Outcome at three months of COPD patients with acute hypercapnic respiratory failure treated with NPPV in an Acute Medicine Ward

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ABSTRACT

Noninvasive positive pressure ventilation (NPPV) is increasingly used for patients with hypercapnic respiratory failure secondary to acute exacerbation of chronic obstructive pulmonary disease (COPD). NPPV has been shown to improve arterial blood gas tensions and dyspnoea and to prevent the need for intubation in patients admitted to hospital with an exacerbation of COPD associated with respiratory acidosis. Although advantages of NPPV over conventional treatment have been convincingly documented in the short period, there are fewer data as to the outcomes following hospital discharge. We have undertaken a prospective descriptive study to obtain comprehensive data on the in hospital and 3 month outcomes of a cohort of 57 COPD patients treated with NPPV for acute hypercapnic respiratory failure as a first intervention in addition to usual medical care. Patients with a COPD exacerbation had better outcomes than patients with COPD complicated by other acute conditions. Pneumonia was specifically associated with a higher in-hospital risk of death. In our series about one in four patients with an indicator of previous severe respiratory disease (past admission for acute respiratory failure, previous use of NPPV, long term oxygen therapy or home NPPV) was dead at three months after discharge and almost one in two was dead or had been readmitted.
On the contrary, patients without indicators of previous severe respiratory disease benefited from NPPV during an acute episode of respiratory failure and had a chance of approximately 80% of being alive and free from recurrence at three months.

Introduction

Patients with chronic obstructive pulmonary disease (COPD) may have recurrent episodes of respiratory failure, often resulting in admission to hospital. Conventional treatment comprehends adequate continuous oxygenation and treating the cause of the exacerbation—usually with bronchodilators, corticosteroids, and antibiotics. Traditionally, patients who do not respond to conventional treatment are given invasive ventilation. This procedure, though often inevitable, may be associated with significant morbidity. Common side effects of invasive ventilation are tissue damage caused by the intubation procedure, ventilator associated infections, difficult weaning with prolonged stay in intensive care unit (ICU). Noninvasive positive pressure ventilation (NPPV) is an alternative treatment for patients with hypercapnic respiratory failure secondary to acute exacerbation of COPD that are admitted to hospital. With NPPV the patient receives air or a mixture of air and oxygen from a ventilator through a full facial or nasal mask, thus unloading fatigued muscles and improving ventilation..
Observational studies and randomised controlled trials in patients admitted to hospital with an exacerbation of COPD associated with respiratory acidosis have shown NPPV to improve arterial blood gas tensions and dyspnoea and to prevent the need for intubation (1-15). Furthermore NPPV is associated with fewer complications than tracheal intubation (16), allows patients to eat and to speak and can be employed outside ICUs. In 2003 a Cochrane systematic review stated that NPPV should be the first line intervention in addition to usual medical care to manage respiratory failure secondary to an acute exacerbation of COPD in all suitable patients (17). According to the results of this meta-analysis NPPV should be tried early in the course of respiratory failure and before severe acidosis, to reduce mortality, avoid endotracheal intubation, and decrease treatment failure.
Although advantages of NPPV over conventional treatment have been convincingly documented in the short period, there are fewer data as to the outcomes following hospital discharge. Infact some patients have such a marginal respiratory reserve that even trivial exacerbations are sufficient to provoke life threatening ventilatory failure bringing them back to hospital. It is quite possible that NPPV, while saving these patients from an acute episode, condemns them to a future life of poor quality at home, punctuated by recurrent admissions to hospital. It is also possible that the subgroup in which death is avoided is a high risk group who will die shortly after discharge in association with another exacerbation. If this occurs, the appropriateness of offering NPPV in the first place might be questioned.
Only a few studies have evaluated long term outcomes in patients with COPD treated with NPPV for acute hypercapnic respiratory failure (AHRF). Some of the studies to date have enrolled small numbers of patients and their focus has been usually limited to survival (18, 19). Not much is known about the risk factors for poor long term survival and for other negative outcomes such as recurrent AHRF requiring repeated NPPV or intubation. However, the few studies that reported a wider set

of outcomes, documented that patients with COPD and AHRF who survive following treatment with NPPV have a high risk of readmission and life threatening events in the following year (20, 21).
We have undertaken a prospective descriptive study to obtain comprehensive data on the outcomes of a cohort of COPD patients treated with NPPV for AHRF in hospital and at 3 months following discharge. These include readmission, recurrent AHRF, and death. Our series of patients differs from other published series since the setting of treatment is an acute medicine ward rather than an intensive or sub-intensive dedicated unit. Favourable results in this setting would make NPPV an even more interesting alternative to conventional therapy because of lower costs and easier availability.

Materials and methods

From November 2007 to June 2008 we have included in our study all consecutive patients admitted to our *Medicina d'urgenza* (1 nurse / 8 beds) for AHFR due to any cause, if they had a history of COPD diagnosed according to the American Thoracic Society/European Respiratory Society guidelines (22). AHRF was indicated by a pH of less than 7.35 with an arterial carbon dioxide tension (PaCO2) >.45 mm Hg (6 kPa) and a PaO2 of <60 mm Hg (8 kPa) on room air. NPPV was started on all patients as a trial to prevent intubation, or as the ceiling treatment in patients who were not considered fit for invasive ventilation. NPPV was considered as a failure when one or more of the following were present after 2-6 hours of treatment: worsening of symptoms, non improvement of arterial blood gases, patient's intolerance of the procedure. In case of failure, and when intubation had not been excluded as a therapeutic possibility, the appropriate clinical decisions were taken in accordance with an intensive care physician.
All patients with an exacerbation of COPD received standard medical treatment with inhaled bronchodilators (salbutamol and ipratropium), prednisolone, antibiotics if there was increased sputum volume and purulence (amoxicillin/clavulanate or levofloxacin). Patients with pneumonia were treated initially with combined antibiotic therapy (ceftriaxone and azitromicine or ceftriaxone and levofloxacin). Standard doses of diuretics and vasodilators were used in patients with heart failure.
NPPV was initiated by trained nurses after the physician's indication according to a standardised protocol. A respiratory physiotherapist or a nurse remained at the bedside during the initial period of acclimatisation. A Vela (Viasys Healthcare) respirator was used to provide pressure support ventilation. Positive end expiratory pressure (PEEP) was titrated upwards from 4 cm H2O to allow effective triggering. Pressure during inspiration was titrated to reduce respiratory distress, targeting a respiratory rate of 25 breaths/min and a tidal volume of 7–10 ml/kg. The fraction of inspired oxygen (FiO2) was titrated to target pulse oximetry oxygen saturation (SpO2) between 90 and 95%. The rise time was set to optimise the patient's comfort. Interfacing with different types of nasal or full face masks was individualised according to nursing assessment, with particular attention paid to leakage, mouth breathing, and pressure over the nasal bridge. NPPV was used for as many hours as possible in the first day with interruptions for food, drinks, communication, when necessary. If improvement occurred, the duration of NIV was gradually reduced. A respiratory physiotherapist offered technical support to nurses on a daily basis.
NPPV was continued at home in patients who still needed NPPV after 7 days, or showed persistent low pH values, according to recognized international guidelines (23).
Patients who survived to discharge were followed at three months with a telephone call and a search in the hospital data base to identify new events causing readmission or death. New episodes of AHFR, use of NPPD or intubation were recorded. For each patient a set of data potentially related with a negative outcome was collected. More specifically the following were recorded: severe comorbidity, home NPPV or long term oxygen therapy (LTOT), hospital admissions for AHRF and use of NPPV in the previous 12 months.

Results

During the 8 month study period, 92 patients underwent NPPV in our General Medicine Ward.
Of these, 57 had a previous diagnosis of COPD (36 men and 21 women with a mean age of 73.7).
The baseline characteristics of patients with COPD are shown in Table 1.
Among patients with a previous diagnosis of COPD the most frequent cause of AHRF was COPD exacerbation (35 cases), followed by pneumonia (13 cases), pulmonary oedema (4 cases), OSAS (3 cases) and sepsis of non respiratory origin (2 cases). Fifteen patients (26.3%) died before discharge. In the group of patients who died in hospital, the cause of AHRF was pneumonia in 7 cases, exacerbation of COPD in 5, sepsis of non respiratory origin in 2 and pulmonary oedema in 1. In hospital mortality was 53.8% in patients with pneumonia and only 14.2% in patients with COPD exacerbation and no radiological evidence of lung consolidation (Table 2).
Only 2 of the 15 patients who died underwent OT intubation

Table 1
Baseline characteristics of the cohort of COPD patients admitted for AHRF

Number of patients	57
Sex (M:F)	36:21
Age (mean)	73.7(+9)
LTOT before index event	24 (42.1%)
Past history endotracheal intubation	3 (5.3%)
Past history of treatment with NPPV	16 (28.1%)
At least 1 admission in the past 12 months for AHRF	21 (36.8%)
Comorbidity (liver or renal failure, diabetes, active neoplasm, congestive heart failure)	47 (82.5%)
Evidence of pneumonia at chest X-rays	13 (22.8%)

Table 2
Cause of AHRF and death rates in the group of COPD patients

Main cause of AHRF	N. Patients	Death rate
COPD exacerbation	35	5 (14,2%)
Pneumonia	13	7 (53,8%)
Pulmonary oedema	4	1 (25%)
OSAS	3	0
Sepsis of non respiratory origin	2	2 (100%)
Total	57	15 (26,3%)

Table 3

Outcome at 3 months for patients who were discharged alive (according to respiratory history).

		Total (42)	Alive and not readmitted (30)	Dead (7)	Dead or readmitted (12)
AHRF in past 12 mths					
	YES	15	9 (60%)	3 (20%)	6 (40%)
	NO	27	21 (77,7%)	4 (14,8%)	6 (22,2%)
Previous NPPV					
	YES	15	8 (53%)	4 (26,6%)	7 (46,6%)
	NO	27	22 (81,4%)	3 (11,1%)	5 (18,5%)
Home LTOT/NPPV					
	YES	18	10 (55,5%)	5 (27,7%)	8 (44,4%)
	NO	24	20 (83.3%)	2 (8.3%)	4 (16.7%)

and were transferred to ICU before death. In the remaining 13 cases intubation was either not indicated or had been excluded by a DNR order. None of the patients who left the hospital alive needed intubation.

NPPV was continued at home in 24 patients with COPD, 16 of which had a diagnosis of mixed COPD/OSAS disease.

Follow up was done at three months for the entire cohort of 42 patients who survived to discharge. For each patient the hospital data base was reviewed for new admissions and patients or their family were contacted by telephone. During the follow up period 12 patients (28%) were readmitted to hospital, 7 of which (16%) died for a new episode of respiratory failure.

Risk of death or readmission for recurrent respiratory failure was separately evaluated for the subgroups of patients with characteristics found by other studies to be associated with a worse outcome (age >80, severe comorbidity, admission for respiratory failure in the past 12 months, previous treatment with NPPV, home LTOT or NPPV).

Age was not an indicator of worse outcome in our cohort since the 8 patients > 80 were all alive at a 3 month follow up, only 2 having been readmitted for recurrence of respiratory failure. Also the presence of comorbidity could not be associated with prognosis, mainly in consideration of the fact that relevant comorbidities were present in the great majority (>80%) of the patients studied.

On the contrary, an association with death or readmission was clearly evident for each of the three descriptors of COPD severity. Infact, admission for AHRF in the past 12 months, previous NPPV, home LTOT or NPPV doubled or more than doubled the risk of death and of the composite outcome of death and readmission (Table 3). Nevertheless, due to the limited numbers, significance was reached only for previous NPPV and home LTOT/NPPV and for the composite outcome of death or readmission (Table 4).

Table 4

Independent risk factors for adverse outcomes following discharge (statistical significance calculated with Fisher's exact test)

	Alive vs dead P value	Alive and at home vs dead or readmitted P value
Age > 80	n.s.	n.s.
Significant comorbidity	n.s.	n.s.
AHRF previous 12 mths	n.s.	n.s.
Previous NPPV	n.s.	0,05
Home LTOT / NPPV	n.s.	0,05

Discussion

Noninvasive positive pressure ventilation (NPPV) is being increasingly used in the treatment of acute respiratory failure, with the aim of reducing potential complications associated with endotracheal intubation. Such effect may have an associated beneficial role in reducing mortality and hospital length of stay.

A consistent number of studies and at least two meta-analyses (17, 24) have shown a significant reduction in mortality and need for mechanical ventilation which was particularly evident in patients with COPD. Positive effects of NPPV have been demonstrated also for pneumonia (25) and other respiratory diseases, although data are more scanty and controversial. While there is little doubt that NPPV improves the short term outcome in COPD patients with AHRF, its benefit in the long term is more questionable. The need to know more on the prognosis after discharge of COPD patients treated with NPPV is particularly strong since this technique has become available in general wards, where it could be used for patients that would not have been traditionally considered for admission to an ICU because of poor general conditions and a perceived negative prognosis in the short term. Infact, the appropriateness of offering NPPV in the first place could be questioned in patients whose risk of death, relapse or low quality of life after hospital discharge is particularly high.

Among the studies that have explored the problem, the most complete and informative was conducted in 2004 by Chu *et al.*(21), who followed for a year after discharge patients who had survived an exacerbation of COPD treated with NPPV in a non-invasive ventilation unit. At the end of the follow up period 79.9% of patients had been readmitted, 63.3% had had another life threatening event, and 49.1% had died. Survivors spent a median of 12% of the subsequent year in hospital.

The study also identified clinical factors that predicted an increased probability of the various adverse outcomes. Factors associated with poor outcomes were: admission to hospital in the past year, low Activities of Daily Living (ADL) score, home LTOT, low BMI, high Apache II score, and high MRC dispnoea score. These variables indicate severity of disease or poor chronic health. In particular BMI has been included as a marker of poor prognosis in other studies on COPD patients (26). Chu *et al* conclude that COPD patients surviving an episode of AHRF treated with NPPV have a high risk of readmissions, life threate-

ning events and death for the same problem within a year after hospital discharge. They also conclude that further studies are necessary to devise strategies to reduce adverse outcomes in this group of patients.
In a randomized controlled trial that enrolled 236 patients, Plant *et al.*(20), showed that survival at one year in patients treated with NPPV (62%) was not significantly better than in the control group (58%). Survival curves converged after three months, suggesting that the benefit of NPPV was mainly that of improving survival during the exacerbation itself. Nevertheless, the median survival of about 15 months was not considered sufficiently poor to render futile or inappropriate NPPV treatment in the acute phase.
Confronting long term outcome between patients treated with intubation vs. NPPV has not been the subject of formal studies, mainly in consideration of the complexity of factors that determine the choice of the ventilation modality more indicated for each patient.
Considered the unsatisfactory long term prognosis of patients ventilated for AHRF, very few studies have turned to investigate instruments and interventions with a potential to prevent and reduce AHRF relapses and the related life threatening events.
For the time being the most convincing evidence stems from studies conducted on COPD patients irrespectively of a history of AHRF episodes. In this setting LTOT is probably the only treatment widely recognized to improve survival (27, 28). The role of chronic treatment with inhaled corticosteroids is more controversial (29).
Long term home NPPV has also been the subject of investigation. Jones *et al* (30) have observed a low rate of readmissions in a small cohort of 11 patients treated with long term NPPV after an episode of AHRF. Similarly Tuggey *et al* (31) have proposed an association between home long term NPPV and reduction in hospital and ICU readmissions, with a significant cost containment in a selected group of COPD patients with recurrent admissions requiring NPPV. Also a randomized controlled trial conducted in Italian centers (32) showed a statistically significant improvement in daytime PaCO2 in the NPPV group and non significant trends towards reduced hospital and ICU admissions.
Most recently, in a prospective controlled non randomized study of a cohort of chronically hypercapnic COPD patients, Tsolaki *et al*. (33), showed that the addition of home NPPV to maximal pharmacological treatment determined an improvement in gas exchange, symptoms and quality of life over a one year period. Readmissions and survival were unaffected, though there was a trend towards a shorter length in hospital stay.
We think that our study, though lacking the numbers and statistical power necessary to improve upon the knowledge already available, may be of interest for some peculiar aspects. In the first place we enrolled a cohort of patients who shared a history of COPD, but had various causes underlying the presenting episode of AHRF. This was done by other groups which compared in-hospital prognosis of patients treated with and without NPPV, but not by the major studies considering post discharge prognosis. Although this choice may limit the homogeneity of the sample, it gives a more realistic picture of the generality of patients that undergo NPPV for AHRF in common practice. A second novel aspect is the setting of treatment (at variance with dedicated ICUs or sub-intensive units of respiratory medicine where most published data have been produced) in an acute medicine ward (Medicina d'Urgenza), similar in many aspects (notably for staffing resources) to most general medicine wards of Italian hospitals.
In our series, acute mortality during the index episode for patients with AHRF due to COPD exacerbation (14.2%) was comparable to that reported by other studies (20,21,24). The same holds true for the larger group of patients with AHRF of mixed aetiologies (24) although this data may obviously be influenced by a different mix of patients. This suggests that NPPV may produce adequate results even when used outside an ICU, in wards with a lower nurse to patient ratio, as long as the staff is adequately formed and standard protocols are employed.
The particularly high mortality in patients with AHRF due to pneumonia (53.8%) confirms that these patients should be considered as early candidates for endotracheal intubation and treatment in the ICU. Yet NPPV can be employed as a ceiling treatment for patients not considered for intubation because of poor general conditions and bad short term prognosis. In our series 6/14 patients with pneumonia had been considered not eligible for intubation before NPPV was started. Only 2 patients who died of pneumonia and none of those who survived were intubated at any time during their hospital stay.
At three months our study shows a mortality of 16% and a composite outcome of mortality and readmission for AHRF of 28% which is difficult to compare, but not at variance with, the results of the two major studies that investigated outcome documenting a mortality of 38-49% and a readmission rate of 79% at 12 months.
Moreover, our study confirms that the severity of the respiratory condition, as indicated by past admission for AHRF, previous use of NPPV or home LTOT or NPPV, is associated with a higher risk of death or readmission after discharge from the index episode. In our series, about one in four patients with an indicator of severe respiratory disease was dead at three months after discharge and almost one in two was dead or had been readmitted.
It is difficult to derive from these data an indication as to which patients with COPD should be treated with NPPV in addition to standard medical treatment. It is clear that patients without a history of previous mechanical ventilation or LTOT have a good chance of benefiting from NPPV during an acute episode of respiratory failure and of being alive and free from recurrence at three months. It is also clear that the 50% chance of being in a similar condition (although likely with a worse performance status) that characterizes patients with a more severe history of respiratory failure is not poor enough to exclude them from an attempt with NPPV, particularly in consideration of the fact that NPPV is associated with improvement of symptoms and a relatively low incidence of complications. The use of NPPV outside an ICU is a growing reality in acute medicine wards and in other general medicine wards in Italy as well as abroad, widening the opportunity to offer non invasive ventilation at a lower economical and organizational cost. In COPD patients considered unsuitable for intubation, reasons to withhold NPPV in the course of AHRF should probably be limited to the well known general contraindications, to patients' unwillingness or intolerance, or to failure in improvement after adequate attempts.
Even in the absence of further studies, it is evident that frequent readmissions and life threatening episodes are markers of a very poor quality of life, which could render NPPV futile in selected cases and make the decision not to employ it a compassionate one. For this reason more studies are needed to better evaluate interventions capable of improving prognosis by reducing exacerbations and readmissions after an acute episode of respiratory failure. Long term home NPPV is a promising opportunity that deserves to be further investigated (34).

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