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A Randomised Crossover Study of Pressure and Volume Non-Invasive Ventilation in Chest Wall Deformity

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This article has an online appendix.

Abstract

Background

Non-invasive ventilation is an established treatment for chronic respiratory failure due to chest wall deformity. There are few data available to inform the choice between volume and pressure ventilators. The aim of this study was to compare pressure and volume targeted ventilation in terms of diurnal arterial blood gas tensions, lung volumes, hypercapnic ventilatory responses, sleep quality and effect on daytime function and health status, when ventilators were carefully set to provide the same minute ventilation.

Methods. 13 patients with chest wall deformity underwent a 4-week single blind randomised crossover study using the Breas PV403 ventilator in either pressure or volume mode with assessments made at the end of each 4-week period.

Results. Minute ventilation at night was less than that set during the day with greater leak, for both modes of ventilation. There was more leak with pressure than volume ventilation (13.8 ± 1.9 v 5.9 ± 1.0 $l \cdot min^{-1}$, p=0.01). There were no significant differences in sleep quality, daytime arterial blood gas tensions, lung mechanics, ventilatory drive, health status or daytime functioning.

Conclusions. These data suggest that pressure and volume ventilation are equivalent in terms of the effect on nocturnal and daytime physiology, and resulting daytime function and health status.

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Keywords:

Positive pressure ventilation, Hypercapnic responses

Health related quality of life, Chronic respiratory failure

Chest wall deformity, non-invasive ventilation

Introduction

Domiciliary non-invasive positive pressure ventilation (NIV) is an established treatment in 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.[1-3] There is also evidence for improved quality of life and survival.[4] 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.[5]

Pressure vs. Volume Ventilation

Most ventilator modes are either pressure or volume targeted, each with potential advantages and disadvantages. Volume ventilation by definition includes a predetermined set tidal volume, however in the presence of interface leak, the set volume is not guaranteed which, theoretically at least, is a problem, particularly during sleep when NIV is conventionally applied.[6] 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.[7] Any differences between the method of delivery of ventilation may have a consequential effect on nocturnal ventilation, sleep quality and daytime physiology and psychometric function.

Epidemiological data suggest that there is an increasing preference to pressure ventilation when NIV is used for home mechanical ventilation [8], 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 [9][10], benefit of pressure [11] or benefit of volume [12] whilst longer term studies have also been conflicting or have used heterogeneous groups of patients.[13][14] In all these studies, the ventilator settings were not equivalent in terms of minute ventilation and therefore 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 non-invasive ventilation when carefully controlled for minute volume, in terms of nocturnal ventilation and leak, sleep quality, and their impact on gas exchange, daytime function and health status. 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 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 or humidification at home.

Ventilator Settings

The Breas PV403 (Mölnlycke, 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 NIPPY 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 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. Inspiratory pressure was then altered during pressure ventilation to obtain the same expired minute ventilation as that delivered during volume ventilation (see online appendix for further explanation). Inspiratory trigger sensitivity was set to -0.1 cmH_2O 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 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.

Study Design (see figure 1)

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

Measurements

Polysomnography 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). Minute leak 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 morning using a radial artery puncture.

Patients underwent a series of physiological and psychometric measurements including resting minute ventilation and occlusion pressure at 100ms (p0.1), hypercapnic ventilatory responses[16], spirometry, maximal (plateau) inspiratory and expiratory mouth pressures (from FRC 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 United Kingdom population norm scores (z score).[25] Physical activity at home was measured using a pedometer in the final week of each treatment period. Patient comfort during ventilation was assessed by visual analogue scales (VAS).

Statistical Analysis

The primary outcome measures were the daytime arterial blood gas tensions during spontaneous breathing. Secondary endpoints included patient orientated outcomes such as daytime function, quality of life and health status. Data was compared using paired student t-tests. The crossover analysis was considered valid provided that no significant order effect was noted from the two treatment periods. The Hochberg procedure was used to adjust for multiple secondary endpoints.[26]

Results

13 patients started the study. 1 patient discontinued the study after 1 month due to intervening (unrelated) medical problems. Baseline data at the time of recruitment are given in table 1. This group represent a population with severe restrictive lung diseases (FEV_1/FVC ratio 87% ± 3%) with mean FVC 0.69 ± 0.05 litres. There was no significant order effect and therefore data from both treatment periods were used.

	Baseline
Number (male)	13 (6)
Age (years)	60.5 (12.7)
Height (m)	1.56 (0.09)
Diagnosis (n)	
Post polio	4
Early onset kyphoscoliosis	7
Pott's disease	1
Thoracoplasty	1
BMI ($kg \cdot m^{-2}$)	25.3 (5.3)
FEV_1 (l)	0.60 (0.04)
FVC (l)	0.69 (0.05)
IPAP (cmH_2O)	23.0 (1.3)
pH *	7.38 (0.01)
HCO_3^- ($mmol \cdot l^{-1}$) *	28.6 (0.68)
P_aO_2 (kPa) *	8.83 (0.26)
P_aCO_2 (kPa) *	6.42 (0.09)
SaO_2 (%)*	91.7 (0.7)

Table 1 Patient demographics, anthropometric measures and established ventilator settings (mean ± SEM) *Unassisted ventilation taken at 8am. BMI: body mass index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity. IPAP: set inspiratory positive airways pressure; P_aO_2, P_aCO_2: arterial oxygen and carbon dioxide tensions; HCO_3^-: bicarbonate; SaO_2: oxygen saturation.

Initial Settings and nocturnal ventilation (table 2)

The modes of ventilation were closely matched as intended during the daytime in terms of expired minute ventilation and leak. 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 ($p<0.01$). The same expired minute volume was achieved with a significantly lower mean inspiratory pressure (IP_{mean}) during volume ventilation (14.8 vs. 20.9 cmH_2O, $p=0.008$). There was significantly greater leak at night during pressure ventilation (13.8 vs. 5.9 $l \cdot min^{-1}$, $p=0.01$).

	Pressure	**Volume**	**p**
Set pressure (cmH_2O)	25.0 (1.1)	-	
Set tidal volume (ml)	-	749.2 (34.5)	
Set volume ($ml \cdot kg^{-1}$)	-	11.9	
Set Ti (s)	-	1.2 (0.1)	
Set backup rate	15	15	
Measured MVe ($l \cdot min^{-1}$)	12.14 (0.65)	12.18 (0.63)	0.93
Measured Leak ($l \cdot min^{-1}$)	2.43 (0.52)	2.22 (0.35)	0.71

Table 2 Initial Daytime Set Parameters (mean ± SEM). Ti: inspiratory time; MVe: expired minute ventilation.

Diurnal arterial blood gas tensions and hypercapnic ventilatory responses (table 3)

There was no significant difference in arterial blood gas tensions or oxygen saturation between pressure or volume ventilation. Resting daytime minute ventilation was identical (10.8 $l \cdot min^{-1}$) and ventilatory drive, as measured by $P_{0.1}$, was similar in both groups. There was no consistent change in the slope of the ventilatory or $P_{0.1}$ hypercapnic responses. The different modes of ventilation had no impact on spirometry, mouth or sniff nasal pressures.

Outcome	Pressure		Volume		p	p_C
pH *	7.38	(0.01)	7.38	(0.01)	0.56	0.56
HCO_3^-	28.6	(0.68)	29.5	(0.66)	0.07	0.28
P_aO_2 (kPa)	9.00	(0.23)	8.68	(0.36)	0.18	0.36
P_aCO_2 (kPa)	6.38	(0.12)	6.61	(0.16)	0.09	0.27
SaO_2	92.3	(0.75)	90.7	(1.17)	0.04	0.20
Pi,max (cmH_2O)	-36.3	(5.1)	-38.5	(4.9)	0.47	1.00
Pe,max (cmH_2O)	66.2	(10.6)	72.1	(10.7)	0.31	1.00
SNIP (cmH_2O)	-36.0	(5.3)	-37.7	(5.8)	0.66	1.00
FEV_1 (l)	0.60	(0.04)	0.61	(0.04)	0.57	0.86
FVC (l)	0.72	(0.06)	0.76	(0.06)	0.86	1.00
Spontaneous Ventilation						
VTe (ml)	439	(26)	396	(34)	0.29	0.58
RR_{spon} (bpm)	25.4	(2.1)	28.4	(2.2)	0.09	0.36
Mve ($l \cdot min^{-1}$)	10.8	(0.5)	10.8	(0.6)	0.80	0.80
$P_{0.1}$ (cmH_2O)	-1.53	(0.17)	-1.26	(0.11)	0.18	0.54
Hypercapnic responses						
$\Delta VE/\Delta pCO_2$ ($l \cdot min^{-1} \cdot kPa^{-1}$)	2.87	(0.41)	3.59	(0.63)	0.15	0.31
MVe @ 8 kPa ($l \cdot min^{-1}$)	14.6	(1.2)	13.7	(1.0)	0.45	0.45
$\Delta P_{0.1}/\Delta pCO_2$ ($cmH_2O \cdot kPa^{-1}$)	-0.91	(0.17)	-0.72	(0.12)	0.07	0.21
$P_{0.1}$ @ 8 kPa (cmH_2O)	-2.60	(0.44)	-1.90	(0.35)	0.008	0.03
Polysomnography						
SaO_2 (mean, %)	92.8	(0.9)	91.8	(1.1)	0.20	1.00
SaO_2 < 90% (minutes)	73	(32)	107	(40)	0.11	1.00
RDI (hr^{-1})	0.7	(0.7)	0	(0)	0.29	1.00
$TcCO_2$ (mean, KPa)	4.3	(0.8)	4.7	(0.6)	0.76	1.00
VTe (ml)	548	(75)	546	(78)	0.98	1.00
MVe ($l \cdot min^{-1}$)	8.34	(0.91)	8.38	(1.3)	0.58	1.00
Minute Leak ($l \cdot min^{-1}$)	13.80	(1.93)	5.87	(1.03)	0.001	0.01
Peak inspiratory flow ($l \cdot min^{-1}$)	149	(21)	152	(21)	0.85	1.00
RR_{vent} (bpm)	15	(0.3)	15.6	(0.3)	0.19	1.00
IP_{peak} (cmH_2O)	24.2	(1.1)	23.4	(1.1)	0.85	1.00
IP_{mean} (cmH_2O)	20.9	(1.1)	14.8	(0.8)	0.001	0.008
Ti (s)	1.53	(0.10)	1.33	(0.05)	0.07	0.56
Te (s)	2.30	(0.13)	2.38	(0.10)	0.58	1.00
Ti/Ti_{TOT}	0.40	(0.03)	0.36	(0.02)	0.11	0.75
Total Sleep Time (TST) (min)	394	(16)	416	(13)	0.10	1.00
Latency (min)	52	(10)	41	(8)	0.38	1.00
Efficiency (%)	77	(8)	85	(2)	0.24	1.00
REM (% TST)	12	(2)	13	(2)	0.52	1.00
NREM 1+2 (% TST)	55	(6)	54	(6)	0.85	1.00
NREM 3+4 (% TST)	26	(6)	25	(5)	0.68	1.00
Respiratory arousals (/hr)	0.8	(0.4)	0.0	(0.0)	0.10	1.00
Non-respiratory arousals (/hr)	16.0	(2.2)	18.4	(4.6)	0.44	1.00
Ventilator hr (/night @ home)	8.1	(0.7)	8.4	(1.1)	0.25	0.25

Table 3 Daytime arterial blood gas tensions and spontaneous ventilation, hypercapnic responses and polysomnography (mean ± SEM) after 4 weeks of each of pressure and volume ventilation. *unassisted ventilation. p: raw probability; p_C: Hochberg corrrection for multiple endpoints. Pi,max: maximal inspiratory mouth pressure; Pe,max: maximal expiratory mouth pressure; SNIP: sniff nasal inspiratory pressure; VTe: expired tidal volume; $RR_{spon:}$ spontaneous respiratory rate; MVe: expired minute ventilation; $P_{0.1}$: pressure at mouth 100ms after an occluded inspiratory effort; $\Delta VE/\Delta pCO_2$: slope of ventilatory response curve to inspired carbon dioxide; $\Delta P_{0.1}/\Delta pCO_2$ slope of $P_{0.1}$ against inspired carbon dioxide; RDI: respiratory disturbance index, number of apnoeas and hypopnoeas per hour of sleep; $TcCO_2$: transcutaneous carbon dioxide; RRvent: respiratory rate during assisted ventilation; IP_{peak}: peak inspiratory pressure; IP_{mean}: 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.

Sleep Quality (table 3)

Compliance was excellent and patients used the ventilators for similar durations over each of the 4 week periods (pressure: 8.07 ± 0.69 hrs/night, volume: 8.40 ± 1.10). 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 (i.e. not associated with periods of desaturation or respiratory events). There was no difference at the end of each four weeks in terms of patient reported ventilator comfort, sleep quality and subjective sensation of breathlessness.

Health Status and physical activity (table 4)

There were no differences between the two ventilatory modes in either measure of health status. 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 reflects very poor physical functioning (physical component score pressure: 14.8±3.9, volume 15.5±3.3) compared to the UK normal population (50±10). Mental health was measured as close to the UK norm (pressure 53.7±3.6, volume 56.3±3.6). There were no differences in daily activity as measured by the pedometer.

Psychometric Tests

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

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

Table 4 Health Status, Psychometric Tests and Visual Analogue scales after 4 weeks of each of pressure and volume ventilation; mean ± SEM). p: raw probability; p_C: Hochberg corrrection for multiple endpoints. MRF-28; Maugeri Foundation Respiratory Failure Questionnaire-28; SF-36: Short Form 36 z scores; AMIPB: The Adult Memory and Information Processing Battery; SCOLP: Speed and capacity of language processing test; STROOP: Stroop color-word test

Discussion

In this carefully controlled randomised crossover study in patients with chest wall deformity, we have demonstrated that there was no significant difference between either pressure or volume modes of non-invasive ventilation in terms of daytime arterial blood

gas tensions and a range of psychological, sleep, health status and daytime functioning measures during one 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, performed at most over a few hours during the daytime.[9-11][27] However NIV is usually delivered each 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. [13][14][28][29] 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.[13] In another crossover study of pressure vs. 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.[14] 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, e.g. health status, cognitive function, and daily activity.

A further strength of our study is that we compared ventilator modes just in patients with chest wall deformity. Most other studies looked at mixed groups of patients. The needs of patients with different conditions from a ventilator will vary and studying heterogeneous patient groups may mask differences important to some patient groups. However these data cannot be extended to ventilator users with other conditions. Indeed, a particular ventilator mode may be better suited in some conditions for other reasons, e.g. volume ventilation in severe neuromuscular disease, allowing patients with impaired cough to breath stack.

Patient selection was not random, but only patients who were already established on NIV and agreeable to participate were recruited. These were likely to represent the 'best' patients in terms of compliance, and it is not surprising that they had minimal hypercapnia at the start of the study. Most patients on home NIV will become experienced users over time so it is important to test for any differences in these patients. The study does not address whether one mode is easier for patients when they first start NIV; this would have required a parallel group study design with larger numbers of patients. Additionally because some patients present acutely unwell and require NIV immediately, it would not have been possible to perform such a comprehensive series of evaluations.

All patients were previously established on a (different) pressure ventilator, which may have biased the results favouring pressure ventilation. We think this unlikely, since patients were blinded and anecdotally could not identify which mode was pressure targeted. Again, uniquely, the same ventilator was used to provide both modes of ventilation to avoid bias and preference for the patients' usual ventilator.

One of the potential concerns in the design of this study, as with similar comparisons of pressure and volume ventilation, was that ventilator settings were titrated during the daytime.[14][29] A further strength of this study is that ventilation was *also* measured during sleep and although expired minute ventilation was significantly less at night than during the day, this difference was seen with both modes of ventilation.

Ventilators differ in methods and sensitivity of both inspiratory and expiratory triggers and the way in which flow is delivered. The results of this study are based on just one ventilator, and therefore should not necessarily be extrapolated to other machines. The difference in waveform between pressure and volume is a likely explanation for equivalent overnight minute ventilation with quite different mean inspiratory pressures. The PV403 does not provide positive end-expiratory pressure (PEEP), which is available in most pressure targeted ventilators. While benefit has been shown from the addition of extrinsic PEEP in patients during an acute exacerbation of COPD, it is unlikely to be as important in stable patients with CWD, although the absence of flow during expiration may increase carbon dioxide rebreathing.[30]

As in previous studies, we chose to use relatively high backup rates.[14][29] 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 to 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 vs. volume 107±40 minutes). Inspection of the raw data suggests that this was predominantly related to leak. 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.[31]

Compared to some studies we, like others, used relatively high inflation pressures. [32][33][14] Using this strategy we showed good control of CO_2 levels overnight, and our patients tolerated the high pressures well. We did see a lot of leak and it is possible that we might have seen comparable CO_2 control but with less leak had we used lower inflation pressures. The level of nocturnal leak with both modes of ventilation was similar to that observed in other studies, but contrasts however in that this did *not* impact on sleep quality or daytime function.[14][34] We have shown greater levels of leak 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 to others may reflect that our patients were well-acclimatised ventilator users.[34] The recent study by Windisch et al. demonstrated similar levels of leak and also identified a trend to greater leak during pressure ventilation.[14] This may reflect differences in expiratory triggering but could only be proven by a direct comparison of support and controlled ventilation. Whilst 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 either mode, albeit with a greater degree of leak during pressure ventilation. Having identified excess leak in the pressure group, in retrospect it would have been informative to have included a measure of nasal symptoms.

Whilst there was no overall significant difference between the two modes, some individuals did show improvements with one mode compared to the other (Figure 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 [29] 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.[28] 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 alternate mode if a patient is not succeeding with one mode of ventilation.[28][29] Our study was powered to detect a clinically significant change in P_aO_2. 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 P_aO_2 worsened, this would not be 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 impact on patients' daytime function and health status.

In conclusion we have shown no advantage to pressure or volume ventilation for patients with chest wall deformity. 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.

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Figure Legends

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

Figure 2 – Individual changes in morning arterial blood gas tensions after each mode of ventilation; A: P_aO_2, B: P_aCO_2. Dark line identifies group mean.

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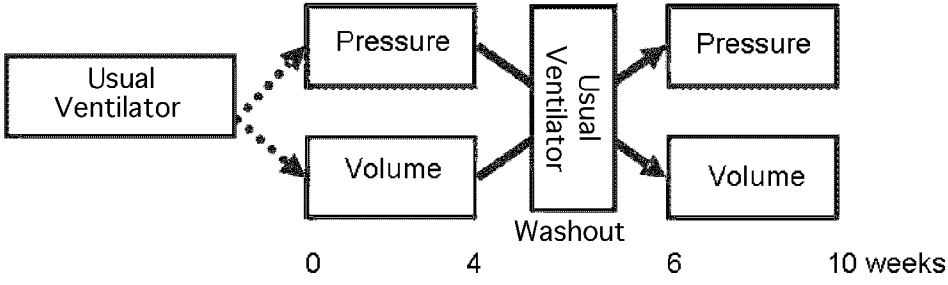
Usual Ventilator
Pressure
Volume
Usual Ventilator
Washout
Pressure
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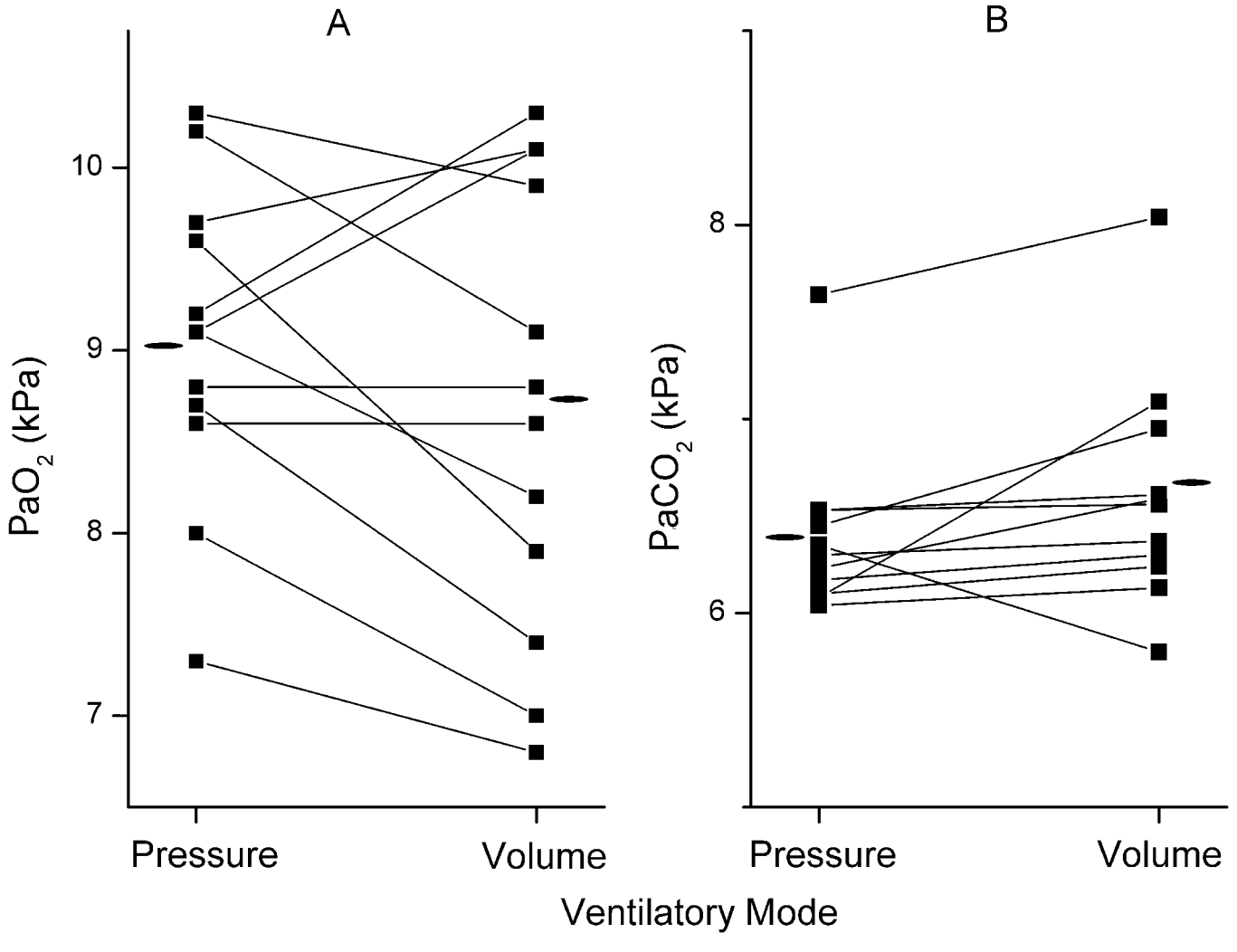
Figure 1



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 (Mölnlycke, 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 (-0.1cmH_2O) 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 ($tcCO_2$) 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 (PI_{max} and PE_{max}, 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).

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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 Pa_{O_2} values at baseline (r=–0.67, p<0.005, n=16).

tx35592.f4

Figure S4 (A) Pa_{O_2}, (B) Pa_{CO_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*

	Pre-treatment (n=14)	**Post-treatment (n=14)**	**p value**
FEV_1 (l)	0.96 (0.10)	0.93 (0.11)	0.35
FEV_1 (% pred)	38.0 (3.4)	37.4 (3.8)	0.61
FVC (l)	2.06 (0.13)	2.00 (0.13)	0.18
FVC (% pred)	66.1 (3.5)	64.5 (4.1)	0.26
FEV_1/FVC (%)	45.7 (2.6)	45.6 (2.7)	0.89

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*

	Pre-treatment (n=14)	**Post-treatment (n=14)**	**p value**
FEV_1 (l)	0.97 (0.11)	0.99 (0.12)	0.68
FEV_1 (% pred)	38.9 (4.0)	39.2 (4.2)	0.87
FVC (l)	2.08 (0.14)	2.09 (0.14)	0.85
FVC (% pred)	66.5 (3.9)	67.1 (4.2)	0.79
FEV_1/FVC (%)	45.2 (2.8)	46.3 (3.3)	0.98

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*

	Visit 1 (n=16)	**Visit 2(n=16)**	**Visit 3 (n=16)**	**p value**
FEV_1 (l)	1.51 (0.11)	1.53 (0.13)	1.49 (0.11)	0.50
FEV_1 (% pred)	59.6 (3.4)	58.5 (3.6)	58.3 (3.2)	0.45
FVC (l)	2.82 (0.18)	2.80 (0.20)	2.78 (0.17)	0.77
FVC (% pred)	85.8 (3.8)	84.0 (3.8)	84.4 (3.4)	0.52
FEV_1/FVC (%)	54.4 (2.6)	54.1 (2.3)	54.0 (2.5)	0.82

COPD, chronic obstructive pulmonary disease; FEV_1, 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*

	Visit 1 (n=15)	**Visit 2 (n=15)**	**Visit 3 (n=15)**	**p value**
Total cell count ($\times 10^5$ cells/ml)	12.0 (6.5–15)	7.2 (4.9–11.6)	7.5 (5.3–10.1)	0.55
Squamous cells (%)	13.0 (10.5–35.5)	13.0 (11.5–17.0)	15.0 (7.0–20.0)	0.77
Macrophages ($\times 10^5$ cells/ml)	2.0 (1.1–2.9)	1.9 (1.1–3.2)	1.4 (1.0–2.5)	0.77
Macrophages (%)	27.7 (14.1–49.0)	31.9 (16.3–45.6)	26.6 (16.4–35.3)	0.31
Neutrophils ($\times 10^5$ cells/ml)	6.6 (1.7–9.5)	4.3 (2.9–5.3)	4.5 (2.8–5.7)	0.77
Neutrophils (%)	67.8 (38.5–75.5)	57.4 (44.3–73.8)	64.6 (56.4–73.8)	0.59
Lymphocytes ($\times 10^5$ cells/ml)	0.8 (0.4–1.2)	0.5 (0.2–1.0)	0.3 (0.2–1)	0.42
Lymphocytes (%)	10.6 (7.9–12.8)	9.1 (6.8–10.8)	8.1 (4.3–11.6)	0.53
Eosinophils ($\times 10^5$ cells/ml)	0.3 (0.1–0.4)	0.2 (0.2–0.3)	0.2 (0.1–0.3)	0.77
Eosinophils (%)	3.1 (2.9–3.6)	3.5 (3.0–3.7)	3.0 (2.9–3.6)	0.69

*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 (25^{th} to 75^{th} 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.