Original Article

Noninvasive ventilation for hypercapnic respiratory failure in COPD: Encephalopathy and initial post-support deterioration of pH and $PaCO_2$ may not predict failure

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Abstract

Objectives: To correlate the degree of encephalopathy, baseline values of $PaCO_2$ and pH, and their early response to NIV with eventual in-hospital outcome in patients of severe acute-on-chronic hypercapnic respiratory failure in COPD. **Design:** Retrospective review. **Setting:** Intensive care unit. **Material and methods:** 24 episodes of acute exacerbation of COPD in 17 patients (10 females, 7 males) with a mean age of 59.5 years (range 48 – 82) where NIV was initiated. Data collected: encephalopathy score at baseline and at 24 hours, respiratory rate, breathing pattern, serial arterial blood gases, duration of NIV support per day and hospital days. **Results:** All patients had severe hypercapnia (mean peak $PaCO_2$ 89.0 mm Hg ± 21; range 66-143), respiratory acidosis (mean nadir pH 7.24 ± 0.058, range 7.14 – 7.33) and tachypnoea (mean respiratory rate 29.5 ± 4.69/mt; range 24 – 40). In 17 episodes, altered mental state was present (encephalopathy score 1.92 ± 1.32, median 2.5). Clinically stable condition occurred over several days (mean 13± 9.6 days; range 5 – 40). Intubation was avoided in 22 out of 24 episodes (91.6%) despite significant initial worsening of $PaCO_2$ and pH. Two patients died. The mean time on NIV was16.5 hours/day (range 4 – 22). **Conclusions:** In selected patients of COPD with acute hypercapnic failure on NIV worsening $PaCO_2$ and pH in the initial hours may not predict failure provided the level of consciousness and respiratory distress improve.

Key Words: Positive pressure ventilation, Noninvasive ventilation, Chronic obstructive pulmonary disease, Respiratory failure, Hypercapnia, Mechanical ventilation

Introduction

It is now well established that most patients of COPD with respiratory failure due to acute exacerbation should receive a trial of NIV.[1] Recent metaanalyses of 8 and 15 randomized controlled studies respectively[2,3] showed that, compared with usual care, adjunctive NIV therapy was associated with improvements in mortality, need for intubation, values of pH, $PaCO_2$ and respiratory rate at 1 hr., complication rates and length of hospital stay.

While early use of NIV is recommended, concerns exist that delay in detecting failure may increase mortality.[4,5,6] Current opinion favors switching to endotracheal mechanical ventilation (ETMV) in the event of deteriorating pH, $PaCO_2$ and persistence of altered sensorium despite initial use of NIV.[7,8,9]

Review of our early experience with NIV in India was prompted by current recommendations in literature at

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variance with our observations. In the last decade, when the full scope of this form of support was relatively unexplored, we found remarkable success with severe exacerbations of COPD where there was no prompt initial response to NIV. The threshold for intubation in our group of patients was higher than in current recommendations. Our later practice was conditioned by key publications in subsequent years that cautioned against delaying intubation and by our growing experience with more aggressive support. This account of our early experience is to stimulate further exploration of predictive factors relating to success with NIV in subsets of COPD patients presenting with severe respiratory acidosis.

Current Indian experience on the use of NIV in COPD patients is limited to a single abstract.[10]

Materials and Methods

Patients of COPD managed by one team who received NIV between August 1994 and July 1996 at Batra Hospital and Medical Research Centre, New Delhi, India.

Care was initiated in the intensive care unit with NIV at admission within a few hours of admission. Standard care included oxygen supplementation, corticosteroids, bronchodilators, antibiotics, rehydration and correction of electrolyte disturbances.

Patients included

The study included patients receiving NIV for acute exacerbation of COPD (based on clinical criteria) in the following circumstances: dyspnoea with respiratory rate (R/R) of >25/mt $PaCO_2$ of > 60mm Hg and / or arterial pH <7.35;acceptance of NIV; altered sensorium, but not deep coma (encephalopathy score < / = 3)

Patients excluded

Following patients of COPD were considered unsuitable for NIV: respiratory arrest, haemodynamic instability; deeply comatose patient (encephalopathy score > 3); pneumonia; excessive secretions or inability to clear secretions; severe sepsis. Patients of COPD with comorbidities such as obstructive sleep apnea, acute-on-chronic renal failure, left ventricular dysfunction, hepatic failure, trauma, neurological diseases receiving NIV were excluded.

Ventilators and interface

NIV was applied with either BiPAP STD (Respironics Inc., USA) or Servo 900 B (Siemens, Sweden) volume ventilator. Only nasal masks were used as well-fitting orofacial masks were unavailable; a good fit and minimal leak were ensured by using a range of mask size and head gear. Chinstraps were used where necessary. "Band-aid" local dressing was applied over bridge of nose at the earliest sign of erythema. Forehead cushions were routine. Nasogastric tubes were not used.

Mode and settings

In most patients bilevel pressure support was applied in the 'S/T' mode. Inspiratory and Expiratory positive airway pressure (IPAP and EPAP) were adjusted thus: EPAP was first adjusted to improve arterial oxygen saturation to above 90% and then to improve triggering. A minimum EPAP of 4 cm. H_2O was applied in most patients (19 out of 24 episodes). IPAP was then increased in steps of 2 Cms.H_2O depending on blood gas measurements and patient tolerance. Timed breaths of 12 - 15 breaths/min were used as 'back up' ventilation during night time support when hypercapnia was difficult to control. A few patients received NIV with a volume ventilator as portable bilevel pressure ventilators were unavailable. The tidal volume in the latter situation was set at 10ml/kg and the rate set at 12 breaths /minute [Table 1].

Duration of support

NIV was applied continuously for as many hours/day as tolerated until sensorium returned to normal, comfort was restored, and blood gas measurements stabilized. Masks were removed for feeding and toilet.

Intubation criteria

NIV failure was recognized if there was: deteriorating level of consciousness after 2 hours of support, hemodynamic instability, persistent hypoxemia <88% despite high-flow oxygen supplementation (>10 l/min through ventimask), exhaustion and inability to synchronize with NIV and vomiting or upper gastrointestinal haemorrhage. Late failure requiring intubation was identified when sensorium or dyspnoea worsened despite increasing NIV support for 2 hours after the change in clinical status. Biochemical deterioration alone (i.e., rising $PaCO_2$ and fall in pH) without clinical deterioration was not an indication for intubation.

Measurements

Respiratory rate, heart rate, arterial blood pressure,

Table 1: Patient characteristics (24 episodes)

Patient Age/Sex	R/R at admission	Conscious State admission (enceph alopathy score)	$PaCO_2$ (mm Hg)		pH (mm Hg)		No of Days to Discharge	Mode of Ventilation	Max. ventilator settings (IPAP / EPAP where BiPAP was used)
			Baseline	Peak	Baseline	Nadir			
68M	24	Agitation[3]	63	70.9	7.252	7.232	11	BiPAP	14/4
69F	29	Drowsiness[3]	71	79.4	7.375	7.275	5	BiPAP	16/8
70F	32	Agitation[3]	79.4	143	7.335	7.141	20	BiPAP	17/2
57F	28	Stupor[3]	75.9	110.6	7.302	7.16	30	BiPAP	14/3
57F	28	Alert[0]	82.2	82.2	7.312	7.309	29	BiPAP	15/4
57F	30	Agitation[3]	85.3	87.6	7.454	7.319	8	BiPAP	14/7
65F	28	Agitation[3]	53.5	69.8	7.296	7.277	10	BiPAP	14/3
65F	40	Agitation[3]	57	78.5	7.406	7.275	9	BiPAP	16/6
50F	25	Disorientation[2]	91	130.8	7.272	7.219	40	BiPAP	16/8
48M	30	Alert[0]	63.2	66	7.240	7.240	12	BiPAP	20/8
75F	24	Agitation[3]	66	83	7.392	7.227	13	BiPAP	14/6
71M	32	Drowsiness[3]	59.6	67.9	7.357	7.227	Died after intubation	BiPAP	14/6
44M	25	Alert[0]	72.3	108.6	7.308	7.213	7	BiPAP	20/8
73F	40	Drowsiness[2]	50.2	99.7	7.378	7.295	Died	BiPAP	14/4
60F	32	Alert[0]	53.1	64.7	7.247	7.247	5	BiPAP	8/3
62M	32	Agitation[3]	78.3	86.3	7.32	7.20	257	Servo B Volume Ventilator	CMV TV900cc Ventilator R/R 12/mt
68F	38	Alert[0]	51.4	81.0	7.298	7.249	7	Servo B Volume Ventilator	CMV TV600cc R/R 12/mt
50M	28	Disorientation[2]	56.6	74.0	7.251	7.14	12	BiPAP	20/14
82F	28	Stupor[3]	66	69.8	7.47	7.339	9	BiPAP	12/4
48M	30	Stupor[3]	88	96	7.37	7.218	8	Servo B Volume Ventilator	CMV TV1000cc R/R 12/mt
57F	29	Disorientation[2]	60.3	112.3	7.351	7.203	7	BiPAP	16/4
57F	25	Disorientation[2]	98.6	110	7.229	7.194	7	BiPAP	14/4
65F	30	Alert[0]	46.5	91.0	7.347	7.22	7	BiPAP	16/6
62M	25	Alert[0]	64.5	67.9	7.358	7.33	5	BiPAP	20/10

Abbreviations: R/R: Respiratory Rate / minute;BiPAP: Bilevel Positive Airway Pressure; IPAP: Inspiratory Positive Airway Pressure (cms of H_2O); EPAP: Expiratory Positive Airway Pressure (cm H_2O); CMV: Controlled Mandatory Ventilation; TV: Tidal Volume.

continuous pulse oximetry, encephalopathy score, hourly temperature and urine output.

The mental state was scored from 0 – 4 (modified Parsons-Smith criteria) (11) for encephalopathy: grade 0 – no abnormality; grade I – trivial lack of awareness, anxiety, shortened attention span; grade 2 – lethargy, tremor, asterixis, disorientation, personality change, inappropriate behaviour; grade 3 – somnolence to semistupor, responsive to stimuli, confused, gross disorientation and agitation; grade 4 – coma.

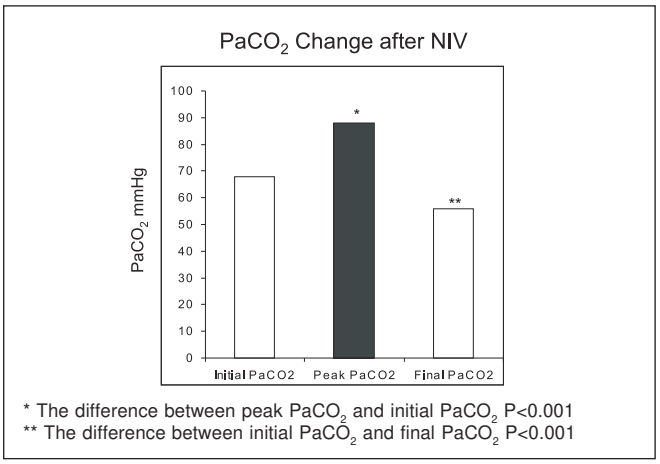
Blood gases were measured at 1 hour and 3 – 8 hours after application of NIV and every morning thereafter, or if there was clinical deterioration. Both baseline $PaCO_2$ and pH values and their worst values in the clinical course were recorded. Oxygen supplementation was given to all patients starting at 1-2L/mt adjusting flow to maintain SPO_2 of 88-92%.

Biochemical tests conducted at admission and thereafter periodically included: blood sugar, renal profile, electrolytes and liver function tests. Chest X-rays were performed daily in the initial unstable period.

Success or Failure of NIV

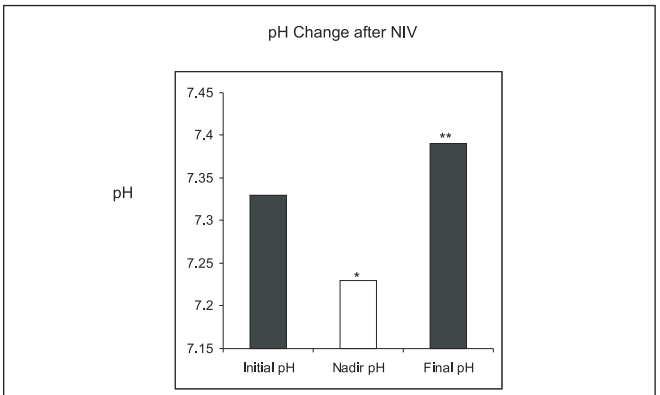
NIV was deemed successful if:

1) Patient was discharged without intubation after at least two days of clinical (alertness with no dyspnea) and biochemical stability (pH>7.35, $PaCO_2$ 55-65 mmHg) without support.
2) Patient was discharged from hospital to continued nocturnal NIV home support without intubation after at least two days of clinical and biochemical stability.



* The difference between peak $PaCO_2$ and initial $PaCO_2$ P<0.001
** The difference between initial $PaCO_2$ and final $PaCO_2$ P<0.001

Figure 1: $PaCO_2$ Trends in patients treated with NIV



* The difference between nadir pH and final pH P<0.001
** The difference between nadir pH and Final pH P<0.001

Figure 2: The pH trends in patients treated with NIV

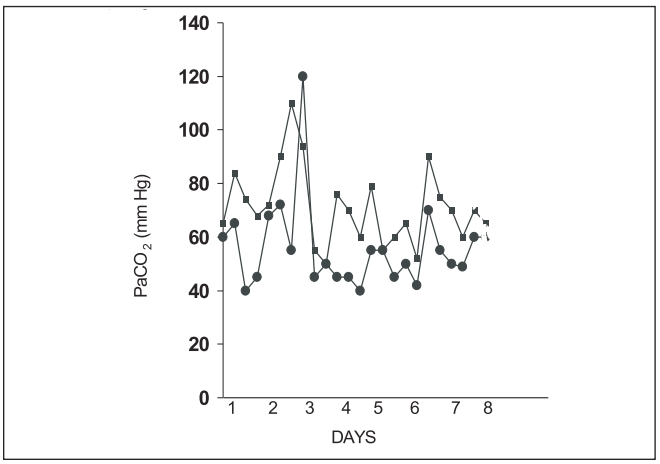


Figure 3: The course of $PaCO_2$ in 2 patients where the peak $PaCO_2$ was more than 100 mm Hg

Statistical analysis

statistical analysis was performed using the Wilcoxon Signed Ranks test for non-parametric data.

Results

During the study period, a total of 44 patients admitted under one team were given NIV support either in the medical intensive care unit or wards depending on illness severity [Table 2].

The study group included 10 women and 7 men with a mean age of 59.5 years (range 48 – 82). All patients had severe hypercapnia: mean peak (i.e., the worst) $PaCO_2$ 89 ± 21 mm Hg (range 66 – 143) with severe respiratory acidosis: mean nadir (i.e., the worst) pH 7.24 ± 0.058 (range 7.14 – 7.33). All had tachypnoea - mean respiratory rate of 29.5 ± 4.69/mt (range 24 – 40). In 17 episodes, there was altered mental status with an Encephalopathy score of grade 3 in 13 episodes and grade 2 in 4 episodes [Table 1]. The mean encephalopathy score at admission was 1.92 ± 1.32 (median 2.5). The mean time on NIV was 16.5 hrs/day (range 4–22). Clinical stability occurred over several days: mean 13 ± 9.6 days (range 5-40).

After NIV, there was initially a rise in the $PaCO_2$ levels in all patients. The mean baseline (immediately before NIV) $PaCO_2$ levels, was 64.7± 14.2 mm Hg (range 46.5 – 98.6). Post NIV $PaCO_2$ rose to peak levels of 89.0 ± 21 mm Hg (range 66 – 143). There was significant difference between the baseline and peak PCO2 levels (20.7 ± 18.4 mm Hg P <0.001) [Figure 1]. Correspondingly, the pH fell from a mean baseline value of 7.330 ± 0.96 to a mean nadir level of 7.24 ± 0.58 (P<0.001) [Figure 2]. The mean IPAP was 15.43 ± 0.62 and mean EPAP was 5.81± 0.62.

NIV was successful in 22 out of 24 episodes (91.67%). The final $PaCO_2$ levels at discharge in these 22 episodes decreased significantly to a mean level of 56.16 ± 9 mm

Table 2: Patients receiving NIV who were excluded from the study

Sl. No.	Name of Diseases	No. of patients
1	Obstructive sleep apnea syndrome	7
2	COPD and severe sepsis	2
3	Pulmonary edema	2
4	Kyphoscoliosis	1
5	ARDS	1
6	Fat embolism syndrome	1
7	Post-laparotomy respiratory failure	3
8	Traumatic chest injury and flail chest	1
9	Guillain-Barre syndrome (to facilitate weaning from ETMV)	1
10	Acute on chronic renal failure with COPD	2
11	Alcoholic liver disease and COPD	2
12	Interstitial lung disease	1
13	COPD (who were offered but could not tolerate NIV)	3

Table 3: $PaCO_2$ evolution in patients (n=6) with severest hypercapnia (Peak $PaCO_2$>100 mmHg)

Sl No	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
1	100	40	70	76	80	95	60	64
2	70	65	100	60	65	85	60	55
3	79	75	90	100	78	70	66	59
4	60	140	125	90	130	125	100	80
5	80	85	75	100	705	90	83	70
6	75	70	80	100	95	101	80	75

Hg as compared to the peak $PaCO_2$ levels (P<0.001). The final pH rose significantly to 7.375 ± 0.06, as compared to nadir values (P<0.001). The mean encephalopathy score after 24 hours was 0.70 ± 0.88 with a median of 0. The difference between mean baseline and 24-hour encephalopathy scores was significant (P = 0.001).

The respiratory rate was significantly reduced from 29.5 ± 4.69/mt at baseline to 22.3 ± 2.1/mt after NIV (P<0.001).

In 6 of the episodes where the peak $PaCO_2$ levels were 100 mm Hg or more NIV was successful and the patients could be discharged to nocturnal home NIV support [Figure 2 and Table 3]. Two patients out of the 17 died, one after intubation and mechanical ventilation for 15 days following a trial of NIV for 2 days, and the other while receiving NIV, as she refused intubation.

No correlation was found between initial pH and $PaCO_2$ with the degree of encephalopathy or with response to NIV.

Few complications occurred in this series. One patient who was indeed the first case to be supported with NIV developed a deep ulcer on the bridge of the nose. Notably this patient was ventilated with a volume ventilator and a less sophisticated mask than presently available. One patient had gastric distension that settled with reduction in pressures and time on NIV support.

Discussion

NIV has been studied extensively in the context of acute exacerbation of COPD and several RCTs have proved its efficacy.[2,3] NIV has not been universally successful, with reported failure rates of 7-50% due mainly to the heterogeneity of the study population.[3] There are concerns about incorrect selection of patients leading to delay in intubation.[4,5,6] Understanding the determinants of success would facilitate accurate patient selection, determine the setting for its application and the timing of intubation when the risk of failure is high.[3,7,9,13]

This review of our earliest experience with NIV focuses on the criteria that are said to be predictive of outcome. The severity of respiratory acidosis at the outset is reported to be predictive of NIV failure. Ambrosino *et al*[4] in a retrospective review of COPD patients found that lower baseline $PaCO_2$ values (79 vs. 98) and higher pH values (7.28 vs. 7.22) correlated with success. This was confirmed in other prospective randomized studies,[12,13] but not in all.[14,15,16]

Hypercapnia in this study (mean peak $PaCO_2$ 89 ± 21 mm Hg, range 66 – 143) is among the highest levels reported hitherto.[3,16,17,18] The acuity of the exacerbations is also reflected in the presence of severe respiratory acidosis (mean nadir pH 7.24 ± 0.058, range 7.14 – 7.33). NIV was successful in 22 out of the 24 episodes (91.67%) testifying to its remarkable efficacy. Notably, in all of the 6 episodes with $PaCO_2$ more than 100 mm Hg, NIV was successful. Previous reports have shown a success rate of 71-96%[9,12,15,13,19] in patients with lesser degrees of respiratory acidosis.

The level of consciousness (LC) at admission has been used to predict outcome. Most studies[3] and guidelines[8,20] excluded patients with altered sensorium due to theoretical concerns about the risk of aspiration. Baseline LC and pH values have been reported to correlate with success.[4,9,13,16] In the study by Brochard *et al*,[12] the encephalopathy score among patients in the NIV group who needed intubation was 1.9 ± 1.2. Based on data from 1,033 patients Confalonieri *et al*[9] have developed a risk prediction model in which GCS<11 and pH <7.25 correlate with the highest risk of failure. Contrary to this view in our series with a high rate of success, disturbed consciousness was present in 17 of the 24 episodes (mean ES 1.92, median 2.5).

Several others have shown successful outcome in this group of patients. Benhamou *et al*[21] showed a relatively high success rate of 65% in elderly pati*ents* with drowsiness, agitation or coma. Intermittent negative pressure ventilation had a high rate of success in the presence of coma (GCS range 3-8).[22] Other studies[23,24] have also found no impact of baseline sensorium on patients' response to NIV. More recently, Gonzalez-Diaz *et al*[18] showed that hypercapnic coma with GCS < 8 can be treated as successfully as awake patients with NIV. The largest subgroup in this series was also COPD in which the success rate of those with severe encephalopathy was 86%, similar to our results.

Once initiated, the response to NIV may also indicate the chances of success. Studies suggest that this can be gauged early within the first 4 hours. In the study by Ambrosino *et al*[4] physicians intubated patients if the pH value remained < 7.35 after 1-2 hrs of NIV. However, after using logistic regression analysis only the baseline pH had a reliable predictive effect among several variables. Moreover, there was no control group of patients with different threshold values for intubation to substantiate this conclusion. Further, pneumonia was far more frequent among those who failed NIV trial as compared to those who succeeded.

In our study, patients with worsening levels of $PaCO_2$ and pH initially after NIV had successful outcomes when support was continued for more sustained periods. Patients of pneumonia were not selected for our study.

In our series it was frequently observed that while the patients were on NIV, paradoxically, the $PaCO_2$ levels rose initially, and this difference between the baseline and peak levels was highly significant ($P<0.001$).

Many prospective studies have demonstrated remarkable reduction of $PaCO_2$ and pH levels within the first few hours[13,15,25,26,27] and the failure of this to occur has been regarded as a predictor of unsuccessful outcome.[4,9,13] Benhamou *et al*[21] noticed that the $PaCO_2$ and pH levels remained unchanged during the first hour, but improved later. Meecham Jones *et al*[28] found that the most severely hypercapnic patients showed a rise in $PaCO_2$ with the addition of nasal ventilation. In our series, all were severely hypercapnic, with possible pre-existing chronic stable respiratory failure, showing similar initial worsening. We also found that the $PaCO_2$ levels fluctuated considerably for a variable period (hours-days) before settling down to stable levels [Figure 3]. The average period for clinical and biochemical stability was 13 ± 9.6 days (range 5 – 40).

Despite the initial rise in $PaCO_2$ often to alarming levels, we persevered with NIV because the patients were clinically better or without deteriorating sensorium. This is in contrast to studies discussed above where support was escalated to invasive ventilation when the expected biochemical response did not occur in the initial hours. Sensorium and dyspnoea in our study improved over several hours even while the blood gas levels were grossly abnormal. Attention to compliance with NIV or mask fit often produced a favorable response in those who had clinical deterioration after initial improvement. In all cases, the inspiratory pressure and the duration of NIV were increased to the maximum tolerated to improve ventilation. A minimum EPAP of 4cms H_2O was applied in most episodes which would perhaps have reduced the chances of carbon-dioxide rebreathing, as a standard whisper swivel was used.[29]

The higher success rate in our series is attributable to a more sustained and aggressive application of NIV together with a disregard for worsening $PaCO_2$ and pH, if the clinical state in terms of sensorium and dyspnoea was stable or improving.

This raises a possibility (hitherto not studied or defined accurately) that the trial period for NIV was far too short in the preceding studies and that longer trials can be safely attempted in patients of COPD.

Possible mechanisms for the paradoxic initial rise in $PaCO_2$ after NIV may be a combination of several factors including resetting of the respiratory drive to high $PaCO_2$ levels in chronic stable hypercapnic failure,[30] loss of hypoxic drive after oxygenation, reduction of minute ventilation from NIV-induced resistive loading of the upper airway[31] and a rebound increase in REM sleep with reduction of alveolar ventilation.[32] The net effect would be a rise in the $PaCO_2$, although the patient is better rested. Improvement in sensorium despite increasing hypercapnia suggests that other factors such as fatigue

may also influence mental alertness.

The decision to intubate patients of COPD is always a difficult one because of the high risk of complications, and the possibility of prolonged mechanical ventilation with attendant morbidity and mortality. In the Third World, given the high cost of intensive care and the scarcity of ventilators this decision is even more difficult. It is disappointing that out of those who can be weaned from invasive ventilation only 38% - 56% survive at the end of one year[33,34] questioning the overall cost-effectiveness of prolonged mechanical ventilation. Often the family, when informed of the uncertain course and the expenses involved, is reluctant to consent to invasive ventilation. For these reasons, the decision for ventilatory support often poses a moral dilemma in those with advanced chronic disability who present with acute respiratory decompensation. The trial with NIV should therefore be aggressive and should not be prematurely abandoned, taking care that intubation, if considered an option, is not delayed. Experience with this series of patients suggests that longer trials of NIV can be safely attempted in a subset who may improve clinically while they may temporarily worsen in terms of biochemical parameters.

Although the patients in this series were spared the problems of prolonged invasive mechanical ventilation, they, nevertheless required prolonged support with NIV. This, in contrast to invasive support was associated with few serious complications. With close monitoring, good mask fit, trained personnel and skilful handling of patients high success rates can be achieved.

The main limitation of the study is that it is retrospective. However, given the well-proven efficacy of NIV in the setting of COPD patients a prospective, randomized study with controls supported invasively without prior trial of NIV cannot be ethically supported. It would appear that the current recommendations for predicting failure of NIV might not be accurate for an individual patient. The question of the optimal duration of trial can perhaps be addressed by a randomized controlled trial comparing different cut-off points for switching from noninvasive to invasive ventilation, rather than using pre-defined rigid and arbitrary criteria for intubation. Our observations certainly challenge the currently accepted boundaries set for NIV since a high proportion of this series of patients with altered sensorium and initially deteriorating biochemical parameters went on to have a favorable outcome.

Conclusions

In selected patients of COPD with severe hypercapnia and respiratory acidosis, NIV may be continued even if $PaCO_2$ and pH deteriorate initially provided there is improvement in clinical status as reflected by sensorium and degree of respiratory distress. As there may be a an initial worsening of $PaCO_2$ and pH without signifying failure of NIV, these values alone should not influence the decision to escalate treatment to invasive support. This decision may be more reliably based on clinical status parameters. The tolerable thresholds for NIV trial may be set too low and need further study.

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