore, in the present controlled study, we measured respiratory muscle endurance (inspiratory threshold loading) and peripheral limb muscle endurance (cycle ergometer and shuttle walking tests) performance in patients with CRF before and after 3 months of treatment with NMV, using a group of patients receiving 3 months of normal care without NMV as control subjects.

**Materials and Methods**

**Patients**

Patients with CRF due to restrictive thoracic disease (post-tuberculosis sequelae or scoliosis) were eligible for inclusion into the study. In addition, subjects were required to be hypcapnic (PCO₂ between 45 mm Hg and 55 mm Hg), in clinically stable condition (no hospital admission for at least 1 month prior to the study), and to have no significant difference in blood gas analysis parameters from samples obtained on hospital admission compared with samples obtained 1 month before hospital admission. Subjects were ineligible for the study if they had (1) rapidly progressive neuromuscular disease (eg, motor neuron disease), (2) an obesity-hypventilation syndrome, (3) COPD, (4) acute respiratory failure (requiring continuous mechanical ventilation), or (5) severe acidosis (defined as pH < 7.3).

A prospective study design with matched pairs (complete matching with respect to diagnosis and sex, and matching for age and body weight with a ±5% variation) was used. In general, patients were alternately allocated to the NMV group or to the normal-care control group, except when a new patient was appropriately matched with a patient already entered into the trial, in which case the new patient was allocated to the opposite group of the matched patient. Ten patients (5 men and 5 women) were assigned to the intervention group (age, 53.5 ± 9.5 years; height, 159.3 ± 10.3 cm; weight, 59.7 ± 19.8 kg) and 10 patients (5 men and 5 women) were assigned to the control group (age, 52.2 ± 9.5 years; height, 159.3 ± 10.3 cm; weight, 61.3 ± 19.8 kg). In each group, two patients had post-tuberculosis sequelae and eight patients had scoliosis. No patient in either group was treated with oxygen during the study. The protocol was approved by the ethical review committee, and all subjects gave written informed consent to participate.

**Measurements**

Baseline measurements were performed prior to the intervention period. Spirometry and whole body plethysmography were performed with a Masterlab (Jäger; Würzburg, Germany). Peak static inspiratory mouth pressure (Pimax) was measured at residual volume using a piezoelectric pressure sensor, with Pimax being recorded as the highest of at least five reproducible values.

Resting tidal volume (VT) and breathing frequency (fresp) were measured while the subject breathed through a mouthpiece connected to a portable pneumotachograph (CP100; Bicore; Medilab; Estenfeld, Germany) with the nasal passages occluded by a noseclip. Resting daytime capillary blood gas levels were determined using a Gas Check (AVL; Bad Homburg, Germany) from a sample obtained from a hyperemic earlobe (rubefacient; finalgon, Boehringer Ingelheim, Ingelheim, Germany) while breathing room air. The perceived intensity of breathlessness and/or leg exertion were rated by each subject using a visual analog scale anchored at 0 (not short of breath/no leg exertion) and 10 (extremely short of breath/extreme leg exertion).

**Inspiratory Threshold Loading Test**

Inspiratory muscle endurance was determined as the symptom-limited endurance time while breathing against a weighted inspiratory plunger, which imposed an adjustable threshold load throughout inspiration. For each patient, the load was set at 33% of the baseline Pimax for both the baseline and postintervention tests. Patients rated the intensity of breathlessness before the test and immediately after the point of symptom limitation.

**Cycle Ergometer Test**

The cycle ergometer test was performed on an electronically braked cycle ergometer (Ergoline; Siemens; Erlangen, Germany). Ventilation was measured by an Oxycon 1000 (Jäger, Würzburg, Germany) with the patients breathing through a low-resistance turbine device. Oxygen and carbon dioxide were continuously sampled, with oxygen being analyzed paramagnetically and carbon dioxide being analyzed by an infrared method. Oxygen consumption (VO₂), carbon dioxide elimination (VCO₂), fresp, VT, and minute ventilation were recorded breath by breath, and results were given as 30-s averages. Heart rate was continuously determined by an ECG (Sirecust 314; Siemens, Erlangen, Germany). Blood lactate concentration was measured before and immediately after each exercise test, and analyzed by the method of Marbach and Well. Arterialized capillary blood gas levels (PO₂ and PCO₂) were determined from a sample taken from a hyperemic earlobe before and after each test.

Prior to the test, patients sat on the ergometer in a semierect position for 10 min, to become accustomed to the breathing apparatus. The constant work rate of the cycle exercise test was determined by an incremental exercise test procedure during initial screening. The test started with 20 W and lasted for 4 min. In most patients, there was more than one test, since each time the patient finished the 4-min interval, the work rate was increased by 10 W until the patient failed to complete at least 2 min; therefore, the maximal work rate was defined as the exercise intensity that the patient was able to tolerate for at least 2 min. If they did not reach the 2-min mark before they stopped the test, the previous exercise intensity (ie, 10 W lower) was considered as the maximal work rate. At maximal work rate, the experimental endurance cycle exercise test was terminated either by the patient (symptoms of fatigue or breathlessness) or by the operator if the patient failed to maintain the given pedal frequency (50 revolutions per min). Before and after the cycle ergometer test, subjects rated the intensity of breathlessness and leg exertion. Exercise response was compared with the predicted normal values of Ruhl et al.

**Shuttle Walking Test**

The shuttle walking test was performed according to a standard protocol. In brief, the patient walked up and down a 10-m course at a progressively increasing speed until either the patient stopped due to symptom limitation (fatigue or breathlessness) or the patient failed to complete a shuttle length in the allowed time, in which case the operator stopped the test. The initial speed was set at 1.8 km/h and increased by 0.6 km/h each minute, with the required walking speed being relayed to the subject by an acoustic signal. The subject rated the intensity of breathlessness and leg exertion before the test and immediately following termination of the test.
### Study Protocol

Following baseline measurements of blood, lung function, and ventilatory variables (Table 1), each subject completed a 3-day familiarization period, during which two bouts of each endurance test were completed (day 1, inspiratory threshold loading test; day 2, cycle endurance test; day 3, shuttle walking test); a rest period of at least 2 h was given between each test.

The day after the final familiarization period, the baseline endurance tests were performed, with the inspiratory threshold loading test being conducted at 8 AM, the cycle endurance test being conducted at 12 noon, and the shuttle walking test being conducted at 4 PM.

Patients then began the intervention period, which comprised NMV or normal care depending on the group allocation (NMV or control group). During this period, all patients received care from their chest physicians; in case of a deterioration, patients were admitted to our hospital. None of the patients participated in an exercise rehabilitation program during the study period. For those patients receiving NMV, the intervention period began with a 5-day run-in period of NMV to determine the optimal ventilator settings. Patients were adapted to NMV at NMV at daytime three times in periods lasting 2 h during the first 2 days. Afterwards, NMV was applied during the night for at least 6 h.

Initially, all patients underwent volume-cycled ventilation (VCV), using either Dräger EV 800 (Dräger; Lübeck, Germany) or PLV 100 (Respironics; Murraysville, PA). However, if after 2 days the patients felt uncomfortable, VCV was replaced by pressure-controlled ventilation (PCV) (BP-T; Respironics).

VCV settings: Before VCV was started, the fresp of the spontaneously breathing patient was determined using a portable pneumotachograph (CP100; Bicore; Medilab), while the patient was in a sitting position without receiving supplemental oxygen. VCV was then started with the pneumotachograph inserted in the tubing system between mask and expiratory valve of the ventilator. The rate of the unit was set at the same rate or slightly higher than that measured during spontaneous breathing in order to suppress the respiratory activity of the patient. The inspiration time was chosen according to the underlying disease (thoracic restriction) between 40% and 50% of the whole breathing cycle.

**PCV Settings:** The rate of the ventilator was again set at the same rate or slightly higher than that measured during spontaneous breathing. Inspiratory time was chosen as described above. Inspiratory pressure support was adapted in order to reach the Vt determined during the preceding VCV. In order to monitor Vt, a pneumotachograph was inserted in the tubing system. In each case, these adjustments were made under permanent observation by experienced personnel in a quiet room. Further details on adaptation to both VCV and PCV have been described elsewhere. After 3 months, measurements of resting blood, lung function, and ventilatory variables were repeated and each patient performed each of the three endurance tests on the same day, in the same order and time of day as at baseline.

### Statistical Analysis

The primary efficacy end points were the changes from baseline in endurance time for each endurance test following the intervention period expressed as a percentage of the baseline endurance time. They were tested for group differences with the exact Wilcoxon-Mann-Whitney two-sided test. The global α of 0.05 was adjusted according to the Bonferroni-Holm procedure, the lowest α being 0.017. Confirmatory p values lower than the adjusted α were taken as statistically significant.

As a secondary analysis, a baseline/3-month (pretreatment/posttreatment) comparison was tested, within the intervention and the control group (exploratory p values calculated with centered Wilcoxon signed rank test), for each endurance test. All other criteria (lung function, blood variables, ventilatory variables, breathlessness, leg exertion) were secondary end points, and were evaluated with descriptive statistics (mean value ± SDs) and exploratory p values (exact Wilcoxon-Mann-Whitney test for group

### Table 1—Blood Gas Data, Lung and Respiratory Muscle Function, and Breathing Pattern at Baseline and After 3 mo of NMV or Control

<table>
<thead>
<tr>
<th>Parameters at Rest</th>
<th>Baseline</th>
<th>3 mo</th>
<th>Baseline</th>
<th>3 mo</th>
<th>NMV vs Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
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<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO₂, mm Hg</td>
<td>55.2 ± 7.2</td>
<td>67.3 ± 7.8</td>
<td>57.1 ± 7.6</td>
<td>56.5 ± 8.9</td>
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</tr>
<tr>
<td>PCO₂, mm Hg</td>
<td>53.1 ± 2.1</td>
<td>43.1 ± 2.6</td>
<td>52.7 ± 2.1</td>
<td>53.1 ± 5.2</td>
<td>¶</td>
</tr>
<tr>
<td>pH</td>
<td>7.37 ± 0.02</td>
<td>7.39 ± 0.02</td>
<td>7.38 ± 0.02</td>
<td>7.38 ± 0.03</td>
<td>¶</td>
</tr>
<tr>
<td>HCO₃⁻, mmol/L</td>
<td>29.7 ± 1.8</td>
<td>25.1 ± 2.0</td>
<td>30.7 ± 3.1</td>
<td>29.7 ± 3.3</td>
<td>¶</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>1.31 ± 0.37</td>
<td>1.19 ± 0.45</td>
<td>1.34 ± 0.56</td>
<td>1.36 ± 0.32</td>
<td>¶</td>
</tr>
<tr>
<td>VC, L</td>
<td>1.10 ± 0.52</td>
<td>1.20 ± 0.5</td>
<td>1.13 ± 0.37</td>
<td>1.10 ± 0.36</td>
<td>¶</td>
</tr>
<tr>
<td>VC, % predicted</td>
<td>35.8 ± 11.3</td>
<td>39.5 ± 8.7</td>
<td>40.8 ± 8.6</td>
<td>38.8 ± 10.1</td>
<td>¶</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.82 ± 0.41</td>
<td>0.90 ± 0.4</td>
<td>0.85 ± 0.25</td>
<td>0.83 ± 0.23</td>
<td>¶</td>
</tr>
<tr>
<td>FEV₁ percent VC</td>
<td>75.4 ± 8.6</td>
<td>73.7 ± 6.5</td>
<td>77.4 ± 9.9</td>
<td>76.5 ± 8.7</td>
<td>¶</td>
</tr>
<tr>
<td>Ptmax, cm H₂O</td>
<td>43.0 ± 15.6</td>
<td>66.0 ± 18.9</td>
<td>45.1 ± 14.7</td>
<td>52.8 ± 16.2</td>
<td>¶</td>
</tr>
<tr>
<td>fresp, L/min</td>
<td>24.0 ± 1.9</td>
<td>20.3 ± 4.5</td>
<td>22.7 ± 1.8</td>
<td>22.3 ± 2.6</td>
<td>¶</td>
</tr>
<tr>
<td>Vt, mL</td>
<td>344.0 ± 116.8</td>
<td>410.0 ± 149.4</td>
<td>354.0 ± 40.5</td>
<td>324.2 ± 58.8</td>
<td>¶</td>
</tr>
<tr>
<td>VCO₂, mL/min</td>
<td>206.8 ± 61.7</td>
<td>237.8 ± 51.9</td>
<td>213.2 ± 55.0</td>
<td>213.7 ± 61.7</td>
<td>¶</td>
</tr>
<tr>
<td>VO₂, mL/min</td>
<td>322.2 ± 74.5</td>
<td>284.3 ± 49.8</td>
<td>267.2 ± 70.3</td>
<td>256.3 ± 82.5</td>
<td>¶</td>
</tr>
<tr>
<td>Respiratory quotient</td>
<td>0.54 ± 0.09</td>
<td>0.54 ± 0.07</td>
<td>0.81 ± 0.09</td>
<td>0.82 ± 0.07</td>
<td>¶</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>105.8 ± 20.3</td>
<td>95.6 ± 13.7</td>
<td>99.0 ± 12.8</td>
<td>98.3 ± 12.4</td>
<td>¶</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
†Internal-group comparison between baseline and 3 months (p < 0.05).
‡Internal-group comparison between baseline and 3 months (p < 0.01).
¶Group differences (percentage of change) between baseline and after 3 months (p < 0.05).
||Group differences (percentage of change) between baseline and after 3 months (p < 0.01).
¶¶Group differences (percentage of change) between baseline and after 3 months (p < 0.001).
results

In accordance with the eligibility criteria for the study, all patients had CRF, with daytime hypoxemia and hypercapnia (Table 1) at baseline. Vital capacity (VC), FEV₁, Pmax, and VT were decreased, and fresp increased (Table 1) compared to normal values. There was no significant difference in baseline VC, FEV₁, PO₂, Pco₂, fresp, VT, and Pmax (Table 1) between the NMV group and control group.

While the two groups were well matched with regards to sex, diagnosis, age, and body weight (± 5% variation), there were noticeable differences between the groups in other parameters, such as Pco₂ (8.9%), PO₂ (13.8%), VC (34.6%), and FEV₁ (39.7%). In the NMV group, five patients used VCV and five patients used PCV; there was no significant difference between devices with respect to improvements in blood gas measurements and endurance times (p > 0.1, Mann-Whitney). On average, NMV was used 7.1 ± 0.9  h during each night.

Since each endurance test showed high reproducibility, any possibility of learning effects during the intervention period can be discounted (Figs 1–3); in all three endurance tests, the factor “repeated measurements” showed no significant effect analysis of variance (p > 0.3). There was no significant difference between the NMV and control group at baseline with respect to endurance times for each endurance test. The responsiveness of each test was confirmed by the occurrence of a significant treatment effect, with NMV significantly improving endurance time in all three tests.

During the inspiratory threshold loading test, subjects breathed against loads of 89.5 ± 49.9 g and 85.8 ± 21.1 g in the NMV and control groups, respectively. The NMV group improved endurance time by 275 ± 269% (Fig 1) after 3 months of NMV, while the control group had no change in endurance time after 3 months of normal care. At peak exercise, the intensity of breathlessness decreased from 21.1 g in the NMV and control groups, 6.2 ± 2.1 at baseline vs 5.9 ± 2.4 postintervention).

In the cycle ergometry test at baseline, patients were severely disabled, with an absolute maximum work rate of 34.0 ± 16.9 W (33% predicted normal) in the NMV group and 39.0 ± 20.8 W (39% predicted normal) in the control group. Following the 3-month intervention period, endurance time during

Figure 1. Mean value (symbol) ± SDs (box) and range (whisker) of exercise times of the inspiratory threshold loading test during the familiarization phase (−), baseline (+), and after 3 months (●) in the NMV group and control group. The improvement of the exercise times from baseline to test after 3 months was significant (p < 0.01) in the NMV group. The group difference (percentage of change) between the exercise times at baseline and after 3 months of NMV was significant (p < 0.0001; p required for a significant difference = 0.017).

Figure 2. Mean value (symbol) ± SDs (box) and range (whisker) of exercise times of the cycle ergometer test during the familiarization phase (−), baseline (+) and after 3 months (●) in the NMV group and control group. The improvement of the exercise times from baseline to test after 3 months was significant (p < 0.01) in the NMV group. The group difference (percentage of change) between the exercise times at baseline and after 3 months of NMV was significant (p < 0.0001; p required for a significant difference = 0.05).
the cycle ergometer test increased by 176 ± 159% (Fig 2) in the NMV group, while no significant improvement was observed in the normal-care control group. At peak exercise, the intensity of breathlessness and leg exertion and V\textsubscript{CO2} significantly decreased after the 3-month intervention period (p < 0.05) in the NMV group but not in the control group (Table 2), while all other measured variables at peak exercise did not change over time in either group.

In the shuttle walking test, endurance time increased (Fig 3) by 32 ± 22% after the 3-month intervention period in the NMV group, while there was no improvement in the normal-care control group. There was no significant change in intensity of breathlessness and leg exertion at peak exercise following the intervention period compared with baseline in either the NMV group (breathlessness, 7.2 ± 1.3 at baseline and 6.7 ± 1.7 postintervention; leg exertion, 2.0 ± 1.4 at baseline and 1.2 ± 1.1 postintervention) or the control group (breathlessness, 6.9 ± 1.5 at baseline and 7.1 ± 1.6 postintervention; leg exertion, 2.2 ± 1.6 at baseline and 2.0 ± 1.9 postintervention). Significant differences were also found between the NMV and control group in the percentage change of the following parameters after the 3-month intervention period (Table 1): PO\textsubscript{2} (p < 0.001); P\textsubscript{CO2} (p < 0.001); pH (p < 0.05); HCO\textsubscript{3} (p < 0.01); V\textsubscript{E} percent predicted (p < 0.05); FEV\textsubscript{1} (p < 0.05); P\textsubscript{max} (p < 0.05); and VT (p < 0.01).

**Discussion**

In this study, we have shown that 3 months of treatment with NMV in patients with CRF due to restrictive thoracic disease results in a marked increase in endurance time during exercise tests involving respiratory and peripheral muscles. The inspiratory threshold loading test showed the greatest improvement, followed by the cycle ergometer test and the shuttle walking test. All three tests assessed muscle endurance without the need for a learning or familiarization period; therefore, all the tests were reproducible and sensitive to any posttreatment improvement.

It is reasonable to assume therefore that the improvement in the endurance times seen in this

### Table 2—Blood Gas Data, Breathing Pattern, and Relevant Variables at the End of the Cycle Ergometer Test at Baseline and After 3 mo of NMV or Control*

<table>
<thead>
<tr>
<th>Parameters at Peak Exercise</th>
<th>NMV</th>
<th>Control</th>
<th>NMV vs Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 mo</td>
<td>Baseline</td>
</tr>
<tr>
<td>PO\textsubscript{2}, mm Hg</td>
<td>47.9 ± 9.6</td>
<td>50.7 ± 7.9</td>
<td>46.5 ± 5.5</td>
</tr>
<tr>
<td>P\textsubscript{CO2}, mm Hg</td>
<td>55.9 ± 5.5</td>
<td>51.1 ± 7.2</td>
<td>53.4 ± 3.1</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>2.66 ± 1.50</td>
<td>2.50 ± 1.3</td>
<td>2.80 ± 1.58</td>
</tr>
<tr>
<td>V\textsubscript{E} (L/min)</td>
<td>37.2 ± 8.4</td>
<td>34.1 ± 7.0</td>
<td>39.9 ± 7.7</td>
</tr>
<tr>
<td>VT, mL</td>
<td>620.7 ± 306.4</td>
<td>664.0 ± 299.4</td>
<td>535.8 ± 152.1</td>
</tr>
<tr>
<td>VE, mL/min</td>
<td>21.4 ± 7.3</td>
<td>21.8 ± 7.8</td>
<td>21.3 ± 6.1</td>
</tr>
<tr>
<td>V\textsubscript{CO2}, mL/min</td>
<td>788.9 ± 236.6</td>
<td>736.1 ± 234.2‡</td>
<td>722.3 ± 221.3</td>
</tr>
<tr>
<td>VO\textsubscript{2}, mL/min</td>
<td>860.4 ± 203.6</td>
<td>834.7 ± 242.6</td>
<td>813.0 ± 259.4</td>
</tr>
<tr>
<td>Respiratory quotient</td>
<td>0.89 ± 0.08</td>
<td>0.88 ± 0.05</td>
<td>0.92 ± 0.12</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>133.7 ± 11.9</td>
<td>124.8 ± 31.0</td>
<td>127.8 ± 17.0</td>
</tr>
<tr>
<td>Dyspnea (VAS)</td>
<td>8.0 ± 2.1</td>
<td>6.4 ± 1.9</td>
<td>7.7 ± 1.9</td>
</tr>
<tr>
<td>Leg effort (VAS)</td>
<td>4.5 ± 0.5</td>
<td>3.0 ± 1.3</td>
<td>3.4 ± 3.0</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SD. VAS = visual analogue scale; VE = minute ventilation.
†Internal-group comparison between baseline and 3-month measurement (p < 0.05).
‡Group differences between baseline and after 3 months (p < 0.05).
study are due to the NMV, especially since patients undertaking other possible confounding interventions (such as exercise training programs) were excluded. In patients with CRF due to restrictive thoracic disease, NMV has also been previously shown to significantly improve daytime blood gas levels. Before discussing these findings further, certain methodologic issues will be addressed:

1. While ideally we would have preferred to investigate the effects of NMV on endurance performance using a prospective randomized control design, the increased number of patients that would have been required to ensure well-balanced groups precluded the use of this design in a study conducted at a single institution. Furthermore, we also had concerns that the use of multiple study centers might introduce important confounding factors such as center differences in NMV management. We therefore elected to use a prospective case-control design, with appropriate matching of patients in the NMV and control groups. Since the two groups had similar physiologic indexes of CRF severity at baseline, we are reasonably confident that any biases resulting from the selection of patients were negligible. Nevertheless, we do acknowledge that the possibility of investigator bias in patient selection by the use of this study design cannot be discounted.

2. The protocols of the endurance tests used in this study were different. The inspiratory threshold and cycle exercise test had a constant load, symptom-limited protocol, and the shuttle walking test was an incremental load exercise test. We chose this complementary combination of tests to assess both targeted muscle groups and specific dynamics of endurance performance. Due to vertebral and thoracic deformity of the investigated patients, predicted normal values are hard to apply.

3. The marked differences in the degree of improvement for the three exercise tests may to some extent have been a consequence of the fixed order of the tests (morning, inspiratory threshold loading; noon, cycle ergometry; afternoon, shuttle walking). However, for each endurance test during the familiarization period, there was no systematic decrease in endurance time during the second test performed on the same day, suggesting that any order effects (for example due to fatigue) were negligible.

To our knowledge, this is the first controlled study to systematically examine the effects of NMV on exercise endurance in patients with CRF. We have recently shown a significant improvement in daily activity levels following NMV in patients with CRF, using a pedometer over a 1-week period in the patients’ natural surroundings at home. A few studies have observed either small or no relevant improvements in endurance performance following NMV in patients with CRF. However, interpretation of these studies is complicated by differences with respect to the size of investigated population, the underlying diagnosis, the mode of exercise and testing protocol, and the mode of NMV.

Determinants of exercise capacity in CRF are multifactorial and include lung function, cardiovascular fitness, nutritional status, endocrinologic abnormalities, and psychological factors as depression, anxiety, and fear of exercise. Altered intrinsic muscle function (neuromuscular junction, metabolism, and fiber-type distribution) and deconditioning may also be important determinants of exercise tolerance. While the present study was not designed to investigate the contribution of the various factors that may limit exercise performance in patients with CRF, it is of interest to speculate about the mechanism by which NMV improves exercise performance, and the factors responsible for the differences in the degree of improvements observed in the three endurance tests.

Differences in the degree of improvement may be related to the activity profile of the three types of exercise; the inspiratory threshold loading test assesses an isolated muscle group, the cycle ergometer test assesses a larger group of muscles including both peripheral and respiratory muscles that support the increasing ventilatory demands, and the shuttle walking test assesses an even more complex group of muscles, with both upper and lower leg muscles being involved, as well as the respiratory muscles. The endurance time of the shuttle walking test, despite being based on familiar physical activities, may have also been negatively influenced by a motor disturbance, due to the orthopedic disabilities (e.g., in shape of chest wall deformity) of the population. Furthermore, the kind of shuttle walk we applied in this study was an incremental test. An endurance shuttle test has been described that may be more sensitive to change than the incremental one.

The marked improvement in P_{max} with NMV (from 43 to 66 cm H_{2}O) could, at least in part, explain the improvement in endurance time during the inspiratory threshold loading test. Since the absolute load was kept constant for both the baseline and postintervention tests, in relative terms patients worked at 33% P_{max} during the baseline test but only at 22% P_{max} during the postintervention test. It would be expected that this reduction in workload relative to the maximal capacity of the respiratory muscles would result in a significant reduction in the magnitude of the sense of effort associated with the task. It may explain the improved endurance performance as the length of time taken to reach an intolerable sense of dyspnea would necessarily increase.

Improvements in the endurance capacity of the
respiratory muscles may also account, at least in part, for the improvements in the endurance performance observed in the cycle ergometry and shuttle walking tests. However, we have found a marked reduction in pulmonary hypertension at rest and during exercise after 1 year of NMV, in patients with CRF due to restrictive lung and thoracic diseases (unpublished data), suggesting that other factors such as hemodynamic adaptations may also contribute.

The proximal limitation to voluntary muscular performance is the inability to tolerate the uncomfortable sensory consequences of the muscular work. As such, an intervention that is able to reduce the intensity of sensory discomfort at a given time during exercise should improve endurance performance, as the exercise time required to reach intolerable symptom intensity is prolonged and endurance time is increased. An implicit assumption of this model is that the symptom intensity perceived as intolerable is the same at peak exercise during both the cycle ergometer and inspiratory threshold loading tests, and also in the intensity of leg exertion at peak exercise during the cycle ergometer test, are intriguing. At face value, these decreases in sensory intensity at peak exercise suggest that tolerance of the discomfort associated with the activities has decreased following NMV, since the patients have terminated exercise at a lower intensity compared with baseline. However, alternative explanations may also be offered: (1) the sensations attended to by the patients (ie, breathlessness and leg exertion) may be qualitatively different from the sensations limiting performance (eg, discomfort with breathing, leg discomfort), (2) reductions in the relative work intensity postintervention (as observed in the inspiratory threshold loading test) may have resulted in alterations in the rate of increase in sensory intensity with time of exercise with a consequent shift in the magnitude of the sensation that is perceived as intolerable.

We found high reproducibility for all endurance tests used in this study, in line with the data of Singh et al. Furthermore, we did not find any learning effect with the shuttle walking test, suggesting that meaningful results can be obtained after one practice walk. Another study has demonstrated that endurance times during constant-load symptom-limited cycled exercise in patients with severe COPD are highly reproducible and responsive. We found reproducible results applying the inspiratory threshold loading technique, using a constant load protocol, which were free of training effects on repetitive testing. However, with respect to a progressive protocol, conflicting results regarding learning effects have been reported. The main reason for this inconsistency may be the different protocol (ie, incremental vs constant). Finally, we investigated a severely disabled population with CRF and therefore our results are not comparable with the previously published data. In future studies, other issues need to be addressed, such as the short-term and long-term effects of NMV on different exercise performances, separate effects of NMV on different compartments, and influence on daily activities and quality of life.

We conclude that 3 months of NMV treatment in patients with CRF due to restrictive thoracic disease resulted in a marked increase in endurance time in tests of respiratory muscle (inspiratory threshold loading) and peripheral muscle (cycle ergometer and shuttle walking test) performance. The inspiratory threshold loading test showed the greatest improvement, followed by the cycle ergometer test, with the shuttle walking test showing the least improvement. All three tests assessed muscle endurance without the need for a learning or familiarization period. Therefore, all tests were reproducible and sensitive to the posttreatment improvement. The improved endurance performances may have implications on a patient’s daily activities and quality of life.

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