Randomized Controlled Trial of Domiciliary Noninvasive Positive Pressure Ventilation and Physical Training in Severe Chronic Obstructive Pulmonary Disease

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The addition of noninvasive positive pressure ventilation (NPPV) to an exercise training (ET) program in severe chronic obstructive pulmonary disease (COPD) may produce greater benefits in exercise tolerance and quality of life than after training alone. Forty-five patients with severe stable COPD—mean (SD) FEV_1 0.96 (0.31) L, Pa_{O_2} 65.4 (9.07) mm Hg, Pa_{CO_2} 45.6 (7.89) mm Hg—were randomized to domiciliary NPPV + ET (n = 23) or ET alone (n = 22). Exercise capacity and health status were assessed at baseline and after an 8-wk training program. There was a significant improvement in mean shuttle walk test (SWT) in the NPPV + ET group: from 169 (112) to 269 (124) m (p = 0.001), compared with the ET group: 205 (100) to 233 (123) m (p = 0.19); mean difference (95% confidence interval [CI]): 72 (12.9 to 131) m. Repeated measures analysis of variance (ANOVA) showed that the differences between the two groups became evident only in the final 4 wk of the training program with a mean end study difference (95% 1CI) of 65.8 (17.1 to 114) m. There was a significant improvement in the Chronic Respiratory Disease Questionnaire (CRDQ) of mean (SD) 24.0 (17.4) (p = < 0.001) in the NPPV + ET group and 11.8 (15.8) (p = 0.003) points in the ET group; mean difference: 12.3 (1.19 to 23.4). Only the NPPV + ET group demonstrated a significant improvement in arterial oxygenation; mean difference: 3.70 mm Hg (0.37 to 7.27). This study suggests that domiciliary NPPV can be used successfully to augment the effects of rehabilitation in severe COPD.

Chronic obstructive pulmonary disease (COPD) is associated with progressive airflow obstruction that leads to considerable disability; these patients have reduced exercise capacity, associated with mood disturbance and impaired quality of life. The addition of nasal positive pressure ventilation (NPPV) to long-term oxygen therapy in hypercapnic COPD patients has been shown to improve daytime arterial blood gases and quality of life (1, 2). Physical training programs that are effective in improving exercise tolerance also improve quality of life (3). However, varying effects of training have been reported, especially in more disabled patients (4).

For patients with severe COPD, dyspnea may preclude high-intensity training (5) and limit physiological training effects (6). There is evidence that inspiratory muscle fatigue during exercise contributes to dyspnea (7, 8). The addition of NPPV during exercise leads to improvements in exercise performance and reduced dyspnea (8), probably through unloading of the respiratory muscles (9). There are practical difficulties associated with the administration of NPPV during exercise training that may limit its clinical relevance. NPPV provided at home may have similar beneficial results by reducing the work of breathing and dyspnea and thus improving exercise tolerance and health status. In hypercapnic COPD patients, NPPV improves sleep quality (1), and it is possible that a similar mechanism could operate in normocapnic patients and lead to improvements in quality of life. However, the long-term effects of domiciliary NPPV combined with a training program are unknown.

In this study, we are testing the hypothesis that nocturnal domiciliary NPPV provided in conjunction with a pulmonary rehabilitation program will lead to greater improvements in exercise capacity, health status, and respiratory muscle performance than training alone. The aim of this study, therefore, is to evaluate the addition of domiciliary nasal ventilation to a pulmonary rehabilitation program in patients with severe COPD.

METHODS

Patients

Forty-five patients with stable severe COPD were recruited from the outpatient clinics of the London Chest Hospital (17 female, 28 male, median age [range] 65 [38–84] yr). Patients had no reported exacerbations in the past 4 wk. Patients included in the study had a history of severe COPD with forced expiratory volume in 1 s (FEV_1) less than 50% predicted and less than 15% reversibility of FEV_1 to inhaled salbutamol (400 μg). All patients had limited exercise tolerance due to dyspnea and had no previous exposure to NPPV. Patients were excluded from the study if they had unstable angina, intermittent claudication, or other mobility-limiting conditions. The study was approved by the Ethics Committee of East London and the City Health Authority, with all patients providing written informed consent.

Study Protocol

The study design was randomized and controlled. Forty-five patients were randomized into two groups using sealed envelopes; either exercise training with domiciliary NPPV (NPPV + ET), n = 23, or exercise training (ET) alone, n = 22. The sample size calculation was based on data on shuttle walking distance from our previous work on pulmonary rehabilitation (4). The study was powered at 80%, with a significance of 5% to detect a difference in walking distance between the two study groups of at least 25%.

At initial assessment (A1), patients in the NPPV + ET group were fitted with noninvasive positive pressure ventilation using the BiPAP ST 30 ventilator (Respironics Inc., Murrysville, PA) and instructed to use the ventilator overnight or for at least 8 h daily throughout the whole study period. All patients underwent a 4-wk run-in period. The NPPV + ET group was contacted twice weekly during this time to encourage compliance; patients in the ET group were given no special instructions and were contacted only once. Two patients on long-term oxygen therapy (LTOT) received 2 L/min of oxygen through the mask and no changes to other medication were made. Reassessment was made at the end of the run-in period (A2). All patients were then entered onto an 8-wk, twice weekly pulmonary rehabilitation program consisting of exercise training and an education program. A midway assessment of the primary outcome measures was made 4 wk into the rehabilitation program (A3). At the end of the 8-wk training period, assessment of all outcome measures was repeated (A4).

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Ventilation Settings and Compliance

Ventilation was provided by nasal masks in the spontaneous mode. In most cases Silicon Gold Seal (Respironics, Inc.) masks were used, although in four patients reusable contour masks provided a better fit. A plateau exhalation valve was inserted into the system, and humidification was provided in four patients at a later stage after complaints were made regarding dry mouth and throat. Ventilator settings were adjusted individually to obtain the maximal pressure tolerated. The median (range) inspiratory positive airway pressure (IPAP) was 16 (13–24) cm H_2O, and the median expiratory positive airway pressure (EPAP) was 4 (4–6) cm H_2O. All patients on NPPV then had resting earlobe gasses taken after 1 h on the ventilator (10).

Hourly use of the ventilator was calculated from the ventilation time counter on the machine, and reported use was derived from daily diary cards. Where patients reported being unable to sleep with ventilation, they were advised to use the machines for at least 6 h during the day. Compliance with rehabilitation was documented by attendance at the training sessions.

Assessments

The following baseline assessments were made.

Lung function, exercise tolerance, and sleep monitoring. Resting blood gases were obtained from earlobe samples, while breathing room air at rest for at least 20 min and analysed on a 278 Blood Gas Analyser (Ciba-Corning, Medfield, MA). Spirometry was performed using a rolling seal spirometer (P. K. Morgan Ltd., Rainham, UK). Maximal inspiratory and expiratory pressures were measured using a mouth pressure monitor (P. K. Morgan Ltd.), and the best of four attempts was documented.

Exercise capacity was assessed using the shuttle walk test (SWT), which is a maximal externally paced incremental exercise test (11). Two walking tests were performed with a rest of at least 20 min between each walk. Arterial oxygen saturation (Sa_{O_2}) was monitored throughout the walk using a pulse-oximeter (Minolta Pulsox 7; AVL Instruments, Schaffhausen, Switzerland), and the lowest Sa_{O_2} was recorded. The patients were asked to indicate their level of breathlessness using the Borg Dyspnea Score before and immediately after each walk (12).

Polysomnography was performed during the run-in period (A1) on six patients on air in the NPPV group and repeated after the exercise program (A4) while using the ventilator overnight. Data were recorded on the Sleepmaster computerized polysomnography system (Nicolet Instruments, Warwick, UK). All sleep staging was performed manually according to the method of Rechtschaffen and Kales (13).

Health status assessment. (i) Quality of life: The Chronic Respiratory Disease Questionnaire (CRDQ) measures health status and was designed for the assessment of change in individuals (14). It comprises four component scores, dyspnea, fatigue, emotional function, and mastery measured, on a seven-point Likert scale. The dyspnea component of the questionnaire is individualized to five activities that cause dyspnea and are assessed in order of importance and severity to the patient. The higher the score the better the health status.

(ii) Mood state: The Hospital Anxiety and Depression (HAD) Scale assesses anxiety and depression and consists of 14 items and is scored from 0 to 21 with a score of greater than 10 in either anxiety or depression representing symptoms of clinical significance (15).

(iii) Activity of daily living assessment: The London Chest Activity of Daily Living Scale (LCADL) is a 15-item questionnaire designed to measure dyspnea during routine daily activities in patients with COPD. It consists of four components: Self-Care, Domestic, Physical, and Leisure. Patients score from 0 "I wouldn't do anyway" to 5 "Someone else does this for me (or helps)," with higher scores representing maximal disability (16).

Exercise training program. The pulmonary rehabilitation program consisted of 16 hourly sessions of physical training supervised by an experienced physiotherapist, followed by an education program standardized for both groups. The programs were performed in groups of six to eight. The exercise program consisted of upper and lower limb training twice a week for 8 wk, each session lasting for 1 h. Arm exercises were performed using dumbbells of 1 kg weight, while lower limb exercises were performed without resistance. The aerobic component of the exercise program involved fast walking over a distance of 10 m; walking intensity was determined on an individual basis and set by the physiotherapist at 80% maximal oxygen consumption ($V_{O_2}max$) from the results of the initial SWT (17). Patients also performed unloaded cycling on a cycle ergometer. Patients exercised for as long as they were able and used the Borg breathlessness score to monitor intensity (18). Progression of training was mediated via an increase in the number of repetitions or an increase in the time spent cycling/walking. All patients were given instructions to exercise at home on alternate days, and diary cards were provided. The education program lasted approximately 45 min and covered topics of medical management of COPD, relaxation, chest clearance and breathing techniques, signs and symptoms of infection, energy conservation, stress management and coping techniques, travel with COPD, the benefits of exercise, and smoking cessation.

Statistical Analysis

The continuous variables were normally distributed. Differences between the groups in response to rehabilitation were identified using the unpaired Student's *t* test, while changes within groups were measured using the paired Student's *t* test. Results are presented as mean (SD) with the 95% confidence intervals (CIs) shown. A value of $p < 0.05$ was taken as significant. Repeated measures analysis of variance (ANOVA) was performed on the 30 patients who underwent all assessments and post hoc paired and unpaired Student's *t* tests were then performed to identify where changes occurred in those 30 patients (19). Relationships between the variables were investigated using Pearson correlations.

RESULTS

Details of Patients Enrolled and Study Design

Forty-five patients were recruited to the study and randomized into two groups, either noninvasive positive pressure ventilation plus exercise training (NPPV + ET) or exercise training (ET) alone. The study design and patient profile are shown in Figure 1. After entry into the study, four patients withdrew, three in the NPPV + ET group (one patient with a transient ischemic attack and two because of noncompliance to the ventilator). One patient withdrew from the ET group because of refusal to attend the training sessions. At A2, 35 patients were available for reassessment. A further six patients were unable to attend (three patients in the NPPV + ET group and three in the ET group). These six patients who were unavailable for reassessment at 4 wk were later able to attend the rehabilitation program and further assessments, with 39 patients available at A3 and 37 patients at A4. Four patients were unable to

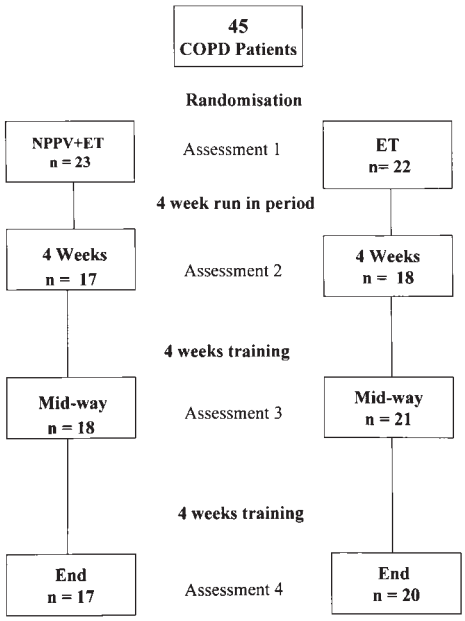

Figure 1. Patient profile and study design.

manage the final assessment due to exacerbation of COPD (two in each group). Paired assessments were therefore made on 35 patients after the run-in period (NPPV + ET = 17, ET = 18) and 37 patients from randomization to end (NPPV + ET = 17, ET = 20). Thirty patients performed all assessments and were included in the repeated measures ANOVA analysis (NIPPV + ET = 13 and ET = 17).

Baseline Characteristics

The patients had severe stable COPD with mean (SD) FEV_1 0.92 (0.28) L, FEV_1% predicted 35.2 (12.8), Pa_{O_2} 65.4 (9.07) mm Hg, and Pa_{CO_2} 45.6 (7.89) mm Hg. Table 1 shows the baseline characteristics of the patients in both groups (n = 45); there were no significant differences between the groups at the start of the study. There were no significant differences in baseline variables between patients who completed all assessments compared with those who withdrew or who were unable to attend an assessment.

TABLE 1

BASELINE CHARACTERISTICS OF THE NONINVASIVE VENTILATION PLUS EXERCISE TRAINING GROUP AND THE EXERCISE ONLY GROUP*

	NPPV + ET (*n = 23*)	ET (*n = 22*)
Age (range), yr	63 (38 to 84)	67 (55 to 79)
FEV_1, L	0.96 (0.31)	0.89 (0.28)
% Predicted FEV_1	33.2 (7.96)	35.1 (9.17)
FVC , L	2.24 (0.85)	2.29 (0.57)
Pa_{O_2}, mm Hg	63.7 (8.55)	67.2 (9.38)
Pa_{CO_2}, mm Hg	44.2 (6.68)	46.1 (9.07)
$P_{I_{max}}$, cm H_2O	−60.2 (19.7)	−61.5 (19.5)
$P_{E_{max}}$, cm H_2O	95.2 (41.7)	98.9 (33.5)
Shuttle walk test (m)	171.3 (103)	191.8 (105)

Definition of abbreviations: ET = exercise training; NPPV = noninvasive positive pressure ventilation; $P_{E_{max}}$ = maximal expiratory muscle strength; $P_{I_{max}}$ = maximal inspiratory muscle strength.

* Data presented as mean (SD), n = 45.

Physiological Parameters

After the run in period (A2), 35 patients were available for reassessment (NPPV + ET = 19 and ET = 16). There were no significant changes in either group for any measure after the initial 4 wk. Table 2 shows the changes in physiological parameters from randomization to end of study. There were no significant changes in spirometry parameters at any time point. Arterial blood gases showed a small but statistically significant increase in Pa_{O_2} after the 12-wk time period in the NPPV + ET group only, from 63.5 to 66.1 mm Hg (p = 0.03), which was significantly different between the two groups, mean difference (95% CI) 3.70 (0.37 to 7.27). There were no significant differences in Pa_{CO_2} at any time period. Only the NPPV + ET group showed a significant increase in inspiratory muscle strength ($P_{I_{max}}$), from mean (SD) 60.2 (19.7) to 66.6 (18.2) cm H_2O (p = 0.02) and from 65.1 (19.5) to 64.0 (23.4) cm H_2O (p = 0.40) in the NPPV + ET group and ET groups, respectively; however, the difference between the groups was not significant (p = 0.28) (Table 4). There were no significant changes in expiratory muscle strength ($P_{E_{max}}$) in either group.

There was a significant increase in walking distance over the trial period from, mean (SD) 169 (112) to 269 (124) m (p < 0.001) in the NPPV + ET group compared with 205 (100) to 233 (123) m (p = 0.19) in the ET group. The change in walking distance was significantly different between the two groups; mean difference (95% CI) 72.0 (12.9 to 131) m (p = 0.01) (Table 4).

The median (range) time asleep (stages 2, 3, and 4 and REM ([rapid eye movement] sleep) was at 56.5 (29–68)% of the night at A1 at the start of the study and at 42.9 (25.9–53.4)% at A4 on the ventilator at the end of the study (p = 0.07). Although patients spent less time asleep on the ventilator, this did not reach significance.

Health Status Measures

Table 3 shows the changes in health status in the two groups. There was an increase in CRDQ total scores from 68.1 (20.9) to 92.2 (17.0) (p < 0.0001) and 73.3 (22.4) to 85.1 (23.9) (p = 0.003) in the NIPPV + ET and ET groups, respectively, mean difference (95% CI) 12.3 (1.19 to 23.4) (p = 0.03) (Table 4). Similarly, there was a significant difference in the changes in the Fatigue component of the CRDQ between groups with the NPPV + ET group showing a larger improvement compared with the ET group (Table 4). Both groups showed significant improvements in activity of daily living scores with a reduction in the LCADL from 45.4 (11.2) to 38.8 (10.1) (p = 0.008) and 40.2 (13.0) to 33.9 (13.8) (p = 0.004) in the NPPV + ET and ET groups, respectively. There were no significant differences in HAD scores over the treatment period in either group.

Repeated Measures ANOVA

Repeated measures ANOVA was performed on the 30 patients who completed all assessments and showed changes over time and a group time interaction. There was no difference in the change in exercise tolerance between the two groups until the final 4 wk of rehabilitation. During the second

TABLE 2

CHANGE IN PHYSIOLOGICAL PARAMETERS FROM RANDOMIZATION TO END OF STUDY (12 wk) IN NPPV + ET AND ET GROUPS*

	NPPV + ET (*n = 17*)				ET (*n = 20*)			
	Pre	Post	Difference	95% CI	Pre	Post	Difference	95% CI
FEV_1, L	0.97	0.94	−0.03	−0.93 to 0.15	0.92	0.88	−0.04	−0.57 to 0.13
FVC, L	2.28	2.52	0.24	−0.45 to 0.05	2.32	2.27	−0.05	−0.63 to 0.25
Pa_{O_2}, mm Hg	63.5	66.1	2.55	4.25 to 0.15†	68.2	66.8	−1.58	−1.16 to 4.20
Pa_{CO_2}, mm Hg	44.6	43.3	−1.30	−1.35 to 3.98	45.3	44.2	−1.10	−0.90 to 3.17
$P_{I_{max}}$, cm H_2O	−60.2	−66.6	6.4	1.14 to 13.1†	−65.1	−64.0	1.10	−3.71 to 8.81
$P_{E_{max}}$, cm H_2O	95.2	113.3	18.1	−4.50 to 33.1	113.3	106.8	−6.50	−8.56 to 16.4
SWT, m	169	269	100	58.5 to 141‡	205	233	28.0	−16.0 to 72.0

Definition of abbreviations: CI = confidence interval; ET = exercise training; NPPV = noninvasive positive pressure ventilation; $P_{E_{max}}$ = maximal expiratory muscle strength; $P_{I_{max}}$ = maximal inspiratory muscle strength; SWT = shuttle walk test.

* p Values represent change over time.

† p < 0.05.

‡ p < 0.001.

TABLE 3

CHANGE IN HEALTH STATUS FROM RANDOMIZATION TO END OF STUDY (12 wk) IN NPPV + ET AND ET GROUPS*

	NPPV + ET (*n = 17*)				ET (*n = 20*)			
	Pre	Post	Difference	95% CI	Pre	Post	Difference	95% CI
CRDQ[§] (total)	68.1	92.2	24.1	15.1 to 33.0[‡]	73.3	85.1	11.8	4.34 to 19.2[†]
Dyspnea	13.1	18.0	4.90	0.63 to 9.24[†]	15.1	16.8	1.70	−0.74 to 4.04
Mastery	16.2	21.1	4.90	2.34 to 7.42[‡]	15.6	18.7	3.10	1.12 to 5.08[†]
Emotion	26.8	35.2	8.40	5.18 to 11.6[‡]	28.6	33.2	4.60	1.75 to 7.45[†]
Fatigue	11.9	17.8	5.90	3.94 to 7.71[‡]	13.9	16.4	2.50	0.44 to 4.36[†]
HAD (total)	16.3	15.0	−1.30	−4.17 to 7.17	17.6	13.8	−3.80	−1.20 to 8.80
Anxiety	8.18	7.64	−0.54	−2.82 to 4.20	8.85	7.65	−1.20	−1.11 to 3.51
Depression	8.13	7.35	−0.78	−2.16 to 3.78	8.75	6.15	−2.60	−0.38 to 5.58
LCADL[‖] (total)	45.4	38.7	−6.70	−11.5 to −1.94[‡]	40.2	33.8	−6.40	−10.5 to −2.22[‡]
Self-care	9.94	8.24	−1.70	−0.27 to 3.67	9.60	8.30	−1.30	−0.05 to 2.65
Domestic	22.1	20.2	−1.90	−1.63 to 5.39	18.6	14.8	−3.80	−6.70 to −0.89[†]
Physical	6.00	4.65	−1.35	−2.33 to −0.37[‡]	5.75	5.05	−0.70	−1.25 to −0.15[†]
Leisure	7.47	5.82	−1.65	−2.46 to −0.83[‡]	6.25	5.70	−0.55	−0.14 to 1.24

Definition of abbreviations: CI = confidence interval; CRDQ = Chronic Respiratory Disease Questionnaire; ET = exercise training; HAD = Hospital Anxiety and Depression Scale; LCADL = London Chest Activity of Daily Living Scale; NPPV = noninvasive positive pressure ventilation.

* Values represent change over time.

† $p < 0.05$.

‡ $p < 0.001$.

§ Higher score reflects better symptoms.

‖ Higher score reflects greater disability.

month of training, the NIPPV + ET group continued to improve with respect to walking distance, from mean (SD) 238 (95.3) m to 290 (118) m ($p = 0.003$) while the ET group showed no change, 256 (118) to 242 (128) m ($p = 0.45$). There was a mean end study difference (95% CI) between the groups of 65.8 m (17.1 to 114), $p = 0.009$ (Figure 2).

CRDQ changes showed a similar pattern to exercise tolerance with a significant effect of time and group time interaction. During the run-in period, no changes were observed in health status in either group; both groups then improved with only the NVVP + ET group showing a further significant increase in CRDQ scores, from mean (SD) 81.9 (17.2) to 93.3 (18.6) ($p = 0.01$) and 80.2 (25.5) to 83.6 (25.4) ($p = 0.24$) in the NPPV + ET and ET groups, respectively (Figure 3). The change in health status during the final 4 wk was not significantly different between the two groups.

Compliance

Only two patients were lost from the study because of noncompliance with the NPPV. The daily use of nasal ventilation was low at median (range) 2.08 h/d (0 to 11.4) from ventilator time counter readings. Of the 17 NPPV patients who reached the end of the study, 29% used the ventilator for more than 4 h and 47% used the ventilator for more than 3 h, when assessed from the counter readings. There was no significant difference in the changes in walking distance between the patients who used the ventilator for more or less than 4 h (mean difference 23 m; $p = 0.47$) or more or less than 3 h (mean difference 53 m; $p = 0.08$). Sixteen patients returned completed diary cards indicating that reported use by the patient was higher at a median of 3.80 (0 to 9.8) h/d. There were no baseline characteristics that identified patients with poorer compliance. Reasons for poor compliance ranged from upper airway problems to

TABLE 4

DIFFERENCE IN CHANGE IN OUTCOMES BETWEEN NPPV + ET AND ET GROUPS FROM RANDOMIZATION TO END (12 wk)*

	NPPV + ET (*n = 17*)	ET (*n = 20*)	Difference in Change between Groups	p Value	95% CI
Δ SWT, m	100 (80)	28 (94)	72.0	0.01	12.9 to 131
Δ Pa_{O_2}, mm Hg	2.30 (2.10)	−1.40 (4.35)	3.70	0.03	0.37 to 7.27
Δ Pa_{CO_2}, mm Hg	1.30 (4.95)	1.10 (4.35)	0.20	0.98	−0.41 to 0.41
Δ $P_{I_{max}}$ cm H_2O	−6.41 (10.8)	−1.10 (13.4)	−5.30	0.28	−13.1 to 4.00
Δ $P_{E_{max}}$, cm H_2O	18.1 (34.0)	−6.50 (26.6)	24.6	0.32	−10.4 to 31.3
Δ CRDQ (total)	24.1 (17.4)	11.8 (15.8)	12.3	0.03	1.19 to 23.4
Δ Dyspnea	4.94 (8.37)	1.65 (5.11)	3.29	0.15	−1.26 to 7.84
Δ Fatigue	5.86 (3.66)	2.45 (4.18)	3.41	0.01	0.78 to 6.07
Δ Emotion	8.40 (4.66)	4.63 (2.19)	3.77	0.59	−3.69 to 6.39
Δ Mastery	4.88 (4.94)	3.10 (4.23)	1.78	0.25	−1.28 to 4.84
Δ LCADL	6.70 (9.27)	6.40 (3.21)	0.30	0.91	−5.69 to 6.40
Δ HAD	1.30 (10.6)	3.81 (10.6)	−2.51	0.52	4.98 to −9.58

Definition of abbreviations: CI = confidence interval; CRDQ = Chronic Respiratory Disease Questionnaire; ET = exercise training; HAD = Hospital Anxiety and Depression Scale; LCADL = London Chest Activity of Daily Living Scale; NPPV = noninvasive positive pressure ventilation; SWT = shuttle walk test; $P_{E_{max}}$ abd $P_{I_{max}}$ = maximal inspiratory and expiratory pressure.

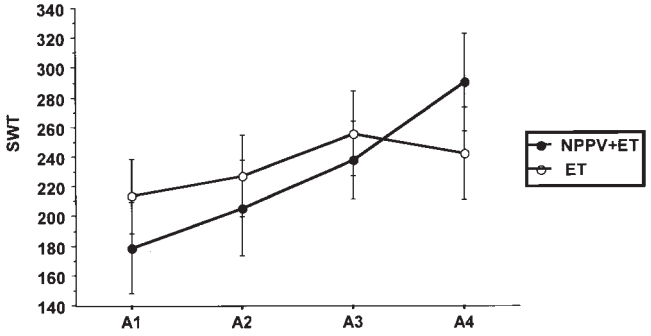

Figure 2. Changes in shuttle walk test (SWT) in both groups at each assessment. p = 0.009 difference between the groups in final 4 wk of training (A3 and A4); p = 0.01 difference between the groups over 12-wk period (A1 and A4). *Open circles* represent the ET group; *closed circles* represent the NPPV + ET group. A1: baseline assessment; A2: pre-rehabilitation assessment (4 wk); A3: mid-rehabilitation assessment (8 wk); A4: postrehabilitation assessment (12 wk).

complaints regarding disturbance to spouse and inability to sleep due to ventilator noise.

The attendance at the rehabilitation program was satisfactory with patients attending a median (range) of 14 (8–16) sessions overall. The median number of sessions missed due to respiratory illness was identical for both groups: median (range) 2.00 (0–7). Sessions missed due to unrelated factors such as visits to dentist and family and work commitments were also similar: median (range) 1.00 (0–2) and 0.00 (0–2) for the NPPV + ET and ET groups, respectively. There was a trend toward a relationship between the number of sessions attended and the changes in exercise tolerance (p = 0.05).

DISCUSSION

This is the first randomized controlled trial to evaluate the role of domiciliary noninvasive intermittent positive pressure ventilation (NPPV) as an adjunct to pulmonary rehabilitation in patients with severe COPD. We have shown support for the hypothesis that NPPV augments the benefits of exercise training in patients with severe COPD. The results of this study show significant improvements in exercise tolerance and quality of life after training in conjunction with NPPV, when compared with exercise training alone. Only the group treated with NPPV showed a significant improvement in inspiratory muscle strength. Our study design enabled us to identify the point at which differences between the two groups occurred. We found that after 4 wk of training improvements in exercise tolerance were similar between the groups, but after this time, the NPPV-treated group continued to improve while the exercise-only group showed no further change.

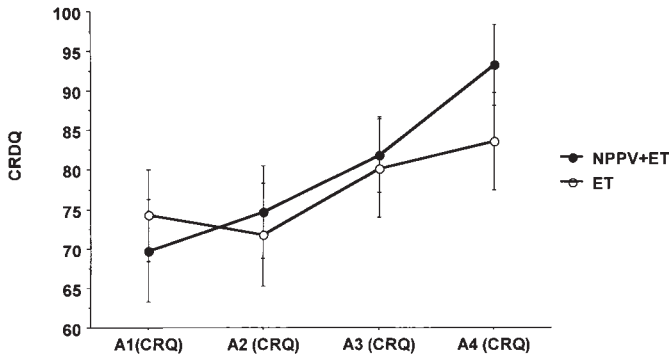

Figure 3. Changes in Chronic Respiratory Disease Questionnaire (CRDQ) total scores in both groups at each assessment. p = 0.01 difference between the groups over 12-wk period (A1 and A4). *Open circles* represent the ET group; *closed circles* represent the NPPV + ET group. A1: baseline assessment; A2: pre rehabilitation assessment (4 wk); A3: mid-rehabilitation assessment (8 wk); A4: postrehabilitation assessment (12 wk).

Previous trials of NPPV have generally shown improvements in quality of life and arterial blood gases in patients with hypercapnic COPD, although the addition of NPPV did not improve exercise tolerance (1, 20). Recently, another study has suggested improvements in 6-min walking distance can occur after long-term ventilation, although patients in this study were randomized according to compliance (21). As our study was concerned with the role of NPPV in conjunction with a pulmonary rehabilitation program, we studied patients with severe COPD whom we felt would be suitable candidates for pulmonary rehabilitation. We have previously reported little effect of an exercise training program in patients with severe COPD housebound by dyspnea (4). Hypercapnia in COPD has been shown to be a strong predictor of hospitalization for acute exacerbation (22), suggesting that these patients may have difficulty attending all rehabilitation sessions. Few studies have investigated the role of NPPV in patients with severe normocapnic COPD, as recruited into this study, yet these patients are frequently enrolled in rehabilitation programs.

Early studies have suffered from low power, often due to poor compliance with noninvasive ventilation (23, 24). In a study reported by Strumpf and colleagues using NPPV, 7 of 19 patients withdrew due to inability to tolerate the ventilator (25). However, in our study only two NPPV patients withdrew because of noncompliance and exacerbation of COPD accounted for the majority of missed assessments. Only one other study has attempted to evaluate the role of noninvasive ventilation using negative pressure ventilation with pulmonary rehabilitation and no benefits of additional ventilation were found (26). However, this study had a small sample size (seven in the active arm) and only a short inpatient rehabilitation program of 3 wk, making interpretation difficult. We incorporated an initial 1 mo run-in period with regular telephone contact with the patient to identify any difficulties with the equipment, and this may have contributed to the relatively few withdrawals observed. Six patients (26%) in the active group withdrew, compared with two (9%) in the control group. Although this could have contributed to study bias, there were no baseline differences between the patients who withdrew and those completing the study.

In patients with COPD, inspiratory muscle load is increased due to the effects of hyperinflation, leading to impaired contractility of the diaphragm and respiratory muscles (27). It has been suggested that in COPD the respiratory muscles are subjected to fatigue and that improvements in lung mechanics and reduction in workload may contribute to a reduction in fatigue (28). Several investigators have shown that in the application of noninvasive ventilation, both positive- and negative-pressure techniques may produce significant reductions in diaphragmatic electromyographic (EMG) activity and work of breathing, implying respiratory muscle rest (29–31). However, no long-term improvements in respiratory muscle function in COPD patients have been reported after ventilatory support. In this study, only the NPPV-treated group showed a significant improvement in inspiratory mouth pressure ($P_{I_{max}}$) after 3 mo domiciliary use. Although this was not significantly different when compared with the control group, we cannot rule out the possibility of a type II error. We did not measure diaphragmatic activity, and therefore cannot demon-

strate that reduced activity was achieved. However, ventilator settings in this study were in accordance with other studies that have shown respiratory muscle unloading (29, 31).

The addition of NPPV administered during exercise slows the maximal relaxation rate of the respiratory muscles, suggesting a delay in onset of fatigue in these muscles (9). This may enable patients to exercise for longer periods while using NPPV (8). Indeed, only the patients in the NPPV + ET group showed a significant improvement in the fatigue component of the CRDQ. However, there are practical difficulties in instituting NPPV during exercise training, and another approach is to use NPPV daily on a domiciliary basis during the training period to achieve unloading of the respiratory muscles. In patients with hypercapnic COPD who have significant nocturnal hypoventilation, NPPV has been shown to improve sleep quality (1, 20). However, in this study, sleep quality was not improved when the patients were studied with NPPV after the exercise program, presumably due to the small degree of nocturnal hypoventilation in the patient study group. Although only a small group of the NPPV patients was studied with sleep studies, there was a trend to worse sleep quality with the ventilator, suggesting that changes in sleep quality are not a factor in the improvements noted in the NPPV group.

The median usage of the ventilator from meter readings over the 12-wk period was 2 h daily and 29% of patients used the ventilator for greater than 4 h/d, while 47% used the ventilator for more than 3 h daily. There were no significant relationships found in this study between changes in exercise tolerance and ventilator compliance. However, although the diary card figure suggested a higher daily usage of 3.8 h, the data from the timer represent ventilator use more accurately, and thus it is likely that patients overestimated the time they took the NPPV. However, the usage found in this study was less than that reported previously in hypercapnic patients at 6.9 h (1). In COPD patients with hypercapnia, NPPV has benefits on sleep quality and this may contribute to the increased compliance observed in this patient group. However, investigation of diaphragmatic activity during ventilation has shown significant unloading of the respiratory muscles after only 20 min use (32) and Cropp and Dimarco demonstrated improvements in respiratory muscle strength after just 3 to 5 h of negative ventilation over 3 d (33). Although daily ventilator use in our study was less than this, our patients were provided with positive pressure ventilation for a longer period (3 mo) than used in these studies. Thus, relatively short episodes of NPPV may be sufficient to achieve benefit if provided for a longer duration.

Hypoxia in COPD patients is associated with further impairment in respiratory muscle strength. In this study there was a small but significant improvement in arterial oxygenation in the NPPV-treated patients compared with the exercise-only patients, which could have made a small contribution to the change in respiratory muscle function. The change in Pa_{O_2} in these patients may have resulted from an improvement in alveolar ventilation and reduced hyperinflation. Moreover, worsening Pa_{O_2} is associated with reduced health status (34), suggesting that the improvements in Pa_{O_2} may lead to improvements in quality of life scores. However, in this study, the small improvements in the arterial oxygenation may have contributed relatively little to the changes in health status.

One of the limitations of this study is that we did not provide sham ventilation to the exercise-only group, and thus it was not possible to blind the investigator or the patient. Sham ventilation could have been provided either by continuous positive pressure ventilation (CPAP) or low-pressure NPPV, though it is possible that these techniques themselves could contribute to effects on outcome measures. Using a nasal mask long term, without any ventilation, has some ethical implications and thus it was decided not to include a sham treatment in the study design. It is thus possible that due to the relatively short usage of the ventilators, some of the results may have arisen due to placebo-like effects. However, our run-in period of 1 mo before the training program, with reassessment after this time, enabled us to identify any changes occurring as a result of NPPV alone, and no significant differences were found. Patients in the NPPV group were contacted frequently in the run-in period to optimize use of the ventilators, and this could also have contributed to some bias, though contact was similar for the two groups once the rehabilitation programs had started. In this study, we used pressure support ventilation and it is possible that volume cycled ventilation could have different effects or improved compliance. However, previous studies have shown no significant difference between the two ventilator modes in efficacy or compliance (35, 36).

For most patients with COPD, training programs alone are sufficient to achieve improvements in exercise tolerance. However, for patients further comprised by ventilatory limitation, domiciliary ventilatory support may augment benefits. This study provides evidence for the use of NPPV as an adjunct to a pulmonary rehabilitation program, but does not support routine use of domiciliary NPPV in normocapnic COPD patients. Further research is recommended to evaluate the mechanisms and longer term benefits of using NPPV with rehabilitation and to ascertain whether patients require administration of long-term ventilation after the initial exercise program to maintain benefits. Thus, the addition of domiciliary NPPV during an exercise program in patients with COPD may have advantages in these patients with disabling dyspnea and provide benefits with respect to exercise tolerance and health-related quality of life.

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