Outcome of COPD patients performing nocturnal non-invasive mechanical ventilation

E. Clini*, C. Sturani†, R. Porta*, C. Scarduelli†, V. Galavotti†, M. Vitacca* and N. Ambrosino*

*Salvatore Maugeri Foundation IRCCS, Pulmonary Department, Medical Centre of Rehabilitation, Guassago (BS); †C. Poma Hospital Pulmonary Division, Mantova, Italy

The role of non-invasive nocturnal domiciliary ventilation (NNV) in chronic obstructive pulmonary disease (COPD) patients with chronic hypercapnia is still discussed. The aims of this study were to evaluate the long-term survival, the clinical effectiveness and side-effects of NNV in these patients.

Forty-nine stable hypercapnic COPD patients on long-term oxygen therapy (LTOT) were assigned to two groups: in Group 1, 28 patients performed NNV by pressure support modality in addition to LTOT; in Group 2, 21 patients continued their usual LTOT regimen. Treatment was assigned according to the compliance to NNV, after an in hospital period. Mortality rate, hospital stay (HS) and ICU admissions (IA) were recorded in the two groups. HS and IA were compared to those recorded in a similar period of follow-back. Lung and respiratory muscle function, dyspnoea, and exercise capacity (by 6-min walk test) were evaluated baseline and every 3-6 months up to 3 yr.

Mean follow-up time was 35 ± 7 months. Mortality rate was not different between the two groups: 16, 33, 46% and 13, 28, 50% at 1, 2 and 3 yr in Groups 1 and 2 respectively. Lung and respiratory muscle function did not significantly change over time. A significant increase in 6-min walk test (from 245 ± 78 to 250 ± 88, 291 ± 75, 284 ± 89 m after 1, 2 and 3 yr respectively, P<0.01) was observed only in patients undergoing NNV. In comparison to the follow back HS significantly decreased in both groups (from 37 ± 29 to 15 ± 12 and from 32 ± 18 to 17 ± 11 days/pt/yr in Groups 1 and 2 respectively, P<0.001) whereas IA significantly decreased only in patients performing also NNV (from 1.0 ± 0.7 to 0-2 ± 0-3/pt/yr, P<0.0001).

Addition of NNV by pressure support modality to LTOT does not improve long term survival but significantly reduces ICU admissions and improves exercise capacity in severe COPD with hypercapnia.

Introduction

Long term oxygen therapy (LTOT) has been shown to improve survival in hypoxaemic patients with chronic obstructive pulmonary disease (COPD) independent of the presence of chronic hypercapnia (1,2). Long term mechanical ventilation has been proposed (3-6) in addition to LTOT in COPD patients able to spontaneously breath with the theoretical rationale: to unload the ventilatory muscles (7,8), to improve gas exchange (9), to reset the respiratory central drive (10). It is usually delivered by either standard volume-cycled ventilators in assisted/controlled (A/C) mode or by pressure support ventilation (PSV).

Physiological studies have shown that non-invasive positive pressure ventilation (NIPPV) may unload the diaphragm in stable COPD (7,8) while some clinical studies suggested that non-invasive nocturnal ventilation (NNV) could be associated with daytime arterial blood gas improvement, and reduced hospitalisation and need of tracheotomy (5,6). While NIPPV has been gaining increasing popularity to reverse acute on chronic respiratory failure (11) and in the management of chronic respiratory failure resulting from neuromuscular and restrictive chest wall diseases (12), controlled trials in stable COPD patients report conflicting results on short-term, clinical and functional outcome (13-15). Even fewer data are reported on long-term effects (5,16,17). In a previous study over 18 months we showed that NIPPV per se was not able to improve survival in these patients (17) in comparison to LTOT alone.

The aims of this study were therefore: (i) to assess the long term survival, (ii) to evaluate the clinical and functional outcomes and (iii) to report the treatment compliance and side-effects of chronically hypoxaemic and hypercapnia COPD patients undergoing addition of NIPPV by means of PSV to LTOT in comparison with a control group of COPD patients undergoing LTOT alone.
Methods

The study was approved by the Ethical Committees of Medical Centre of Gussago, S. Maugeri Foundation, and Azienda Ospedaliera C. Poma, Mantova, Italy. The study was conducted according to the declaration of Helsinki. Patients gave their informed consent to participate in the study.

PATIENTS

Forty-nine severe COPD patients defined by the American Thoracic Society (ATS) guidelines (18) were recruited from December 1991 to December 1994. All patients were ex-smokers, met the criteria for LTOT (19) and had been on oxygen for at least 12 months. At the time of the study the patients had to be free from exacerbations. Prior to and during the study, all of them received regular treatment (18–20); no change in medical and oxygen therapy was made the month preceding the inclusion in the study. Thirty-five patients had previously experienced the use of nasal PSV during an exacerbation over the last 2 yr.

At hospital admission, all the following inclusion criteria had to be met: (1) stable clinical state i.e. stability in blood gas values and pH (>7.35), and lack of exacerbation in the preceding four weeks; (2) PaO₂ <8 kPa and PaCO₂ >6 kPa respectively, during spontaneous breathing room air at the time of the study; (3) at least one ICU admission due to severe exacerbation in the two years preceding the study; (4) evidence of family support or availability of a care-giver at home; and (5) geographical allocation allowing the patients to easily reach the hospital. Patients with other organ failure, cancer and inability to cooperate in long-term trials were excluded. Patients were also excluded if they had a 12% or more than 200 ml increase in FEV₁ after administration of an inhaled bronchodilator, or a suspicion of sleep apnoea as assessed by nocturnal monitoring of arterial oxygen saturation (SaO₂) (21).

FUNCTIONAL MEASUREMENTS

Lung volumes and forced vital capacity (FVC) were measured by means of a volume constant body plethysmograph (1085 Medical Graphic Corp, St. Paul MN, U.S.A.). The predicted values according to Quanjer (22) were used. Arterial blood gases were assessed at baseline and every 3 months. PaO₂, PaCO₂, and pH were measured by means of an automated analyser (ABL 500, Radiometer, Copenhagen, Denmark) on blood samples taken from radial artery while patients in the sitting position were breathing room air for at least 1 h. Diffusing capacity for carbon monoxide (DLCO) was determined by the single-breath method Medical Graphic Corp. St. Paul, MN, U.S.A.). SaO₂ was monitored by pulse oximetry by means of a portable recorder with a memory chart (Pulsox 5, Minolta, Osaka, Japan). The inspiratory muscle strength was assessed by measuring the maximal inspiratory pressure (MIP) at the level of functional residual capacity (FRC) according to the method of Black & Hyatt (23) using a respiratory module system (Medical Graphic Corp, St. Paul, MN, U.S.A.). Each patient performed a minimum of five MIP manoeuvres with at least 1 min interval between efforts until two acceptable values not differing from each other by more than 5% were obtained. The best value was recorded. Dyspnoea sensation was assessed at baseline and every 6 months according to the ATS scale (24). Subjective rating of dyspnoea under NIPPV trial was performed by means of a visual analogue scale (VAS) (26).

Exercise capacity was evaluated by means of the 6-min walk test (25), at admission and every 12 months. A baseline 6-min walk test was performed with three practice tests in two consecutive days. The highest value was recorded. A single measurement was performed during the follow-up. The 6-min walk test measurements were performed and recorded under the supervision of a nurse not involved in the study.

CLINICAL OUTCOME

Days of hospital stay (HS), number of events (in particular need of endotracheal intubation) of ICU admissions (IA) were recorded by hospital registrars, interviewing relatives or the general practitioner and comparing the follow-up period to a similar period before entering the study (follow-back). In all cases IA was defined as hospitalisation due to severe exacerbation leading to acute respiratory failure and needing ventilatory assistance (either invasively or non invasively). Endotracheal intubation (EI) was decided by the attending physicians in ICUs (also of different Hospitals) unaware of the study. Criteria of endotracheal intubation were those commonly used in the clinical practice in the ICUs in Italy. The days spent in the hospital, when in stable state, for NNV training were not taken into account. Finally, mortality rate was recorded in the follow-up in both groups.

PROTOCOL

Patients were divided into two groups: Group 1 performed both LTOT and NNV, Group 2 performed LTOT alone. The assignment was not random. All the patients meeting the inclusion criteria performed an in-hospital trial of NNV (see below) spending at least 15 days in the hospital. The effectiveness of NIPPV was assessed by means of evaluation of arterial blood gases and dyspnoea (by VAS) during 1 h of continuous ventilation. After two daily practice trials in which effects of NIPPV were tested, patients were instructed to perform non-invasive ventilation for at least five consecutive hours at night. At the end of this period patients were divided in the two groups according to the compliance to the ventilator treatment: they were allocated in the LTOT group if they showed no compliance to NNV or refused it. Lack of compliance was defined according to the patient's inability to use properly (subjective intolerance, excessive air leaks) the ventilatory device for the scheduled 5 h/night even on one night during the trial. No specific rehabilitation program was provided for either group during the follow-up period. When necessary,
changes in medical therapy of each patient were prescribed by physicians of our departments or by his/her general practitioner who was instructed to communicate to our departments.

VENTILATORY ASSISTANCE

Pressure support ventilation was delivered through a commercial nasal mask (Respironics, Murrysville, PA, U.S.A.) by means of a portable ventilator able to compensate for leaks (BiPAP, Respironics, Murrysville, PA, U.S.A.) (9,27). The ventilatory device was set during the daily practice attempt by an attending physician unaware of the study with the minimal inspiratory positive airway pressure (IPAP) able to achieve an expiratory tidal volume >8 ml/kg was considered as the normal reference value (IPAP ranged from 10 to 16 cm H₂ O). The expiratory positive airway pressure (EPAP) was set in order not to overcome the supposed intrinsic positive expiratory pressure (PEEP) of these stable patients (28) and ranged from 2 to 4 cm H₂O. Spontaneous-time mode with the adopted pressure support device was set with a back up respiratory frequency of 10 bpm. Patients of both groups continued LTOT as previously prescribed. In Group 1, supplemental oxygen during NNV was administered via a cannula attached to a side-port of the nasal mask at a FIO₂ able to achieve a baseline SaO₂ >92% which was also the target value for Group 2.

TREATMENT COMPLIANCE

Compliance to LTOT was assessed in the follow-up by measuring the weekly use and by interviewing the patients and their relatives. The time patients used the ventilator at home was assessed by interviewing them and their relatives and by controlling the device time-counter. Side effects due to the prolonged use of both oxygen and NNV were also recorded in the follow-up.

STATISTICS

Data are shown as mean ± SD. Differences within and between groups were tested by means of analysis of variance (ANOVA) with repeated measures. Post hoc analysis was performed when requested by ANOVA. A P value of less than 0.05 was considered to be statistically significant. Mortality was described by the Kaplan-Meier survivor analysis and the significance of differences in survival between groups were tested by log-rank test. Differences in frequency distribution were tested by means of χ² analysis.

Results

Twenty-one of the 49 patients (43%) were not compliant with or refused NNV, and were included in the control group (Group 2). Demographic, anthropometric and functional characteristics of patients in study are shown in Table 1. The two groups were not different for anthropometric and functional characteristics: they suffered from similar severity of airway obstruction and hyperinflation. Previous smoking habit and medical therapy did not differ between the two groups. 12 patients (six in each group) were on long-term B₂-agonists and five patients (three in Group 1 and two in Group 2), were taking oral theophylline. Number of patients who experienced NIPPV during acute exacerbation over 2 yr prior the study (20/28 and 14/21 patients in Groups 1 and 2 respectively) and the rate of related endotracheal intubation (5/20 and 3/14 patients in Groups 1 and 2 respectively) were similar in both groups.

An inverse significant relationship (r = -0.62; P<0.0001) was found between baseline PaCO₂ and δPaCO₂ under NIPPV. The practice daily attempts of NIPPV resulted in a mean 8% decrease in PaCO₂ in comparison with baseline level (9 and 6% decrease in Groups 1 and 2 respectively). All the patients of Group 1 and 18 out of 21 (85%) patients of Group 2 showed a decrease from the baseline PaCO₂ value. χ² analysis showed that this difference was not significant. NIPPV resulted in improvement in dyspnoea as assessed by VAS (−23 ± 12% and −16 ± 20% in Groups 1 and 2 respectively).

Mean duration of follow-up was 35 ± 7 months. In Fig. 1 the survival rates of the two groups evaluated by Kaplan-Meier analysis are shown. Mortality rate was not different between groups at any time (16, 33, 46% and 13, 28, 50% at 1, 2 and 3 yr in Groups 1 and 2 respectively).

In either group dynamic lung volumes, MIP and arterial blood gases did not significantly change over time. These parameters did not differ between groups at any time up to 3 yr. In Table 2 time course of arterial blood gases during the follow-up is shown. Dyspnoea sensation (Fig. 2) did not change over time in either group. The walked distance significantly increased (from 245 ± 78 to 250 ± 88, 291 ± 75, 1217

Table 1. Demographic, anthropometric and functional characteristics of patients in study

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Patients (n)</td>
<td>28</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>M/F</td>
<td>22/6</td>
<td>14/7</td>
<td>NS</td>
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<tr>
<td>Age (yr)</td>
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<td>NS</td>
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<tr>
<td>BMI</td>
<td>23 ± 4</td>
<td>23 ± 1</td>
<td>NS</td>
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<tr>
<td>Length of disease (yr)</td>
<td>9 ± 2</td>
<td>9 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁ (%pred)</td>
<td>31 ± 8</td>
<td>32 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>FVC (%pred)</td>
<td>57 ± 9</td>
<td>57 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>RV (%pred)</td>
<td>154 ± 24</td>
<td>159 ± 44</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁/FVC(%)</td>
<td>46 ± 15</td>
<td>47 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Dl,CO (%pred)</td>
<td>43 ± 13</td>
<td>47 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>MIP (cmH₂O)</td>
<td>42 ± 11</td>
<td>45 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO₂ (kPa)*</td>
<td>7.0 ± 0.6</td>
<td>6.8 ± 0.6</td>
<td>NS</td>
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<tr>
<td>PaO₂ (kPa)*</td>
<td>6.5 ± 0.9</td>
<td>6.4 ± 1.0</td>
<td>NS</td>
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<tr>
<td>Hospital admissions (n/pt/yr)</td>
<td>2.0 ± 0.6</td>
<td>1.9 ± 0.4</td>
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</table>

*Breathing room air.
Discussion

This study indicates that, in comparison to LTOT alone, the addition of NNV by PSV does not improve 3 yr survival but is able to increase the exercise tolerance and to reduce the rate of admission and endotracheal intubation in the ICU of severe COPD patients with chronic hypercapnia.

NIPPV has been gaining increasing popularity in the management of chronic respiratory failure. The benefit is more clearly demonstrated for chronic respiratory failure consequent upon non-obstructive conditions than for patients with COPD (10,12,16). Indeed results in COPD patients with hypercapnia are still discussed (13–15). Differences in patient selection (13–15) or in ventilation modalities (29), may explain different results. In this study PSV was used. This modality of ventilation is considered to be well tolerated for an overnight delivery on COPD patients (13,30,31) and compliance to the machine increases with prolonged use (32). The rate of refusal to the ventilator (43%) was similar to our previous experience on similar patients (17). Goldstein et al. (32) also found a difficult initial coping to the ventilator in 56% of in COPD patients.

The practice daily attempts of NIPPV resulted in a mean 8% decrease in $\text{PaCO}_2$ in comparison with baseline level in most of the patients and only three patients of Group 2 did not show any $\text{PaCO}_2$ improvement after 1 h: a relationship existed between benefit (in terms of $\text{PaCO}_2$ decrease) from NIPPV during practical attempt and the higher $\text{PaCO}_2$ value at baseline, however it was the same in both groups. The lack of significant difference in all baseline characteristics between the two groups is surprising and may suggest that other factors not specifically assessed in this study like psychological factors (e.g., claustrophobia), home environmental facilities, etc., may have influenced the compliance rate to NNV.

Survival proportion obtained from the Kaplan-Meier model in the two groups was similar (see Fig. 1) suggesting that NNV per se is not able to influence this outcome. The observed survival was also similar to that reported

<table>
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<tr>
<th>pH</th>
<th>Basal</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>$P$</th>
</tr>
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<tbody>
<tr>
<td>Group 1</td>
<td>7.37 ± 0.03</td>
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<td>7.38 ± 0.03</td>
<td>7.38 ± 0.02</td>
<td>n.s.</td>
</tr>
<tr>
<td>Group 2</td>
<td>7.38 ± 0.02</td>
<td>7.38 ± 0.02</td>
<td>7.38 ± 0.01</td>
<td>7.38 ± 0.01</td>
<td>n.s.</td>
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<th><em>$\text{PaCO}_2$</em> kPa</th>
<th>Basal</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>7.0 ± 0.6</td>
<td>6.9 ± 0.8</td>
<td>6.9 ± 1.1</td>
<td>6.8 ± 1.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Group 2</td>
<td>6.8 ± 0.6</td>
<td>6.5 ± 0.5</td>
<td>6.6 ± 0.8</td>
<td>6.7 ± 1.1</td>
<td>n.s.</td>
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<tr>
<th>$\text{PaO}_2$ kPa</th>
<th>Basal</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>6.5 ± 0.9</td>
<td>6.5 ± 0.9</td>
<td>6.9 ± 0.5</td>
<td>6.8 ± 0.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Group 2</td>
<td>6.4 ± 1.1</td>
<td>6.5 ± 0.5</td>
<td>6.8 ± 0.4</td>
<td>6.6 ± 0.4</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

No differences between groups at any time.

*Breathing room air.*
in COPD with chronic insufficiency undergoing LTOT (1,2).

In our study lung volumes and arterial blood gases did not change over time in either group. At difference with our study, Meecham-Jones et al. (14) found that diurnal \( \text{PaO}_2 \) and \( \text{PaCO}_2 \) significantly improved over a 3 month nocturnal non-invasive PSV. The range of IPAP of our study is slightly lower than used by Meecham-Jones et al. (14), but is similar to values reported by Lin (15), and by Gay et al. (33), two studies showing no significant effect of NNV in COPD patients. Strumpf et al. (13) with a IPAP adjusted to match patients' spontaneous breathing rate and to provide a 20–50% increase in resting minute ventilation and a reduction of at least 5 mmHg in end tidal \( \text{PCO}_2 \) (mean IPAP: 15 cm H\(_2\)O) did not show any change in arterial blood gases in a 3-month study. Values of IPAP like those used in our study have been shown to be able to reduce the electromyographic and mechanical activity of the diaphragm in stable hypercapnia COPD patients (7–9). Whether the difference with the study by Meecham-Jones et al. (14) has to be ascribed to the lower levels of IPAP used in our study remains to be elucidated. The proposed mechanism by which NNV may produce changes in respiratory function and/or diurnal blood gases in such patients remains controversial. In our patients undergoing NNV \( \text{PaCO}_2 \) showed a slight although not significant trend toward improvement over time (see Table 2). The lack of statistical significance may well be due to the relatively small sample size; nevertheless a lack of worsening in \( \text{PaCO}_2 \) all over a 3-yr period in patients on LTOT has been previously reported (34). Chronic hypercapnia may be considered as a consequence of a breathing pattern adopted as a means to unload respiratory muscles in COPD patients (35) although the rate of deterioration over time in \( \text{PaCO}_2 \) was found to be related to the necessity of ICU admissions (34). The hypothesis that chronic respiratory muscle fatigue could play a role in chronic \( \text{CO}_2 \) retention was not confirmed (36) and the role of intermittent rest of loaded respiratory muscles as one of the possible mechanisms through which NNV can improve daytime arterial blood gases and symptoms is still questioned (5). Elliott et al. (6) found no relationship between slight changes in MIP and changes in \( \text{PaCO}_2 \) in COPD patients undergoing NNV by means of volume-cycled ventilators. Also of interest is a randomised study of NIPPV versus sham in COPD (33). Patients in the active limb received inspiratory positive pressure of up to 10 cm H\(_2\)O; those in the sham limb received inspiratory pressure at the lowest possible level. No overnight monitoring of \( \text{SaO}_2 \) and \( \text{PaCO}_2 \) was carried out. Results showed that NIPPV offered no improvement in arterial blood gas tensions, sleep efficiency and exercise tolerance over the sham group. In our study forced lung volumes (as expressed as % of predicted) remained unchanged despite the use of NNV, this is in agreement

![Graphical representation](image-url)
with previous studies over shorter follow-up (6,16,17). Deterioration of lung volumes in COPD is expected over years (37,38), nevertheless the lack of significance over 3-yr changes in $FEV_1$ (from $895 \pm 310$ to $830 \pm 303$ and from $855 \pm 304$ to $744 \pm 202$ ml in Groups 1 and 2 respectively), as in the present study, may be due to the low baseline absolute values at the beginning of the study.

In our study the result improvement in the 6-min walk test only in patients under NNV (Fig. 2, bottom) might be ascribed to a learning or a motivation effect. In particular, the different methodology assessed to test the 6-min walk during the follow-up (one test compared to three tests on two consecutive days at baseline) could have favoured only the most motivated and compliant patients. However, the operator performing the tests during the follow-up was not involved in the study as the 6-min walk test is a routine measurement we perform in our outpatients. Indeed, another measurement prone to be influenced by motivation and learning that is MIP did not improve in either group. Indeed at variance with our previous report (17), we failed to demonstrate any significant improvement in MIP in the ventilated group. Previous studies (12,14) showed no improvement in MIP in COPD patients using NNV. The longer duration of the present study could have balanced the effect of shorter observation in respiratory muscle strength. Dyspnoea sensation was unchanged over time in both groups (Fig. 2, top). In short (8) and medium-term (13) trials of NNV in COPD, dyspnoea measurements showed conflicting results. Our results could have been influenced by the kind of scale we used. Indeed dyspnoea scale of the ATS may not prove to be the ideal indicator of therapy response as other (i.e. Borg or visual analogue scale) because of its narrow range (24).

The main positive clinical result in this study was the significant decrease in the rate of IA compared to the follow-back period observed only in NNV patients (Fig. 3). This observation is in agreement with our previous preliminary study (17): at variance with that experience, in this study patients of both groups were initially similar for the clinical severity and the number of hospitalisations. Nevertheless, HS significantly decreased in both groups (Fig. 3). Indeed, the reduction in hospital stay of both groups may be due to the increased follow-up period. Other studies (3,5) suggested a reduction in number of hospitalisations of ventilated COPD over a period of 2 yr indicating a possible cost saving effect. Our study, confirming our previous results (17), is the first to show an improvement in the quality of hospitalisation (reduction in IA and endotracheal intubation rate) in severe COPD under NNV over a period of more than 2 yr. This result deserves a comment. Due to the historical way to collect information on IA, this results could be considered as a soft outcome measure. Nevertheless, decision for admitting and treating patients in the ICUs was taken by physicians not aware of the study. It can be argued that it is possible that there was a lower threshold

| TABLE 3. Side effects associated with NIPPV |
|-----------------|-------|---------|
| Nasal skin lesion | 6 | 21 | |
| Gastric distension | 4 | 14 | |
| Rhinorrhea | 4 | 14 | |
| Mucosal dryness | 2 | 7 | |
| Skin inflammation | 1 | 4 | |
| None | 11 | 40 | |
for admitting LTOT patients to the ICUs whereas patients on NNV where deemed not to need it because they were already receiving ventilatory support. Due to this consideration we cannot speculate that NNV has improved pathophysiological condition so to reduce the physiological need of IA. However, independently of the mechanism underlying this result, as a matter of fact the use of NNV resulted in a lower rate of endotracheal intubation and related life threatening complications (39).

In Group 1, NNV was used 7.4 ± 1.3 h/night and it was associated with side effects in most of patients (Table 3) but none of them had to discontinue the treatment. The long night use of NNV is not surprising: indeed Goldstein et al. (32) found in six out of nine COPD patients selectively used NIPPV during the night and the mean duration of use in patients including COPD was 9 ± 2 h/day. Side effects are comparable with those of Meecham-Jones et al. (42): also in that study the major problem was the skin abrasion/ulceration over the nasal bridge.

Our study was prospective, without limitations of an historical comparison (40), nevertheless it has some important limitations. The patients were not randomised and controls were selected according to the compliance/refusal to the ventilator: therefore, we cannot exclude that a better clinical outcome was observed in the most motivated patients. The sample size is small, without the power necessary to detect differences between groups in outcome measures: an analysis to define a priori primary outcome measures was not performed. With these limitations and although the reduced rate of IA and endotracheal intubation may be very useful, our data on survival do not justify a generalised use of NNV by pressure ventilators in stable hypercapnia COPD. Encouraging results are coming from the preliminary results of a large prospective and randomised European multicentre study performed using volume-cycled ventilators and nasal industrial masks. In that study, the first actuarial survival analysis showed a trend towards a positive impact of NNV which at the moment of observation did not reach statistical significance (41).

In conclusion, the addition of NNV to LTOT in compliant COPD patients with chronic hypercapnia does not improve survival but significantly reduces ICU admissions and slightly improves exercise capacity, prompting the need for further randomised studies.

Acknowledgement

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