MECHANISMS OF IMPROVEMENT OF RESPIRATORY FAILURE IN
PATIENTS WITH RESTRICTIVE THORACIC DISEASE TREATED WITH
NON-INVASIVE VENTILATION

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Running head Mechanism of action of NIV in restrictive disease

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ABSTRACT
Nocturnal non-invasive ventilation (NIV) is an effective treatment for hypercapnic respiratory failure in patients with restrictive thoracic disease. We hypothesized that NIV may reverse respiratory failure by increasing the ventilatory response to carbon-dioxide (CO₂), reducing inspiratory muscle fatigue or enhancing pulmonary mechanics. We studied 20 patients with restrictive disease at baseline (D0) and at 5-8 days (D5) and 3 months (3M). Daytime PaCO₂ reduced from 7.1 ± 0.9 kPa to 6.6 ± 0.8 kPa at D5 and 6.3 ± 0.9 kPa at 3M (p = 0.004), with the hypercapnic ventilatory response increasing from 2.8 ± 2.3 l/min/kPa to 3.6 ± 2.4 l/min/kPa at D5 and 4.3 ± 3.3 l/min/kPa at 3M (p = 0.044). We observed no increase in measures of inspiratory muscle strength including twitch transdiaphragmatic pressure, nor in lung function or respiratory system compliance. These findings suggest that increased ventilatory response to CO₂ is the principal mechanism underlying the long-term improvement in gas-exchange following NIV in patients with restrictive thoracic disease. A new finding is that increases in respiratory muscle strength (sniff oesophageal pressure and sniff nasal pressure) correlated with reductions in Epworth Sleepiness Score, possibly indicating an increase in the ability of patients to activate inspiratory muscles rather than an improvement in contractility.

Abstract word count 206

Some of this data has previously been presented in abstract form.¹³
INTRODUCTION

Domiciliary nocturnal non-invasive ventilation (NIV) is a well-established therapy for patients with symptomatic, hypercapnic respiratory failure secondary to restrictive thoracic disease. NIV has been shown to alleviate symptoms of headache and daytime somnolence, improve intellectual capacity, reduce hospital admissions, increase exercise tolerance and improve gas exchange. Furthermore, subsequent studies with long-term follow up, have demonstrated that improved gas-exchange and control of symptoms are maintained for up to five years with the majority of patients continuing NIV. In contrast, a study in which NIV was withdrawn from patients established on therapy, led to recurrence of daytime somnolence, morning headaches, reduced energy and dyspnea at rest.

It is intriguing that a treatment delivered at night should result in an improvement in symptoms and physiological measures during the day. Despite the widespread use of NIV, the mechanism by which ventilatory failure is reversed is not fully understood. In 1993, Hill proposed three hypotheses by which NIV might work. Firstly, NIV may increase ventilatory sensitivity to CO\textsubscript{2} during spontaneous breathing, secondly it may rest fatigued respiratory muscles so increasing their strength and endurance, and lastly it may improve pulmonary mechanics by increasing compliance and lung volumes. Such changes would improve gas exchange by optimising the load-capacity-drive balance of the respiratory system. A number of studies have assessed these proposed mechanisms in isolation, but few studies have examined all three hypotheses simultaneously, making understanding of the inter-relationship between these mechanisms limited. Furthermore, due to their invasive nature and complexity, non-volitional assessment of respiratory muscle strength (i.e. independent of patient effort) and detailed assessment of respiratory system compliance have not previously been
performed in patients with restrictive thoracic disease receiving NIV. Thus the aim of the current study was to investigate these hypotheses concurrently to determine the relative importance of each mechanism.

METHODS
The study was approved by the hospital’s ethics committee, and written informed consent obtained. Consecutive restrictive patients with symptomatic hypercapnic respiratory failure, admitted to hospital for 5–8 days for elective nocturnal NIV by a multidisciplinary team, were invited to participate. Ventilators were chosen according to availability and generally set up in pressure-control mode (mean ± SD inspiratory pressure 20.9 ± 4.8 cmH₂O). Three types of ventilators were used: NIPPY 1 (n=9, B&D Electromedical, Stratford-Upon-Avon, UK), VPAP II ST (n=4, ResMed, Oxford, UK) and BREAS PV 403 (n=7, BREAS Medical, Mölnlycke, Sweden). Patients participated in physiological studies at baseline (D0), 5-8 days (D5) and three months after commencing NIV (3M). On each occasion clinical assessment was carried out and symptoms of respiratory failure and subjective sleepiness using the Epworth sleepiness score (ESS) were assessed. Gas-exchange was assessed by measuring daytime arterial blood gases (after 20 minutes rest seated breathing air), overnight pulse oximetry (SaO₂, pulse oximeter 200–E, Nellcor, Pleasanton, USA) and trans-cutaneous CO₂ (PtcCO₂, Radiometer A/S, Copenhagen, Denmark). Ventilator pressures were titrated upwards as tolerated to control nocturnal hypoventilation, by ensuring there was a fall in both peak nocturnal PtcCO₂ and daytime PaCO₂. Mean hours of use per night was determined at D5 by averaging the preceding 3–4 night’s use recorded by ward nursing staff, and at 3M using the ventilator’s hour counter. With the exception of standard lung function, all testing was
performed at the same time of day for each patient, starting at either 10am or 2pm, and took approximately 2½ hours. Apart from measurements of compliance, all data were acquired, stored and analysed on a Macintosh computer using customised software (Labview™, National Instruments, Austin, TX, USA). Patients refrained from caffeine for at least two hours prior to the start of the tests. The following tests were carried out at D0, D5 and 3M.

The hypercapnic ventilatory response (HCVR) was determined using a re-breathing technique. With oesophageal and gastric balloon-pressure-catheters in situ, the following measures of respiratory muscle strength were determined as described previously; sniff nasal inspiratory pressure (SNIP), sniff oesophageal pressure (Sniff Poes), maximum inspiratory mouth pressure (PiMax), maximum expiratory mouth pressure (PeMax), cough gastric pressure (Pga), sniff transdiaphragmatic pressure (Sniff Pdi) and twitch transdiaphragmatic pressure (TwPdi), assessed using bilateral anterolateral phrenic nerve magnetic stimulation. Full pulmonary function was measured at D0 and 3M (lung volumes by spirometry and body plethysmography and carbon-monoxide transfer factor), and lung volumes by body plethysmography alone at D5. Static lung and chest wall compliance were determined on all three occasions, using a quasi-static technique and standard lung function testing equipment and software (Jaeger Compact Body, Viasys Systems Ltd, Warwickshire UK).

All values are expressed as mean ± SD unless otherwise stated. Statistical analysis was carried out using SPSS V10 (SPSS Inc, Chicago). Statistical significance was defined as p < 0.05. One-way repeated measures of analysis of variance was used to compare variables measured on the different occasions, linear regression analysis for examination of the relationship between changes in variables and Mann Whitney-U
test for comparisons of baseline variables between patients with neuromuscular weakness and kyphoscoliosis. All data was normally distributed (Kolmogorov-Smirnov test).

RESULTS

Patient characteristics

Of 21 patients approached, 20 took part in the study; 12 had respiratory neuromuscular weakness and 8 kyphoscoliosis. Their characteristics are shown in Table 1. Three patients with predominant restrictive disease also had co-existing airways obstruction (2 with COPD, and 1 with bronchiectasis). Compared to patients with kyphoscoliosis, those with neuromuscular weakness were significantly heavier with a higher BMI, they had a higher TLC, higher chest wall compliance and lower lung compliance. By definition they had reduced respiratory muscle strength.
Table 1: Baseline patient characteristics of patients with neuromuscular weakness and kyphoscoliosis, and statistical difference between the two sub-groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Neuromuscular Weakness (n = 12)</th>
<th>Kyphoscoliosis (n = 8)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometrics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, M: F</td>
<td>9: 3</td>
<td>4: 4</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 ± 14</td>
<td>56 ± 14</td>
<td>0.23</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28 ± 6</td>
<td>21 ± 6</td>
<td>0.041</td>
</tr>
<tr>
<td>PaO₂ (kPa)</td>
<td>8.3 ± 1.2</td>
<td>8.3 ± 1.4</td>
<td>0.76</td>
</tr>
<tr>
<td>PaCO₂ (kPa)</td>
<td>7.2 ± 1.9</td>
<td>7.2 ± 0.9</td>
<td>0.76</td>
</tr>
<tr>
<td>Peak noct PtcCO₂ (kPa)</td>
<td>9.1 ± 1.3</td>
<td>9.1 ± 1.7</td>
<td>0.58</td>
</tr>
<tr>
<td>ESS (out of 24)</td>
<td>10.0 ± 4.2</td>
<td>8.4 ± 5.2</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Muscle strength</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PiMax (cmH₂O)</td>
<td>30 ± 1</td>
<td>41 ± 14</td>
<td>0.021</td>
</tr>
<tr>
<td>Poes (cmH₂O)</td>
<td>41 ± 14</td>
<td>47 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PeMax (cmH₂O)</td>
<td>67 ± 28</td>
<td>70 ± 30</td>
<td>0.19</td>
</tr>
<tr>
<td>Sniff Pdi (cmH₂O)</td>
<td>33 ± 24</td>
<td>78 ± 43</td>
<td>0.005</td>
</tr>
<tr>
<td>TwPdi (cmH₂O)</td>
<td>2.1 ± 3.0</td>
<td>10.8 ± 7.4</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC (% Predicted)</td>
<td>62 ± 9</td>
<td>50 ± 7</td>
<td>0.09</td>
</tr>
<tr>
<td>FRC (% Predicted)</td>
<td>73 ± 15</td>
<td>65 ± 14</td>
<td>0.19</td>
</tr>
<tr>
<td>RV (% Predicted)</td>
<td>92 ± 28</td>
<td>87 ± 21</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Static compliance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_Lung (mls/ cmH₂O)</td>
<td>85 ± 18</td>
<td>71 ± 20</td>
<td>0.048</td>
</tr>
<tr>
<td>C_CW (mls/ cmH₂O)</td>
<td>104 ± 29</td>
<td>63 ± 26</td>
<td>0.018</td>
</tr>
</tbody>
</table>
Use and efficacy of NIV

Mean use was 6.7 ± 1.9 hours per night at D5 and 4.2 ± 2.6 hours per night at 3M. Following NIV there was a significant fall in PaCO₂ (p = 0.004), increase in PaO₂ (p = 0.02), fall in bicarbonate (p = 0.002) and fall in ESS (p = 0.001), as is illustrated in Figure 1. Group nocturnal PtcCO₂ and SaO₂ are shown in Table 2. Three patients were initiated on supplementary oxygen, and their nocturnal SaO₂ values are not included. There was a trend towards a reduction towards start of night PtcCO₂ and no significant reduction in peak PtcCO₂. There was a significant reduction in both the nadir SaO₂ and the proportion of the night spent with an SaO₂ less than 90%.

Table 2: Mean ± SD nocturnal PtcCO₂ (n = 20) and SaO₂ (n = 17)

<table>
<thead>
<tr>
<th></th>
<th>D0</th>
<th>D5</th>
<th>3M</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PtcCO₂ Start of night (kPa)</td>
<td>7.5 ± 1.0</td>
<td>6.7 ± 1.0</td>
<td>6.6 ± 1.0</td>
<td>0.09</td>
</tr>
<tr>
<td>PtcCO₂ Peak (kPa)</td>
<td>9.1 ± 1.4</td>
<td>8.9 ± 3.4</td>
<td>8.3 ± 1.4</td>
<td>0.56</td>
</tr>
<tr>
<td>SaO₂ Start of night (%)</td>
<td>92 ± 4</td>
<td>95 ± 3</td>
<td>93 ± 5</td>
<td>0.22</td>
</tr>
<tr>
<td>SaO₂ Nadir (%)</td>
<td>67 ± 13</td>
<td>83 ± 6</td>
<td>79 ± 13</td>
<td>0.005</td>
</tr>
<tr>
<td>Time with SaO₂ &lt; 90% (%)</td>
<td>52 ± 30</td>
<td>12 ± 18</td>
<td>29 ± 40</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Ventilatory response to carbon-dioxide

Following NIV there was a significant increase in HCVR from 2.8 ± 2.3 l/ min/ kPa at D0 to 3.6 ± 2.4 at D5 and 4.3 ± 3.3 l/ min/ kPa at 3M (p = 0.044, Figure 2). There was no relationship between the increase in HCVR and changes in any measures of lung volume (at 3M FRC r² = 0.005; p = 0.80 and FVC r² = 0.003; p = 0.83) or muscle strength (at 3M Sniff Poes r² = 0.058; p = 0.45 and TwPdi r² = 0.001; p = 0.40).
Respiratory muscle strength

Measures of respiratory muscle strength are illustrated in Figure 3. Following NIV there was a small but significant increase in one volitional measure of expiratory muscle strength: PeMax increased from 67 ± 28 cmH₂O to 77 ± 23 cmH₂O at D5 and 72 ± 29 cmH₂O at 3M (p = 0.04). There was a trend towards an increase in one volitional measure of inspiratory muscle strength, sniff Poes, which increased from 43 ± 13 cmH₂O to 48 ± 14 cmH₂O at D5 and 53 ± 11 cmH₂O at 3M (p = 0.064). There were no changes in other measures of respiratory muscle strength.

Pulmonary mechanics

Lung function

There were no significant changes in any component of lung function following NIV, including spirometry, lung volumes and carbon-monoxide gas transfer. Of particular importance given the dependence of respiratory muscle strength on lung volume, there was no group mean change in TLC or FRC. Although some individuals had changes in lung volumes, there was no relationship between changes in FRC and any measures of muscle strength (e.g. at 3M PiMax r² < 0.001, p = 0.98; Sniff Poes r² = 0.034, p = 0.57 and TwPdi r² = 0.001, p = 0.93).

Respiratory system compliance

At baseline, static chest wall compliance was significantly lower in patients with kyphoscoliosis than neuromuscular weakness, at 53 ± 14 and 106 ± 30 mls/ cmH₂O respectively (p = 0.019), but there was no significant difference in static lung compliance between patients with kyphoscoliosis and neuromuscular weakness, at 64 ± 14 and 85 ± 20 mls/ cmH₂O respectively (p = 0.22). Following NIV there were no
significant changes in static lung or chest wall compliance. Group and sub-group values of compliance at D0, D5 and 3M are shown in Table 3.

<table>
<thead>
<tr>
<th></th>
<th>Static lung compliance</th>
<th>Static chest wall compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D0</td>
<td>D5</td>
</tr>
<tr>
<td>All patients</td>
<td>80 ± 19</td>
<td>103 ± 35</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>85 ± 18</td>
<td>117 ± 32</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
<td>71 ± 20</td>
<td>72 ± 17</td>
</tr>
</tbody>
</table>

Comparisons between neuromuscular weakness and kyphoscoliosis

Larger sample sizes would be required for meaningful statistical comparison between the patients with neuromuscular weakness and kyphoscoliosis. Our data, however, does not suggest any differences in response to NIV between the two sub-groups, with respect to hours of use, changes in arterial blood gases, drive or muscle strength.
Table 4: Mean ± SD values of hours of use, arterial blood gases, Epworth Sleepiness Score (ESS), the HCVR and two measures of inspiratory muscle strength in patients with neuromuscular weakness and kyphoscoliosis at D0, D5 and 3M.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Neuromuscular Weakness (n = 12)</th>
<th>Kyphoscoliosis (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D0</td>
<td>D5</td>
</tr>
<tr>
<td>Hours</td>
<td>-</td>
<td>6.3 ± 1.7</td>
</tr>
<tr>
<td>PaCO₂ (kPa)</td>
<td>7.2 ± 0.9</td>
<td>6.6 ± 0.8</td>
</tr>
<tr>
<td>PaO₂ (kPa)</td>
<td>8.3 ± 1.2</td>
<td>8.9 ± 1.6</td>
</tr>
<tr>
<td>Bicarbonate (mM/l)</td>
<td>32.6 ± 2.5</td>
<td>30.4 ± 1.7</td>
</tr>
<tr>
<td>ESS</td>
<td>10.0 ± 4.2</td>
<td>-</td>
</tr>
<tr>
<td>HCVR (l/ min/ kPa)</td>
<td>3.3 ± 2.8</td>
<td>4.3 ± 2.9</td>
</tr>
<tr>
<td>PeMax (cmH₂O)</td>
<td>68 ± 28</td>
<td>77 ± 22</td>
</tr>
<tr>
<td>Poes (cmH₂O)</td>
<td>42 ± 14</td>
<td>44 ± 14</td>
</tr>
<tr>
<td>FEV₁ (% Predicted)</td>
<td>44 ± 11</td>
<td>-</td>
</tr>
<tr>
<td>FVC (% Predicted)</td>
<td>44 ± 11</td>
<td>-</td>
</tr>
</tbody>
</table>

‘Dose response’ of NIV

Mean hours of NIV use at 3M was available for 14 patients. At 3M there was a significant relationship between hours of use and both the decrease in PaCO₂ ($r^2 = 0.48; p = 0.006$), and decrease in ESS ($r^2 = 0.39; p = 0.017$), as illustrated in Figure 4. There appeared to be a ‘threshold effect’, with little consistent change in PaCO₂ or ESS until NIV had been used for at least 4 hours per night. The same relationship was not observed between hours of use and PaCO₂ at D5 ($r^2 = 0.08; p = 0.30$). To further
highlight that HCVR was the principal mechanism underlying reduction in daytime PaCO₂, the change in HCVR was divided into those patients using NIV for more than 4 hours per night at 3M (n = 9, mean use 5.9 ± 0.8 hours) who were judged to be compliant, and those patients who used NIV for less than 4 hours per night (n = 5, mean use 1.0 ± 1.0 hours). At D5, while still in hospital, NIV use was similar and physiological changes in patients who subsequently became compliant and non-compliant at 3 months was comparable. However at 3 months the ‘poor’ users had a return in arterial blood gases, HCVR and respiratory muscle strength to baseline, and little change in ESS. Besides the significant relationship between hours of use and decrease in PaCO₂ at 3M described above, there were no significant relationships between changes in PaCO₂ and other parameters including HCVR and muscle strength on simple or multiple linear regression.

Relationship between physiological changes and subjective sleepiness

There was a significant relationship between the fall in ESS and hours of use at 3M as described above. At 3M there were also significant relationships between the fall in ESS and increase in two measures of respiratory muscle strength, sniff Poes (r² = 0.41, p = 0.02) and SNIP (r² = 0.39, p = 0.005). There was a trend towards a relationship between ESS and sniff Pdi (r² = 0.27, p = 0.10) and PiMax (r² = 0.20, p = 0.067), and no relationship with Pgas, TwPdi or PeMax.

DISCUSSION

This study examined the three proposed hypotheses by which NIV improves arterial blood gases in patients with symptomatic, hypercapnic respiratory failure secondary to restrictive thoracic disease: by increased ventilatory sensitivity to CO₂, increased respiratory muscle strength and by enhanced pulmonary mechanics. The principle
findings support the first hypothesis, with NIV treatment being associated with an
increase in ventilatory sensitivity to CO₂. Furthermore, the relationship between hours
of use and fall in arterial carbon-dioxide level and Epworth Sleepiness Score suggests
a ‘dose response’ effect, once a threshold of use of approximately 4 hours per night
has been reached.

Critique of the method

Study design

It would have been preferable for patients to undergo a standardized run-in period for
optimisation of medical therapy before commencing NIV, and to have a matched
control group who had similar medical contact time and support without NIV.
However, this was not possible for logistical and ethical reasons. In particular it
would have been difficult to admit patients to hospital without offering NIV.
Furthermore it was not considered ethical to delay treatment of the patients for three
months following assessment. All patients were referred for NIV by external
respiratory specialists, and had undergone optimisation of medical therapy prior to
entry in to the study.

Test reproducibility

HCVR

There is a high degree of intrinsic variability in HCVR. This was minimised by using
the mean of two tests, and carrying out testing at the same time of day by the same
investigator in a quiet room. In 30 patients with respiratory failure studied on two
occasions in our laboratory there was no significant difference in HCVR between the
first and second tests (2.51 ± 2.91 and 2.65 ± 2.63 l/ min/ kPa respectively, p = 0.78).
Respiratory muscle strength

In our laboratory there is good long term reproducibility of Sniff Pdi and TwPdi with follow up over 1 to 5 years in healthy volunteers, and over 1 week to 10 months in patients with normocapnic moderate to severe COPD. To our knowledge there has not been a study of sequential measurement of TwPdi patients with severe chest wall deformity, and abnormal anatomy of the cervical region. Reasonable reproducibility is suggested by the much greater inter- than intra-subject variability on repeat testing at D0, D5 and 3M. Values of TwPdi were small however, and any genuine physiological changes may have been beyond the resolution of the test.

Respiratory compliance

We have demonstrated in our laboratory that static lung and chest wall compliance measurements are useful in identifying physiological differences between diagnostic groups, however it is possible that this technique is not sufficiently sensitive to detect small within subject changes. Despite this, the absence of changes in lung volumes makes it unlikely that significant changes in compliance occurred.

Significance of findings

Use and efficacy of NIV

In our patient group NIV resulted in a significant improvement in daytime arterial blood gases and a reduction in subjective sleepiness. In contrast to most previous studies, we did not exclude patients with combined restrictive and obstructive ventilatory defects because such patients are common in clinical practice. Our patient group is therefore likely to include individuals who are more challenging to ventilate successfully, but perhaps to be more representative of the wider population of patients with respiratory failure. Greater NIV use at D5 than 3M may reflect several factors: in
the early days in hospital there may be greater patient motivation due to high expectations of a new therapy and intensive support from the multi-disciplinary team. In addition, nurses may select the start and end times of NIV use. Later on at home NIV use may reduce as patients determine the optimal balance between symptomatic benefit and NIV tolerability for them.

Increased ventilatory sensitivity to CO₂

HCVR increased significantly following NIV. Such an increase in the ventilatory response to CO₂ enables a more appropriate increase in ventilation to occur in response to transient increases in PaCO₂, so diminishing hypercapnia. It is likely that the increase in HCVR is brought about by reduced renal retention of bicarbonate, so reducing acid buffering capacity. In this way chemoreceptors could be ‘reset’ to become responsive at a lower level. The increase in HCVR appeared to be directly attributable to an increase in central ventilatory drive rather than to ‘unmasking’ of drive, since it occurred independently of changes in lung volumes, respiratory muscle strength or compliance. It is of course also possible that the improvement in HCVR is due to a small increase in capacity and reduction in load, which in isolation are not significant, but in combination have a much larger effect. Multiple linear regression of measures of capacity and load with HCVR were not significant, however our study was not powered to examine this relationship. Our findings are similar to those of Annane and coworkers¹¹ but not to those of Dellborg and coworkers¹². This may be attributable to the fact that patients in this latter study had a higher baseline HCVR at 3.8 l/ min/ kPa, compared to 2.9 l/ min/ kPa in our own study.

There was a non-significant trend for the increase in HCVR to be associated with a decrease in PaCO₂ in compliant patients at 3 months. This suggests that PaCO₂ may
be determined in part by the ventilatory response to CO₂, but is likely to also be dependent on other factors. This is not surprising, since even when HCVR is increased by over 50% at 3M, it is still markedly sub-normal compared to healthy controls, enabling PaCO₂ to fluctuate, albeit around a lower mean value than prior to initiation of NIV. The relationship between HCVR and PaCO₂ is also weakened by the intrinsic variability of both these measures. Annane and coworkers found a significant relationship between changes in HCVR and PaCO₂ following NIV, however their analysis was carried out in a different way: repeated testing was carried out at 6 months, 1, 2, and 3 years and the maximum change for each individual was used, rather than all data at a given time interval. Our data was not analysed in this way, as it might have introduced a more favourable bias, rather than giving a true reflection of the changes at a given time interval. Dellborg and coworkers found no correlation between changes in HCVR and PaCO₂.

Changes in respiratory muscle strength

The second hypothesis regarding the mechanism of action of NIV is that hypercapnic respiratory failure is associated with respiratory muscle fatigue, and that NIV provides muscle rest, so relieving fatigue and increasing muscle strength. We found a significant increase in only one measure of strength, PeMax. Reports of changes in muscle strength in the literature are variable, with some finding no difference in muscle strength and others isolated increases in single measures. To our knowledge, ours is the first study to investigate a non-volitional measure of respiratory muscle strength, and it is of interest that there was no change in TwPdi. To our knowledge, ours is also the first study to examine the relationship between changes in muscle strength and subjective sleepiness. Although the ESS has not been formally validated in patients with hypercapnic respiratory failure, previous
investigators have observed it to fall in this patient group following NIV\textsuperscript{19}. We found a significant correlation (sniff Poes and SNIP) and trend towards correlation (sniff Pdi and PiMax) of measures of global inspiratory strength with ESS.

The respiratory muscle strength data does not support the respiratory muscle fatigue hypothesis, since only one measure of expiratory muscle strength and no measures of inspiratory or trans-diaphragmatic strength changed significantly. This hypothesis cannot be completely rejected however, since respiratory muscle endurance was not tested. The absence of change in respiratory muscle strength may have two underlying explanations. Firstly, it may not be possible for patients with neuromuscular weakness to undergo an increase in muscle strength. Secondly, it has been suggested that fatigue of respiratory muscles is avoided by alteration in breathing pattern by the central nervous system\textsuperscript{20}. The relationship between ESS and several volitional measures of respiratory muscle strength but not TwPdi is of interest. It may be interpreted as showing an increased ability to activate the respiratory muscles rather than improved contractility \textit{per se}. This could arise due to a greater sense of ‘well-being’, enabling more effort to be applied. Against this, however, Hill and coworkers\textsuperscript{9} found no decrements in respiratory muscle strength following withdrawal of NIV from patients established on it for respiratory failure despite a recurrence of somnolence. It may be that in some way central facilitation occurs following NIV, enabling patient’s effort to be more effectively translated into force.

In this study we did not assess changes in respiratory muscle endurance following NIV, which may be more relevant to sustained respiratory effort in the face of increased respiratory load than respiratory muscle strength. One study has previously
examined this relationship, and suggested that endurance was increased following NIV.

Optimisation of pulmonary mechanics

The final hypothesis regarding the mechanism of action of NIV in restrictive disease is that pulmonary mechanics in hypercapnic respiratory failure are disadvantaged due to both chronic hypoventilation and distortion of the thoracic cage, leading to an increase in work of breathing, and that NIV reverses some of these changes so tending to restore the balance between capacity and load of the respiratory system. In our study there was no change in spirometry, lung volumes or carbon monoxide transfer factor following NIV. This enables us to be confident that changes in other parameters that may be dependent on lung volume, such as inspiratory muscle strength and HCVR occurred as primary effects, and were not merely secondary to changes in pulmonary mechanics. Our findings are in keeping with most previous studies. Dellborg and coworkers observed a small but statistically significant increase in vital capacity from 1.2 to 1.3 l, the clinical significance of which is not entirely clear. In the current study no significant changes in static compliance were observed in the group as a whole or in sub-groups of patients, however it is interesting to note that there was a greater numerical increase in static lung compliance in patients with neuromuscular weakness and greater numerical increase in static chest wall compliance in patients with kyphoscoliosis. It is likely that numbers of patients were too small to demonstrate significant differences within the sub-groups. In addition, the reproducibility of static lung compliance in patients with critically compromised respiratory function may be insufficient to detect small changes. Simonds and coworkers have previously compared intermittent hyperinflation for 5 minutes 2-3 times a day for 3 months using either volume- or pressure-preset ventilation in
patients with kyphoscoliosis. They found volume but not pressure-preset ventilation resulted in a significant increase in vital capacity. Since respiratory muscle strength remained unchanged, this was thought to be due to an increase in compliance of the respiratory system. The improvement with volume but not pressure-preset ventilation was thought to be due to the higher inspiratory pressures achieved (33 and 30 cmH$_2$O respectively). In our study, the mean inspiratory pressure used was 21 cmH$_2$O (22 cmH$_2$O for patients with neuromuscular weakness and 20 for patients with kyphoscoliosis). It seems likely that higher inflation pressures and transient hyperinflation is necessary to increase respiratory system compliance.

Conclusions

In conclusion, this study confirms NIV to be an effective treatment in patients with symptomatic hypercapnic respiratory failure secondary to restrictive disease alone, both in terms of daytime CO$_2$ and sleepiness. It supports the hypothesis that NIV reverses ventilatory failure by increasing the ventilatory response to CO$_2$. 
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COMPETING INTERESTS

AN has received contributions from various companies to contribute towards the cost of attending professional meetings (ERS, ATS): Glaxo-Wellcome, Astra Pharmaceuticals, Cephalon, Medic-Aid and Breas Medical. AS has received research grants from Breas medical (£75,000) and ResMed (£62,000) to investigate the appropriate time to initiate non-invasive ventilation and inpatient versus outpatient initiation, and the use of a ventilator in patients with congestive heart failure, respectively. These projects are unrelated to the current study. She has received financial support from Cephalon to attend a Scientific meeting. MP has received fees for lecturing from the following companies totalling £2674 between 2003 and 2004: Astra Zeneca, Glaxo Smith Kline, Nutricia and Cephalon. He has also attended professional meetings (ERS, ATS, APSS) as a guest of various companies: Glaxo Wellcome, Astra Zeneca, Cephalon, 3M & Ciba. NH, NH and JM have no competing financial interests.

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APPENDIX: FIGURE LEGENDS

Figure 1: Effect of NIV on arterial blood gases and ESS in patients with neuromuscular weakness (open circles) and kyphoscoliosis (closed triangles). Mean (SEM) PaCO₂, PaO₂, bicarbonate and ESS at D0, D5 and 3M are shown. For the group as a whole, there was a significant fall in PaCO₂ (p = 0.002), bicarbonate (p = 0.001) and ESS (p < 0.001), and rise in PaO₂ (p = 0.02).

Figure 2: Effect of NIV on HCVR in patients with neuromuscular weakness (open circles) and kyphoscoliosis (closed triangles). Mean (SEM) HCVR at D0, D5 and 3M is shown. For the group as a whole there was a significant rise in HCVR (p = 0.04).

Figure 3: Effect of NIV on inspiratory, expiratory and diaphragmatic respiratory muscle strength. Mean (SEM) values at D0, D5 and 3M is shown. Abbreviations used: Sniff Poes = sniff oesophageal pressure; PiMax = maximum inspiratory pressure; SNIP = sniff nasal pressure; PeMax = maximum expiratory pressure; Pga = cough gastric pressure; Sniff Pdi = sniff trans-diaphragmatic pressure and TwPdi = twitch trans-diaphragmatic pressure. Significance values are given.

Figure 4: The ‘dose response’ of NIV; the change in PaCO₂ (left panel) and ESS (right panel) at 3M compared to baseline with mean hours of use is shown for individual patients. There was a significant relationship both for PaCO₂ (r² = 0.48; p = 0.006) and ESS (r² = 0.39; p = 0.017). The grey dotted line denotes a threshold of NIV use below which NIV does not appear to have a consistent effect upon PaCO₂ and subjective sleepiness.
Figure 1.

- **PaCO₂ (kPa)**
  - D0: Lower than D5, both decrease by 3M.
  - D5: Slightly higher than D0.
  - 3M: Further decrease from D5.

- **PaO₂ (kPa)**
  - D0: Lower than D5, both increase by 3M.
  - D5: Further increase from D0.
  - 3M: Highest value.

- **Bicarbonate (mM/l)**
  - D0: Highest among D5 and 3M.
  - D5: Second highest.
  - 3M: Lowest value.

- **Epworth Sleepiness Score (Out of 24)**
  - D0: Highest.
  - D5: Lower than D0.
  - 3M: Further decrease from D5.
Hypercapnic ventilatory response (l/min/kPa)

Figure 2
Figure 3.

Respiratory Muscle Strength (cmH₂O)

Inspiratory

- Sn Poes p=0.06
- SNIP p=0.67
- PiMax p=0.14

Expiratory

- Pga p=0.21
- PeMax p=0.04 *

Diaphragmatic

- Sniff Pdi p=0.80
- TwPdi p=0.53
Figure 4