Domiciliary non-invasive positive pressure ventilation (NIV) is an established treatment for chronic respiratory failure due to chest wall deformity (CWD). It is beneficial in terms of improvements in symptoms, daytime function, arterial blood gas tensions, and sleep quality. There is also evidence for improved quality of life and survival. A recent Cochrane systematic review including four eligible studies with a total of 51 patients confirmed improvements in symptoms of hypoventilation, daytime hypercapnia, and nocturnal oxygenation.

Most ventilator modes are either pressure or volume targeted, each with potential advantages and disadvantages. By definition, volume ventilation includes a predetermined set tidal volume but, in the presence of interface leakage, the set volume is not guaranteed which, theoretically at least, is a problem, particularly during sleep when NIV is conventionally applied. Also, if the impedance to inflation is increased, airway pressures may be high. This may be transient if, for instance, the patient swallows or coughs and may be uncomfortable for the patient. Conversely, pressure targeted ventilators deliver a preset airway pressure but variable tidal volume, depending on chest wall compliance, airway resistance, and patient effort. The constant airway pressure even during swallowing may explain the trend towards better tolerance of pressure targeted ventilation in some studies.

Any differences between the method of delivery of ventilation may have a consequential effect on nocturnal ventilation, sleep quality, daytime physiology, and psychometric function. Epidemiological data suggest that there is an increasing preference for pressure ventilation when NIV is used for home mechanical ventilation, but clinical studies are divided on which, if either, is the better mode of ventilation in terms of gas exchange or overnight oximetry. Short term studies have shown either equivalence, benefit of pressure, or benefit of volume, while longer term studies have also been conflicting or have used heterogeneous groups of patients. In all these studies the ventilator settings were not equivalent in terms of minute ventilation, so they were not really comparing the mode of delivery of the ventilation. Furthermore, these studies have evaluated physiological outcomes but none have assessed outcomes that are important to patients such as daytime functioning and health status.

The aim of this study was therefore to compare volume and pressure ventilation when NIV is used for chronic respiratory failure due to CWD. The hypothesis was that pressure ventilation is superior to volume ventilation due to better leak compensation.

METHODS
The study protocol was approved by the local research ethics committee. Patients gave written consent to participate.

Patients
An a priori power calculation suggested that a sample size of 10 would have 90% power to detect a difference in mean arterial oxygenation of 1 kPa using a paired t test at the 95% significance level. Thirteen patients with chronic respiratory failure due to CWD were invited to participate in the study. All were established on and compliant with nocturnal NIV (mean (SE) duration of NIV 32 (8) months) and had been stable for at least 6 weeks. All patients had been using the NIPPV 1 ventilator (B & D Medical, Stratford upon Avon, UK), which provides pressure controlled ventilation. None were using oxygen or humidification at home.

Ventilator settings
The Breas PV403 (Mölndal, Sweden) was chosen because this ventilator offers both pressure support and volume ventilation as an option within the same machine, and was therefore useful in reducing patient bias. Like the NIPPV 1, it uses an exhalation valve and does not provide positive end expiratory pressure. During a daytime titration period using the patient’s usual nasal mask, ventilator settings (set tidal
was measured using a pedometer in the final week of each
latory responses,16 spirometry, maximal (plateau) inspiratory
capacity and total lung capacity, respectively), and sniff nasal
score).25 Physical activity at home treatment period. Patient comfort during ventilation was
assessed using a visual analogue scale (VAS).

Study design
The study design was a 4 week crossover with 2 week
washout during which time the patients used their usual
ventilator (fig 1). Patients were randomised to receive either
targeted or volume targeted ventilation using
settings as above, which were concealed from the patient.
Check overnight oximetry was performed in the home after
1 week. At the end of each 4 week period the patients
returned for full polysomnography using the ventilator in the
same mode, and daytime measurements as described below.
A washout period of 2 weeks followed during which
the patient used their usual established ventilator before a
further 4 weeks using the alternate ventilatory mode.

Measurements
Polysonmography was performed using the Alice 4 System
(Respironics, Murrysville, PA, USA) and scored according to
standard criteria.15 Overnight flow and pressure waveforms
were recorded (Model 3700 Pneumotachometer, Hans
Rudolph, Germany). Minute leakage was calculated as the
difference between inspired and expired tidal volumes
multiplied by the respiratory rate. Ventilator compliance
(hours used) was downloaded from the ventilator to a
personal computer the following day. Arterial blood gas
tensions were measured off ventilation the following morn-
ing using a radial artery puncture.

Patients underwent a series of physiological and psycho-
metric measurements including resting minute ventilation
and occlusion pressure at 100 ms (PO2); hypercapnic venti-
atory responses,4 spirometry, maximal (plateau) inspiratory
and expiratory mouth pressures (from functional residual
capacity and total lung capacity, respectively), and sniff nasal
inspiratory pressures (SNIP).17 Psychometric measures included a battery of tests sensitive to changes due to chronic
hypoxia and sleep deprivation.18–21 Health status was assessed
by validated disease specific (MRF-28)22 and generic (SF-
36v2)23 questionnaires together with the Hospital Anxiety and
Depression Scale.24 The SF-36 was transformed to UK
population norm scores (z score).25 Physical activity at home
was measured using a pedometer in the final week of each

<table>
<thead>
<tr>
<th>Table 1 Mean (SE) patient demographic data, anthropometric measures and established ventilator settings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>No (male)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Height (m)</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>Post polio</td>
</tr>
<tr>
<td>Early onset kyphoscoliosis</td>
</tr>
<tr>
<td>Pott’s disease</td>
</tr>
<tr>
<td>Thoracoplasty</td>
</tr>
<tr>
<td>BMI (kg/m)</td>
</tr>
<tr>
<td>FEV1 (l)</td>
</tr>
<tr>
<td>FVC (l)</td>
</tr>
<tr>
<td>IPAP (cm H2O)</td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>HCO3⁻ (mmol/l)*</td>
</tr>
<tr>
<td>PaCO2 (kPa)*</td>
</tr>
<tr>
<td>PaO2 (kPa)*</td>
</tr>
<tr>
<td>SO2 (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2 Mean (SE) initial daytime set parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pressure</strong></td>
</tr>
<tr>
<td>Set pressure (cm H2O)</td>
</tr>
<tr>
<td>Set tidal volume (ml)</td>
</tr>
<tr>
<td>Set volume (ml/kg)</td>
</tr>
<tr>
<td>Set Ti (s)</td>
</tr>
<tr>
<td>Set backup rate</td>
</tr>
<tr>
<td>Measured MVe (l/min)</td>
</tr>
<tr>
<td>Measured leak (l/min)</td>
</tr>
</tbody>
</table>

Ti, inspiratory time; MVe, expired minute ventilation.

Figure 1 Study protocol. Measures were performed at the end of each
treatment period (4 and 10 weeks).

RESULTS
Thirteen patients started the study; one withdrew after
1 month because of intervening (unrelated) medical pro-
blems. Baseline data at the time of recruitment are given in
table 1. This group represents a population with severe
restrictive lung diseases (FEV1/FVC ratio 87 (3)%) with mean
FVC 0.69 (0.05) l. There was no significant order effect and
therefore data from both treatment periods were used.

Initial settings and nocturnal ventilation
The modes of ventilation were closely matched as intended
during the daytime in terms of expired minute ventilation
and leakage (table 2). Similarly, at night there was no
difference in expired minute ventilation between pressure
and volume modes, although both were significantly lower
than during the daytime titration periods (p<0.001). The same

volume and inspiratory time) were altered during volume
ventilation to obtain the highest comfortable tidal volume
with a set ventilator back up rate of 15 breaths/min.
Inspiratory pressure was then altered during pressure
ventilation to obtain the same expired minute ventilation as
that delivered during volume ventilation (see online appen-
dix available at http://www.thoraxjnl.com/supplemental for
further explanation). Inspiratory trigger sensitivity was set to
–0.1 cm H2O in both modes, expiratory trigger to 50% of
maximal flow, and rise time to the shortest available
(pressure ventilation only). Adequacy of ventilation was
confirmed by comparison with the daytime minute ventila-
tion obtained with the patients “usual” ventilator and pulse
oximetry. Minute ventilation was at least equivalent to that
achieved with the patient’s usual ventilator.
lower mean inspiratory pressure (IP mean) during volume ventilation was achieved with a significantly greater leakage at night during pressure ventilation (13.8 v 5.9 l/min, p = 0.01).

**Diurnal arterial blood gas tensions and hypercapnic ventilatory responses**

There was no significant difference in arterial blood gas tensions or oxygen saturation between pressure or volume ventilation (table 3). Resting daytime minute ventilation was identical (10.8 l/min) and ventilatory drive, as measured by P0.1, was similar in both groups. There was no consistent change in the slope of the ventilatory or P0.1 hypercapnic responses. The different modes of ventilation had no impact on spirometry, mouth, or sniff nasal pressures.

**Sleep quality**

Compliance was excellent and patients used the ventilators for similar durations over each of the 4 week periods (pressure: 8.07 (0.69) hours/night, volume: 8.40 (1.10) hours/night, table 3). Total sleep time, sleep efficiency, and the proportion of sleep spent in each stage were identical (table 3). In both groups the majority of arousals were non-respiratory—that is, not associated with periods of desaturation or respiratory events. There was no difference at the end of each 4 week period in terms of patient reported ventilator comfort, sleep quality, and subjective sensation of breathlessness.

<table>
<thead>
<tr>
<th>Table 3 Mean (SE) daytime arterial blood gas tensions and spontaneous ventilation, hypercapnic responses, and polysomnography parameters after 4 weeks each of pressure and volume ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>pH*</td>
</tr>
<tr>
<td>HCO3−</td>
</tr>
<tr>
<td>PaCO2 (kPa)</td>
</tr>
<tr>
<td>Paco2 (kPa)</td>
</tr>
<tr>
<td>Spo2</td>
</tr>
<tr>
<td>Pm,max (cm H2O)</td>
</tr>
<tr>
<td>Pe,max (cm H2O)</td>
</tr>
<tr>
<td>SNIAP (cm H2O)</td>
</tr>
<tr>
<td>FEV1 (l)</td>
</tr>
<tr>
<td>FVC (l)</td>
</tr>
</tbody>
</table>

**Spontaneous ventilation**

- VTe (ml) | 439 (26) | 396 (34) | 0.29 | 0.58 |
- RRvent (bpm) | 25.4 (2.1) | 28.4 (2.2) | 0.09 | 0.36 |
- MVe (l/min) | 10.8 (0.5) | 10.8 (0.6) | 0.80 | 0.80 |
- P0.1 cm H2O | −1.53 (0.17) | −1.26 (0.11) | 0.18 | 0.54 |

**Hypercapnic responses**

- ΔVE/ΔPCO2 (l/min/kPa) | 2.87 (0.41) | 3.59 (0.63) | 0.15 | 0.31 |
- MVe at 8 kPa (l/min) | 14.6 (1.2) | 13.7 (1.0) | 0.45 | 0.45 |
- ΔP0.1/ΔPCO2 (cm H2O/kPa) | −0.91 (0.17) | −0.72 (0.12) | 0.07 | 0.21 |
- P0.1 at 8 kPa (cm H2O) | −2.60 (0.44) | −1.90 (0.35) | 0.008 | 0.03 |

**Polysomnography**

- PaCO2 (kPa) | 92.8 (0.9) | 91.8 (1.1) | 0.20 | 1.00 |
- PaO2 (kPa) | 273 (32) | 107 (40) | 0.11 | 1.00 |
- RDI (/hour) | 0.7 (0.7) | 0 (0) | 0.29 | 1.00 |
- RRvent (bpm) | 4.3 (0.8) | 4.7 (0.6) | 0.76 | 1.00 |
- VTe (ml) | 548 (75) | 546 (78) | 0.98 | 1.00 |
- MVe (l/min) | 8.34 (0.91) | 8.38 (1.3) | 0.58 | 1.00 |
- Minute leak (l/min) | 13.80 (1.93) | 5.87 (1.03) | 0.001 | 0.01 |
- Peak inspiratory flow (l/min) | 1.49 (21) | 1.52 (21) | 0.85 | 1.00 |
- RRspon (bpm) | 15.0 (3.0) | 15.6 (3.0) | 0.19 | 1.00 |
- IPpeak (cm H2O) | 24.2 (1.1) | 23.4 (1.1) | 0.85 | 1.00 |
- IPmean (cm H2O) | 20.9 (1.1) | 14.8 (0.8) | 0.000 | 0.008 |
- Ti (s) | 5.53 (0.07) | 1.33 (0.05) | 0.07 | 0.56 |
- Te (s) | 2.30 (0.13) | 2.38 (0.10) | 0.58 | 1.00 |
- Ti/TiTOT | 0.40 (0.03) | 0.36 (0.02) | 0.11 | 0.75 |

**Ventilator hours (/night at home)**

- 394 (16) | 416 (13) | 0.10 | 1.00 |
- 52 (10) | 41 (8) | 0.38 | 1.00 |
- 77 (8) | 85 (2) | 0.24 | 1.00 |
- 12 (2) | 13 (2) | 0.52 | 1.00 |
- 55 (6) | 54 (6) | 0.85 | 1.00 |
- 26 (6) | 25 (5) | 0.68 | 1.00 |
- 0.8 (0.4) | 0.0 (0.0) | 0.10 | 1.00 |
- 1.60 (2.2) | 18.4 (4.6) | 0.44 | 1.00 |
- 8.1 (0.7) | 8.4 (1.1) | 0.25 | 0.25 |

*Unassisted ventilation. p, raw probability; pC, Hochberg correction for multiple end points; Pm,max, maximal inspiratory mouth pressure; Pe,max, maximal expiratory mouth pressure; SNIP, sniff nasal inspiratory pressure; VTe, expired tidal volume; RRvent, spontaneous respiratory rate; MVe, expired minute ventilation; P0.1, pressure at mouth 100 ms after an occluded inspiratory effort; ΔVE/ΔPCO2, slope of ventilatory response curve to inspired carbon dioxide; ΔP0.1/ΔPCO2, slope of P0.1 against inspired carbon dioxide; RDI, respiratory disturbance index, number of apnoeas and hypopnoeas per hour of sleep; TcCO2, transcutaneous carbon dioxide; RRvent, respiratory rate during assisted ventilation; IPpeak, peak inspiratory pressure; IPmean, mean inspiratory pressure; Ti, measured inspiratory time; Te, measured expiratory time; TST, total sleep time; REM, rapid eye movement sleep; NREM, non-rapid eye movement sleep.
**Health status and physical activity**

There were no differences between the two ventilatory modes in either measure of health status (table 4). The overall scores for the Hospital Anxiety and Depression Scale were raised indicating “possibly abnormal”, but there were no differences between the two modes. The norm-based SF-36 data reflect very poor physical functioning (physical component score: pressure 14.8 (3.9), volume 15.5 (3.3)) compared with the UK normal population (50 (10)). Mental health was indicated “possibly abnormal”, but there were no differences in either measure of health status (table 4). The overall scores for the Hospital Anxiety and Depression Scale were raised indicating “possibly abnormal”, but there were no differences between the two ventilatory modes. Most other studies looked at mixed groups of patients. The needs of patients with different conditions from a ventilator will vary, and studying heterogeneous groups of patient may mask differences important to some patient groups. However, these data cannot be extended to ventilator users with other conditions.

**Psychometric tests**

There were no differences in terms of performance in the psychometric test battery between pressure and volume modes.

**DISCUSSION**

In this carefully controlled randomised crossover study in patients with CWD, we found no significant difference between either pressure or volume modes of NIV in terms of daytime arterial blood gas tensions and a range of psychological, sleep, health status, and daytime functioning measures during 1 month of ventilation with either pressure or volume targeted ventilation.

This study improves upon the design of previous studies comparing pressure and volume ventilation. Earlier studies were short term, being performed at most over a few hours during the daytime. However, NIV is usually delivered at night during sleep over a prolonged period of time. More recent studies have tended to be longer term and have included either physiological, functional, or health status outcome measures, but not the combination of all three as in the current study.

In a 1 month crossover study of patients with kyphoscoliosis, pressure and volume modes were equally effective in terms of gas exchange, sleep quality and comfort but no assessment was made of ventilatory drive, patient function, or health status. In another crossover study of pressure versus volume in a heterogeneous sample of 10 patients with COPD and CWD, no difference was identified except for an excess of gastrointestinal side effects in the volume group. This study did not control for minute ventilation and did not assess health status or daytime function.

Uniquely, we established identical volumes of delivered ventilation with the two modes and have therefore studied differences in the way that ventilation is delivered. Additionally, our study evaluated end points likely to be of immediate importance to patients such as health status, cognitive function, and daily activity. A further strength of our study is that we compared ventilator modes only in patients with CWD. Most other studies looked at mixed groups of patients. The needs of patients with different conditions from a ventilator will vary, and studying heterogeneous groups of patient may mask differences important to some patient groups. However, these data cannot be extended to ventilator users with other conditions.

---

**Table 4** Mean (SE) health status, psychometric tests, and visual analogue scores after 4 weeks each of pressure and volume ventilation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pressure</th>
<th>Volume</th>
<th>p</th>
<th>pc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRF-28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily activity</td>
<td>50.3 (19.8)</td>
<td>49.1 (17.0)</td>
<td>0.57</td>
<td>1.00</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>29.2 (22.4)</td>
<td>25.0 (19.1)</td>
<td>0.81</td>
<td>1.00</td>
</tr>
<tr>
<td>Invalidity</td>
<td>33.3 (16.2)</td>
<td>26.7 (13.1)</td>
<td>0.44</td>
<td>1.00</td>
</tr>
<tr>
<td>Total</td>
<td>39.3 (13.1)</td>
<td>36.8 (12.7)</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>SF-36</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>19.0 (3.1)</td>
<td>20.1 (3.2)</td>
<td>0.81</td>
<td>1.00</td>
</tr>
<tr>
<td>Role physical</td>
<td>29.8 (2.6)</td>
<td>32.9 (3.4)</td>
<td>0.28</td>
<td>1.00</td>
</tr>
<tr>
<td>Body pain</td>
<td>23.9 (4.1)</td>
<td>23.9 (4.1)</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>General health</td>
<td>21.5 (3.2)</td>
<td>21.4 (2.9)</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>Physical Component Summary</td>
<td>14.8 (3.9)</td>
<td>15.5 (3.3)</td>
<td>0.91</td>
<td>1.00</td>
</tr>
<tr>
<td>Vitality</td>
<td>43.0 (2.3)</td>
<td>45.6 (2.7)</td>
<td>0.38</td>
<td>1.00</td>
</tr>
<tr>
<td>Social functioning</td>
<td>38.6 (3.1)</td>
<td>41.7 (3.6)</td>
<td>0.36</td>
<td>1.00</td>
</tr>
<tr>
<td>Role emotional</td>
<td>41.7 (4.2)</td>
<td>44.3 (4.1)</td>
<td>0.61</td>
<td>1.00</td>
</tr>
<tr>
<td>Mental health</td>
<td>50.1 (3.0)</td>
<td>51.7 (2.9)</td>
<td>0.69</td>
<td>1.00</td>
</tr>
<tr>
<td>Mental Component Summary</td>
<td>53.7 (3.6)</td>
<td>56.3 (3.6)</td>
<td>0.51</td>
<td>1.00</td>
</tr>
<tr>
<td>HAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>6.5 (1.3)</td>
<td>6.3 (0.4)</td>
<td>0.21</td>
<td>0.42</td>
</tr>
<tr>
<td>Depression</td>
<td>4.1 (0.2)</td>
<td>3.8 (0.2)</td>
<td>0.81</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Physical activity (steps/day)</strong></td>
<td>1216 (277)</td>
<td>1734 (761)</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Psychometric tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serial boxes (s)</td>
<td>16.1 (0.5)</td>
<td>15.8 (0.6)</td>
<td>0.77</td>
<td>0.77</td>
</tr>
<tr>
<td>Trailmaking B-A (s)</td>
<td>39.6 (6.3)</td>
<td>43.2 (6.9)</td>
<td>0.64</td>
<td>1.00</td>
</tr>
<tr>
<td>Rey List Learning</td>
<td>50.2 (3.5)</td>
<td>47.3 (2.9)</td>
<td>0.21</td>
<td>1.00</td>
</tr>
<tr>
<td>AMIPB (info processing)</td>
<td>39.9 (4.3)</td>
<td>35.6 (1.9)</td>
<td>0.19</td>
<td>1.00</td>
</tr>
<tr>
<td>AMIPB (design learning)</td>
<td>36.5 (1.8)</td>
<td>33.0 (2.0)</td>
<td>0.08</td>
<td>0.64</td>
</tr>
<tr>
<td>Digit span</td>
<td>3.5 (0.3)</td>
<td>3.7 (0.2)</td>
<td>0.58</td>
<td>1.00</td>
</tr>
<tr>
<td>SCOLP (no correct)</td>
<td>61.6 (5.5)</td>
<td>58.6 (5.6)</td>
<td>0.40</td>
<td>1.00</td>
</tr>
<tr>
<td>STROOP C (no correct)</td>
<td>99.4 (5.2)</td>
<td>95.4 (5.7)</td>
<td>0.19</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Visual analogue scales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator comfort</td>
<td>6.0 (1.9)</td>
<td>6.7 (1.4)</td>
<td>0.57</td>
<td>1.00</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>6.5 (1.5)</td>
<td>6.1 (2.1)</td>
<td>0.79</td>
<td>0.79</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>6.3 (0.9)</td>
<td>5.7 (1.8)</td>
<td>0.59</td>
<td>1.00</td>
</tr>
</tbody>
</table>

p, raw probability; pc, Hochberg correction for multiple end points; MRF-28, Maugeri Foundation Respiratory Failure Questionnaire-28; SF-36, Short Form 36 z scores; AMIPB, Adult Memory and Information Processing Battery; SCOLP, Speed and Capacity of Language Processing test; STROOP, Stroop colour word test.
of flow during expiration may increase carbon dioxide rebreathing.  

As in previous studies, we chose to use relatively high backup rates. This was based on our observation during pilot studies that patients when asleep would often default to a very low ventilator backup rate, even when this significantly compromised nocturnal oxygenation. Controlled ventilation improved oxygenation and did not adversely affect patient comfort when compared with their usual ventilator (data not reported). Despite this, patients in both groups spent a significant period of the night with saturations less than 90% (pressure 73 (32) minutes; volume 107 (40) minutes). Inspection of the raw data suggests that this was predominantly related to leakage. It is not known whether mild nocturnal hypoxia is harmful and when supplemental oxygen should be added with NIV. By using controlled ventilation, we also tried to minimise the effect of patient-ventilator interaction. It was not possible from the data to establish the frequency of ineffective efforts, but we think it unlikely that there were many—both from direct observation of the patients receiving NIV during the day and because of our early experience that when the back up rate was set low patients made very little respiratory effort.

Compared with some studies we, like others, used relatively high inflation pressures. Using this strategy we showed good control of carbon dioxide levels overnight and our patients tolerated the high pressures well. We did see a lot of leakage, and it is possible that we might have seen comparable carbon dioxide control with less leakage had we used lower inflation pressures. The level of nocturnal leakage with both modes of ventilation was similar to that observed in other studies, but contrasts in that this did not impact on sleep quality or daytime function. We have shown greater levels of leakage during pressure ventilation, but this did not translate into an increase in arousals, worsening of quality of life, health status or daytime function. The low arousal index in this study compared with others may reflect the fact that our patients were well acclimatised ventilator users. A recent study by Windisch et al found similar levels of leakage and also identified a trend to greater leakage during pressure ventilation. This may reflect differences in expiratory triggering but could only be proved by a direct comparison of support and controlled ventilation. While inspiratory time during pressure mode was longer, indicating some degree of “hang up”, we have shown that the same expired minute volume is maintained in both modes, albeit with a greater degree of leakage during pressure ventilation. Having identified excess leakage in the pressure group, in retrospect it would have been informative to have included a measure of nasal symptoms.

While there was no overall significant difference between the two modes, some individuals did show greater improvements with one mode than with the other (fig 2). This is consistent with other studies which have shown a deterioration in a subgroup of patients with CWD switched from volume to pressure targeted ventilation, or improved symptoms and gas exchange in a select group of patients who had deteriorated with volume ventilation but who were then switched to pressure ventilation. It was not possible to identify which patients would perform better with which mode from baseline characteristics, and this may just represent spontaneous variation. However, in keeping with the work of others, this observation supports the concept of using the alternative mode if a patient is not succeeding with one mode of ventilation. Our study was powered to detect a clinically significant change in PaO2. The reason for this was that correction of hypoxia has been shown to improve survival and we argued that, even if there were other benefits from one mode but PaO2 worsened, this would not be

**Figure 2** Individual changes in morning arterial blood gas tensions after each mode of ventilation; (A) PaO2; (B) PaCO2. Horizontal lines indicate group means.
desirable. It may be that there are subtle benefits with one mode which were not detected because the study lacked sufficient power, but any such differences are likely to be small and do not appear to have an impact on patients’ daytime function and health status.

In conclusion, we have shown no advantage to pressure or volume ventilation for patients with CWD. There is therefore no indication to change the mode of ventilation for existing users. For new users the choice will be determined by other factors, including cost and the experience and expertise of the unit in which NIV is initiated.

ACKNOWLEDGEMENTS
The authors are indebted to Mr Wayne Gardner for the development of the computer hardware and software required for this study and also acknowledge the assistance of Dr Anthony Coughlan from the Department of Clinical Psychology at the same institution with the psychometric test battery used. Ventilators were loaned by Breams (UK) Ltd.

Further details of the methods used in the study are given in the online appendix available at http://www.thoraxjnl.com/supplemental

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JMT was funded by a research fellowship from the NHS Northern and Yorkshire Executive.
Competing interests: none declared.

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A randomized crossover study of pressure and volume non-invasive ventilation in chest wall deformity

Online Appendix – Detailed Methodology

Justin M Tuggey MRCP, Mark W Elliott MD FRCP

Methods

The study protocol was approved by the Local Research Ethics Committee of Leeds Teaching Hospitals. Patients gave written consent to participate in the study.

Patients

An a priori power calculation suggested that a sample size of 10 would have 90% power to detect a difference in mean arterial oxygenation of 1kPa using a paired t-test at 95% significance level. 13 patients with chronic respiratory failure due to chest wall deformity were invited to participate in the study. All were established on and compliant with nocturnal NIV (Mean duration (standard error) of NIV 32 (8) months) and had been stable for at least six weeks. All patients had been using the NIPPY 1 ventilator (B & D Medical, Stratford upon Avon, UK). These ventilators provide pressure controlled ventilation. None were using oxygen at home.

Ventilator Settings

The Breas PV403 (Möllycke, Sweden) was chosen for this study since this ventilator offers both pressure support and volume ventilation as an option within the same machine, and was therefore useful in reducing patient bias. Like the NIPPY 1, it uses an exhalation valve and does not provide positive end expiratory pressure. In either mode inspiration is triggering either by patient effort or when the backup setting of the ventilator takes over. During volume ventilation it delivers a constant flow achieving the desired tidal volume (Vt) by the end of a set inspiratory time (Ti). During pressure ventilation, the PV403 delivers a maximal (set) pressure which is maintained until inspiratory flow has dropped to the level of the expiratory trigger or a maximum of 3 seconds has passed. During both modes the inspiratory trigger was set at the most sensitive (-0.1cmH₂O) without autotriggering, and that of the expiratory trigger to 50% of maximal flow (pressure ventilation only). The plateau function (i.e. rise time) was set at the shortest available on the ventilator (arbitrary scale).

During a daytime titration period the patient was initially ventilated using their usual nasal mask (adjusted to minimise leak) and ventilator. Baseline measures of tidal volume, minute ventilation and ventilator set pressure were obtained using a pneumotachometer (Model 3700, Hans Rudolph, Kansas City, MO, USA) placed proximal to the exhalation valve in the ventilator circuit.

The patients were then setup using the Breas ventilator initially in volume mode. The ventilator settings (set tidal volume and inspiratory time) were altered during volume ventilation to obtain the highest comfortable tidal volume with a set ventilator back up rate of 15 breaths per minute. The resultant expired minute ventilation (MVe) was recorded. The ventilator was then changed to pressure mode. Backup rate was kept at 15 min⁻¹. The level of pressure support chosen was that which delivered the same expired minute ventilation as obtained during volume ventilation. Adequacy of ventilation was confirmed by comparison with the daytime minute ventilation obtained with the patients ‘usual’ ventilator and pulse oximetry. Minute ventilation was at least equivalent to that achieved with the patient’s usual ventilator.
Crossover Study

The study design was a 4 week crossover with 2 week washout during which time the patients used their usual, established ventilator. Patients were randomized (concealed computer generated randomization allocation) to receive either four weeks pressure targeted ventilation or four weeks volume targeted ventilation. Settings were defined as obtained above. Patients spent the first (acclimatization) night in the sleep laboratory using their usual ventilator. Full polysomnography and daytime measurements as described below were performed. Patients were then instructed on how to use the ‘new’ ventilator and went home. The chosen settings were concealed from the patient by a tamperproof cover. A check telephone call was made after 48 hours, and a check overnight oximetry (Pulsox-3, Minolta Corporation, Ramsey, NJ, USA) was performed in the home. Ventilator settings were changed if necessary during the first week to improve patient comfort or to improve oxygenation. When this was performed, the settings for the other period of ventilation (pressure or volume) were altered to maintain equivalence of minute ventilation. At the end of the four week period, patients returned for a full sleep study using the Breas ventilator using the same mode, and subsequent measures as described. A washout period of two weeks then followed when the patient used their usual ventilator before a further sleep study and a further four weeks using the alternate ventilator mode.

Overnight Measurements

At each of the 4 hospital attendances, patients slept in a quiet familiar room. The following measurements were made. Full polysomnography was performed using the Alice 4 sleep system (Respironics, Murrysville, PA, USA). Electro-encephalogram, submental-electromyogram and electro-oculogram were measured with silver cup electrodes and standard lead placements (C3A1, C4A2, O1A1, O2A2)[1]. Oximetry was recorded continuously using a finger probe connected to the Alice 4 system. Transcutaneous carbon dioxide tensions (tcCO₂) were measured using a heated skin electrode (TINA, Radiometer, Copenhagen, Denmark). Flow and pressure waveforms were recorded using a calibrated pneumotachometer (model 3700, Hans Rudolph) connected to the Alice 4. Polysomnographs were scored according to standard criteria.[1] The following morning (8am), arterial blood gas tensions were measured using a radial artery puncture (Model 1604, Instrumentation Laboratories, Warrington, England). Patients were awake, and off ventilation for at least 30 minutes prior to arterial puncture.

Daytime Measurements

Following a light breakfast without any caffeinated drinks, patients underwent a series of psychometric and physiological measurements. Spirometry was measured using a Microlab portable spirometer (Micromedical, Gillingham, UK). Maximal (peak) inspiratory and expiratory mouth pressures (PIₘₐₓ and PEₘₐₓ, from residual volume and total lung capacity respectively) and sniff nasal inspiratory pressures (SNIP)[2] were recorded using Pmax Mouth Pressure Monitor (P. K. Morgan, Rainham-Gillingham, Kent, UK). Spontaneous minute ventilation was measured using a heated pneumotachograph connected to a flanged mouthpiece. 3 minutes of recording was made using proprietary software (Research Pneumotach System version 3.07, Hans Rudolph, Kansas City, MO, USA). Hypercapnic ventilatory responses (minute ventilation and mouth pressure 100ms after an occluded inspiratory effort, p0.1) were
recorded using standard techniques.[3][4] The signals from the pneumotach and pressure transducer (MPX 5100, Motorola, Denver, CO, USA) were processed by PC and in-house written software. Further analysis was performed using Origin version 6.1 (Originlab Corporation, MA, USA). A nose clip was worn during these tests.

Chronic hypoxia and sleep deprivation affect frontal lobe function. A series of psychometric measures sensitive to changes in frontal lobe function were used.[5][6][7][8] Health status was assessed by disease specific (MRF-28[9]) and non-specific (SF-36[10]) questionnaires together with the Hospital Anxiety and Depression Scale.[11] The SF-36 has recently been validated for use in patients receiving non-invasive ventilation.[12] Patient activity was estimated using an actimeter (Fitty 3, Kasper & Richter Company, Uttenreuth, Germany), which was used at home in the final week of each pressure or volume 4 week period.[13] Patient comfort in each mode was assessed by 10 centimetre visual analogue scales (VAS).
Reference List for Online Appendix


Online supplement

**Results**

There was a correlation between exhaled LTB$_4$ and PGE$_2$ concentrations before treatment with ibuprofen ($r=0.68$, $p<0.01$, $n=14$) and before ($r=0.65$, $p<0.01$, $n=14$) and after matched placebo ($r=0.70$, $p<0.005$, $n=14$), but not after ibuprofen ($r=-0.09$, $p=0.75$, $n=14$) (see fig S1A–C available online only). There was a correlation between LTB$_4$ and PGE$_2$ concentrations in EBC at baseline ($r=0.58$, $p<0.02$, $n=16$) and before treatment with rofecoxib ($r=0.60$, $p<0.02$, $n=16$), whereas there was a trend towards a correlation between LTB$_4$ and PGE$_2$ concentrations which did not reach statistical significance ($r=0.49$, $p=0.054$, $n=16$) after treatment with rofecoxib (see fig S2A–C available online only). 8-Isoprostane concentrations in EBC were not correlated with the concentration of either LTB$_4$ or PGE$_2$ in either the ibuprofen or the rofecoxib study.

**tx35592.f1**

Figure S1 Correlation between LTB$_4$ and PGE$_2$ concentrations in exhaled breath condensate (A) before treatment with oral ibuprofen ($r=0.68$, $p<0.01$, $n=14$), (B) before matched placebo ($r=0.65$, $p<0.01$, $n=14$), and (C) after placebo (400 mg four times a day for 2 days) ($r=0.70$, $p<0.005$, $n=14$).

**tx35592.f2**

Figure S2 Correlation between LTB$_4$ and PGE$_2$ concentrations in exhaled breath condensate (A) at baseline ($r=0.58$, $p<0.02$, $n=16$), (B) before ($r=0.60$, $p<0.02$, $n=16$), and (C) after treatment with oral rofecoxib (25 mg once a day for 5 days) ($r=0.49$, $p=0.054$, $n=16$).

**tx35592.f3**

Figure S3 Correlation between 8-isoprostane concentrations in exhaled breath condensate and PaO$_2$ values at baseline ($r=-0.67$, $p<0.005$, $n=16$).
Figure S4 (A) PaO$_2$, (B) PaCO$_2$, and (C) pH values in 10 patients with COPD at baseline (day –14), before (day 0), and after treatment with oral rofecoxib 25 mg once a day for 5 days (day 5). Values are expressed as means.

Table S1 Effects of oral ibuprofen (400 mg qid) for 2 days on pulmonary function tests in patients with COPD*

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment (n=14)</th>
<th>Post-treatment (n=14)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$ (l)</td>
<td>0.96 (0.10)</td>
<td>0.93 (0.11)</td>
<td>0.35</td>
</tr>
<tr>
<td>FEV$_1$ (% pred)</td>
<td>38.0 (3.4)</td>
<td>37.4 (3.8)</td>
<td>0.61</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>2.06 (0.13)</td>
<td>2.00 (0.13)</td>
<td>0.18</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>66.1 (3.5)</td>
<td>64.5 (4.1)</td>
<td>0.26</td>
</tr>
<tr>
<td>FEV$_1$/FVC (%)</td>
<td>45.7 (2.6)</td>
<td>45.6 (2.7)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity.

*One patient was excluded from the study because of lack of compliance with treatment.

Data are expressed as mean (SE).

Table S2 Effects of oral placebo (400 mg qid) for 2 days on pulmonary function tests in patients with COPD*

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment (n=14)</th>
<th>Post-treatment (n=14)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$ (l)</td>
<td>0.97 (0.11)</td>
<td>0.99 (0.12)</td>
<td>0.68</td>
</tr>
<tr>
<td>FEV$_1$ (% pred)</td>
<td>38.9 (4.0)</td>
<td>39.2 (4.2)</td>
<td>0.87</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>2.08 (0.14)</td>
<td>2.09 (0.14)</td>
<td>0.85</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>66.5 (3.9)</td>
<td>67.1 (4.2)</td>
<td>0.79</td>
</tr>
<tr>
<td>FEV$_1$/FVC (%)</td>
<td>45.2 (2.8)</td>
<td>46.3 (3.3)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity.

*One patient was excluded from the study because of lack of compliance with treatment.
Data are expressed as mean (SE).

**Table S3** Effects of oral rofecoxib (25 mg/day) for 5 days on pulmonary function tests in patients with COPD*

<table>
<thead>
<tr>
<th>Visit</th>
<th>FEV₁ (l)</th>
<th>FEV₁ (% pred)</th>
<th>FVC (l)</th>
<th>FVC (% pred)</th>
<th>FEV₁/FVC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.51 (0.11)</td>
<td>59.6 (3.4)</td>
<td>2.82 (0.18)</td>
<td>85.8 (3.8)</td>
<td>54.4 (2.6)</td>
</tr>
<tr>
<td>2</td>
<td>1.53 (0.13)</td>
<td>58.5 (3.6)</td>
<td>2.80 (0.20)</td>
<td>84.0 (3.8)</td>
<td>54.1 (2.3)</td>
</tr>
<tr>
<td>3</td>
<td>1.49 (0.11)</td>
<td>58.3 (3.2)</td>
<td>2.78 (0.17)</td>
<td>84.4 (3.4)</td>
<td>54.0 (2.5)</td>
</tr>
<tr>
<td>p</td>
<td>0.50</td>
<td>0.45</td>
<td>0.77</td>
<td>0.52</td>
<td>0.82</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity.

*Seventeen patients were enrolled. One patient was excluded from the study because of COPD exacerbation during treatment with rofecoxib.

Data are expressed as mean (SE).

**Table S4** Effects of oral rofecoxib (25 mg/day) for 5 days on absolute and differential cell counts in sputum in patients with COPD*

<table>
<thead>
<tr>
<th>Visit</th>
<th>Total cell count ($\times 10^5$ cells/ml)</th>
<th>Squamous cells (%)</th>
<th>Macrophages ($\times 10^5$ cells/ml)</th>
<th>Macrophages (%)</th>
<th>Neutrophils ($\times 10^5$ cells/ml)</th>
<th>Neutrophils (%)</th>
<th>Lymphocytes ($\times 10^5$ cells/ml)</th>
<th>Lymphocytes (%)</th>
<th>Eosinophils ($\times 10^5$ cells/ml)</th>
<th>Eosinophils (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.0 (6.5–15)</td>
<td>13.0 (10.5–35.5)</td>
<td>2.0 (1.1–2.9)</td>
<td>27.7 (14.1–49.0)</td>
<td>6.6 (1.7–9.5)</td>
<td>67.8 (38.5–75.5)</td>
<td>0.8 (0.4–1.2)</td>
<td>10.6 (7.9–12.8)</td>
<td>0.3 (0.1–0.4)</td>
<td>3.1 (2.9–3.6)</td>
</tr>
<tr>
<td>2</td>
<td>7.2 (4.9–11.6)</td>
<td>13.0 (11.5–17.0)</td>
<td>1.9 (1.1–3.2)</td>
<td>31.9 (16.3–45.6)</td>
<td>4.3 (2.9–5.3)</td>
<td>57.4 (44.3–73.8)</td>
<td>0.5 (0.2–1.0)</td>
<td>9.1 (6.8–10.8)</td>
<td>0.2 (0.2–0.3)</td>
<td>3.5 (3.0–3.7)</td>
</tr>
<tr>
<td>3</td>
<td>7.5 (5.3–10.1)</td>
<td>15.0 (7.0–20.0)</td>
<td>1.4 (1.0–2.5)</td>
<td>26.6 (16.4–35.3)</td>
<td>4.5 (2.8–5.7)</td>
<td>64.6 (56.4–73.8)</td>
<td>0.3 (0.2–1)</td>
<td>8.1 (4.3–11.6)</td>
<td>0.2 (0.1–0.3)</td>
<td>3.0 (2.9–3.6)</td>
</tr>
<tr>
<td>p</td>
<td>0.55</td>
<td>0.77</td>
<td>0.77</td>
<td>0.31</td>
<td>0.77</td>
<td>0.59</td>
<td>0.42</td>
<td>0.53</td>
<td>0.77</td>
<td>0.69</td>
</tr>
</tbody>
</table>
*Seventeen patients were enrolled. One patient was excluded from the study because of COPD exacerbation during treatment with rofecoxib; three samples from another patient had more than 50% squamous cell contamination and were therefore excluded from analysis.

Values are expressed as median (25th to 75th percentile).

Squamous cells are expressed as the percentage of all cells. Macrophages, neutrophils, lymphocytes, and eosinophil counts are expressed as the percentage of non-squamous cells.