

NONINVASIVE POSITIVE PRESSURE VENTILATION IN ACUTE ON CHRONIC RESPIRATORY FAILURE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE*Esra Karabiber¹, Nejat Altintas², Muzaffer Sariaydin¹, Ozgur Ince¹*¹ Ondokuz Mayıs University, Istanbul, Turkey² Namik Kemal University, Istanbul, Turkey**НЕИНВАЗИВНАЯ ВЕНТИЛЯЦИЯ С ПОЛОЖИТЕЛЬНЫМ ДАВЛЕНИЕМ ПРИ ОСТРОЙ ХРОНИЧЕСКОЙ ДЫХАТЕЛЬНОЙ НЕДОСТАТОЧНОСТИ У БОЛЬНЫХ С ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ***Эсра Карабибер, Нейат Альтинташ, Музафер Сарьидин, Озгур Инче*

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Summary. Background: Noninvasive positive pressure ventilation (NIMV) has been proposed in COPD patients with acute respiratory failure (ARF) in order to avoid endotracheal intubation and to improve immediate outcome. In our study, we aimed to compare the early results of medical treatment alone to medical treatment plus NIMV in the acute exacerbation of COPD.

Methods. Between may 2007 to august 2010, a total of 56 COPD patients with ARF were recruited. A total of 26 were assigned to medical therapy and 30 to medical therapy plus NIMV.

Results. The two groups had similar clinical characteristics on admission to the hospital. Arterial oxygen pressures (PaO₂) were significantly increased after treatment in both medical treatment group (from 58.1±11.1 to 75.8±31.2 mmHg, p<0.05) and NIMV group (from 58.1±1.8 to 69.3±18.1 mmHg, p<0.05). The effect of NIMV on arterial carbondioxide pressures (PaCO₂) and Ph was more prominent than medical treatment alone. PaCO₂ was significantly improved from the first hour until the discharge only in NIMV group (from 73.5 ± 4.7 mmHg to 69.8±12 mmHg and 52.1±7.6 mmHg p<0.05 respectively) however, while there was no difference in medical treatment group in the first hour (55.8±5.1mmHg to 55.3±5.4mmHg, p>0.05), however PaCO₂ improved on discharge (55.8±5.1mmHg to 48.2±6.6 mmHg).

There was no statistically significant difference in the respiratory rate improvement and the number of patient required mechanical ventilation in both groups.

The mean hospital stay was significantly shorter for patients receiving NIMV than medical treatment alone (16±8 days vs. 25±10 days, P=0.005). Hospital survival rate was not significantly different in both groups.

Conclusions. In selected patients with acute exacerbations of COPD, the NIMV with medical treatment improved arterial blood gases earlier than medical treatment alone and shortened the length of the hospital stay. However no difference in mortality rate was found between two groups in the early period.

Keywords: noninvasive mechanical ventilation, chronic obstructive pulmonary disease

Резюме. Проблематика: неинвазивная вентиляция с положительным давлением (НВПД) рекомендуется при острой хронической дыхательной недостаточности (ОХДН) у больных ХОБЛ в целях недопущения развития эндотрахеальной интубации и усовершенствования конечного результата. Целью исследования стало сравнение результатов медикаментозной терапии острой хронической дыхательной недостаточности у больных ХОБЛ с результатами подобной терапии, но уже с применением неинвазивной вентиляции с положительным давлением.

Методы: в период с мая 2007 года по август 2010 года для участия в исследовании было набрано, в общей сложности, 56 больных ХОБЛ с ОХДН. 26 из них были назначены на медикаментозное лечение, остальные 30 пациентов были назначены на медикаментозное лечение с применением плюс НВПД.

Результаты: на момент госпитализации пациенты каждой группы имели схожие

клинические показатели. После осуществления лечения артериальное давление кислорода (P_{aO_2}) было весьма высоким как в группе обычного медикаментозного лечения (от 58.1 ± 11.1 до 75.8 ± 31.2 мм рт.ст., $p < 0.05$), так и в группе медикаментозного лечения с применением НВПД (от 58.1 ± 1.8 до 69.3 ± 18.1 мм рт.ст., $p < 0.05$). Эффект, произведенный НВПД на артериальное давление диоксида углерода (P_{aCO_2}) и Ph был более заметен, чем эффект от обычного медикаментозного лечения. P_{aCO_2} значительно улучшилось с первого часа до выписки только в группе НВПД (от $73,5 \pm 4,7$ мм рт.ст. до $69,8 \pm 12$ мм рт.ст. и $52,1 \pm 7,6$ мм рт.ст. $< 0,05$ соответственно), однако, несмотря на то, что в группе обычного медикаментозного лечения в первый час не наблюдалось особой разницы в показателях (от $55,8 \pm 5.1$ мм рт.ст. до $55,3 \pm 5.4$ мм рт.ст., $p > 0,05$), к моменту выписки пациентов они улучшились (от $55,8 \pm 5.1$ мм рт.ст. до $48,2 \pm 6,6$ мм рт.ст.).

В обеих группах не наблюдалось статистически значимого различия в показателях улучшения частоты дыхания и числа пациентов, которым необходима искусственная вентиляция легких.

Средняя продолжительность госпитализации была значительно короче для пациентов, получающих медикаментозное лечение с применением НВПД, чем у тех, кто проходил обычное лечение (16 ± 8 дней против 25 ± 10 дней, $P = 0,005$). Частота выживания не различалась в обеих группах.

Заключение: среди отобранных пациентов с острой хронической дыхательной недостаточностью при ХОБЛ, после лечения с применением НВПД, показатели артериального газа в крови улучшились раньше, чем у тех, кто лечился обычным медикаментозным методом, а также сократился период госпитализации. Однако, не было существенных различий в показателях смертности в больнице.

Ключевые слова: неинвазивная искусственная вентиляция, ХОБЛ

Introduction. Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow obstruction and the destruction of lung parenchyma which in the turn leads to reduced alveolar ventilation; nocturnal and daytime gas exchange abnormalities, dyspnea, increased work of breathing and sleep disordered breathing. The eventual development of chronic respiratory failure is characterized by varying degrees of ventilation perfusion mismatch, hypoxia and hypercapnia [1]. Once hypercapnia develops, the 2 year mortality is approximately 30-40% [2]. Respiratory failure occurs when the respiratory system cannot oxygenate the blood and/or remove carbon dioxide from the blood. It can be either acute or chronic and is classified as either hypoxemic (type I) or hypercapnic (type II) respiratory failure. Acute hypercapnic respiratory failure frequently occurs in COPD patients experiencing acute exacerbations of COPD, due to a decrease in the drive to breathe [3].

Patients with severe COPD, especially those who have chronic respiratory failure, are vulnerable to a wide range of insults that lead to acute respiratory distress (acute on chronic respiratory failure) that requires hospital admission and often mechanical ventilation (4). Medical treatment of this common condition includes oxygen supplementation, drugs, removal of secretions and, when necessary, mechanical ventilation. Even if medical treatment is rapidly undertaken, patients often require prolonged hospitalization with poor prognosis when mechanical ventilation is not provided [4]. Noninvasive positive pressure mechanical ventilation (NIMV) with medical therapy improves the outcome of patients with acute respiratory failure due to hypercapnic decompensation of COPD. NIMV improves oxygenation, decreases work of breathing, improves V/Q matching, decreases fatigue and increases minute ventilation [5,6]. Some of these physiological benefits may be sustained, thereby conferring possible long-term benefits. Compared to endotracheal (ET) intubation, there are also the added advantages of simplicity, patient comfort, maintenance of the ability of the patient to talk and swallow, and ease of implementation and discontinuation. Further, the need for ET intubation and its attendant complications, may be avoided [7].

The aim of the present study was to evaluate the clinical efficacy of the early administration

of NIMV in COPD patients with acute on chronic respiratory failure (ACRF) compared with medical therapy alone.

Material and method. The study was carried out in the emergency room at a University hospital. Patients were eligible for the prospective controlled study if they were admitted as an emergency with an acute exacerbation of COPD on the basis of the clinical history, physical examination, and chest radiograph. The local ethics committee approved the study protocol. Informed consent was obtained from the patients or the first-degree relative.

To be included in the study protocol, patients needed to fulfill criteria of the diagnose of acute hypercapnic respiratory failure (AHRF). We defined the AHRF as severe dyspnea, hypercapnia (partial carbon dioxide pressure (PaCO_2) > 45 mmHg) and a pH ranging between 7.35 and 7.26.

Exclusion criteria were: a pH below 7.25, a Glasgow coma scale below 8, pneumothorax, unable to spontaneously clear secretions from the airway, unable to cooperate to NIMV, airway or facial deformity and severe organ dysfunction.

Patients were assigned to receive medical treatment or medical treatment plus NIMV

Medical treatment. Patients assigned to medical treatment received controlled oxygen with fixed percentage masks (or nasal cannulae if masks could not be tolerated) to maintain a target oxygen saturation (recorded by pulse oximetry) of 85–90%. The standard drug protocol consisted of nebulised salbutamol (5 mg every 4 h) or terbutaline, nebulised ipratropium bromide (500 µg every 6 h), corticosteroids (prednisolone 30 mg every day for a minimum of 5 days), and an antibiotic. Aminophylline and doxapram could be used at the discretion of the attending medical staff.

NIMV. Patients assigned to the NIMV group received the same medications as the patients in the medical treatment group. NIMV was delivered with the BPAP S/T-D (Respironics, Murrysville, PA). An experienced physician in all patients initiated NIMV. The full face mask (Quattro Air, Resmed, Sandiego, CA) best fitting the patient's face was chosen and the tolerance of mask by patient was controlled closely and changed to nasal mask if necessary. The inspiratory positive airway pressure (IPAP) was initially set at 8-10 cm H₂O and adjusted according to patient's tolerance to obtain a tidal volume of 7-10 ml/kg. The expiratory positive airway pressure (EPAP) was set initially at 5 cm H₂O and increased in increments of 1 cm H₂O until fractional inspired oxygen (FiO₂) requirement was less than 0.5. The humidification was not used during NIMV. Oxygen was entrained into the mask to maintain oxygen saturations between 85% and 90%. Initially the patients were encouraged to continue NIMV as much as he/she could. Intervals were permitted for eating, drinking or expectoration. When clinical findings and blood gases improved, the duration of NIMV was decreased. For associated complications, factors reported by Jimenez et al were used(8).

Treatment Failure and Endotracheal Intubation. Patients who were deemed unstable (haemodynamic instability, altered state of consciousness), in need of intubation or of closer monitoring were transferred to ICU. For the need of intubation, the criteria used by Brochard et al. were used (9). Endotracheal intubation was considered if any of the following criteria were met: (1) pH below 7.20, (2) pH: 7.20-7.25 on two occasions 1 h apart, (3) hypercapnic coma (glasgow coma scale (GCS) <8 and PaCO_2 >8kPa), (4) partial oxygen pressure (PaO_2) below 6 kPa despite maximum tolerated FiO₂ and (5) cardiorespiratory arrest.

Statistical Analysis. All statistical analyses were performed using the SPSS version 19.0 For the comparison of groups, T-test, Chi-Square test and Mann-Whitney test were used. For variables that were not normally distributed, nonparametric test were used. For both groups, comparison of baseline pH, PaCO_2 and PaO_2 and oxygen saturation with those recorded after NIMV was performed by using multiple comparison test and Friedman test with Bonferroni correction. A p value of less than 0.05 was considered as statistically significant. The primary outcome variable was the improvement in the physiologic parameters. Secondary end points were the length of the hospital stay, complications not present on admission (such as pneumonia, baro-trauma,

gastrointestinal hemorrhage, renal insufficiency, neurologic events, and pulmonary embolism), the duration of ventilatory assistance, and the mortality rate during hospitalization.

Results. Of the 279 patients applied to the emergency room with exacerbation of COPD, 62 were enrolled in the study, 216 were not included (109 did not have acute hypercapnic respiratory failure, 108 were already undergoing mechanical ventilation or required immediate intubation or excluded for various other reasons). The flow of participants is outlined in Figure 1.

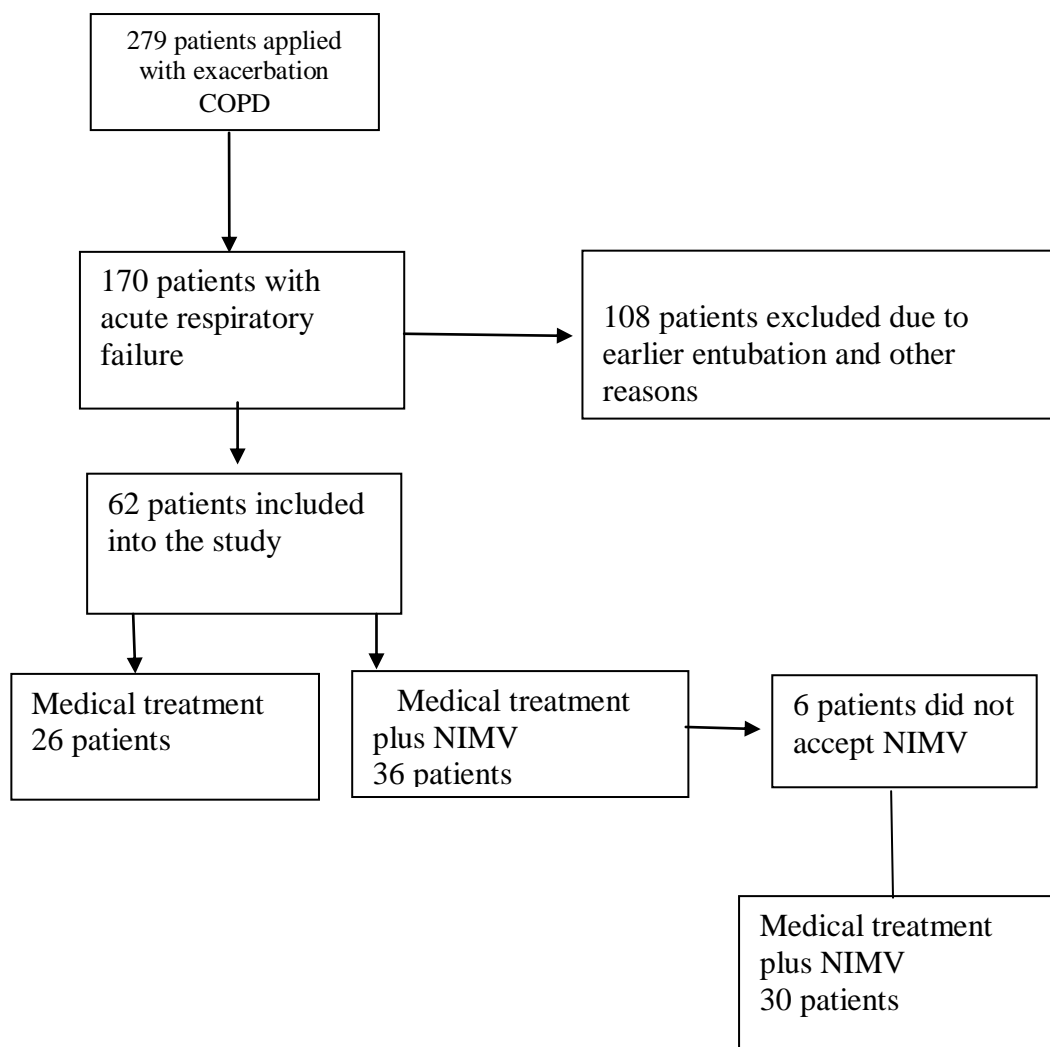


Figure 1 - Flow chart of participants

Twenty-six patients were assigned to medical treatment and 36 patients to NIMV. Patients in the groups were not strictly matched, sicker patients were assigned to NIMV group since proven benefit of NIMV on acute respiratory failure. Of the 36 patients, 6 patients did not accept the NIMV treatment; five due to claustrophobia, and the one unable to co-operate because of anxiety. These six patients were excluded from further analysis.

In NIMV group, PaCO₂ was higher, PH was lower in arterial blood and smoking packet/year was higher than medical treatment arm. Other measurements were statistically not different. Baseline characteristics of the study groups were shown in table 1.

Table 1 - Characteristics of patients with acute exacerbations of COPD assigned to standard treatment or NIMV, at admission

	Medical treatment arm	Medical treatment plus NIMV*	P
Mean age, years	67 ±7.8	66.4 ±11.0	>0,05
Sex(M/F)	24 /2	30 / 0	>0,05
Smoking,packet/year	40.7 ± 24.3	58.5 ± 36.5	<0,05
BMI kg/m ²	26.7 ± 4.3	27.0 ± 6.2	>0,05
Respiratory rate/min	30.0 ± 6.0	28.4 ± 3.3	>0,05
pH	7,36 ± 0,06	7,27 ± 0,08	<0,05
PaO ₂ (mmHg)	58,1 ± 11,1	58,2 ± 12,3	>0,05
PaCO ₂ (mmHg)	55,8 ± 5,1	73,9 ± 13,6	<0,05
SpO ₂ * (%)	88,4 ± 4,59	85,8 ± 5,02	>0,05
FEV1(%)	35,3 ± 12,2	31,7 ± 13,2	>0,05
FVC (%)	43,4 ± 13,9	39,6 ± 16,0	>0,05
FEV1/FVC (%)	61,1 ± 11,2	60,7 ± 16,3	>0,05

NIMV*: noninvasive mechanical ventilation

Physiologic parameters. In both groups, respiratory rate, PO₂, SPO₂ were significantly improved in the first hour and improvement trend was the same from the baseline until the discharge for both groups (figures 2-5).

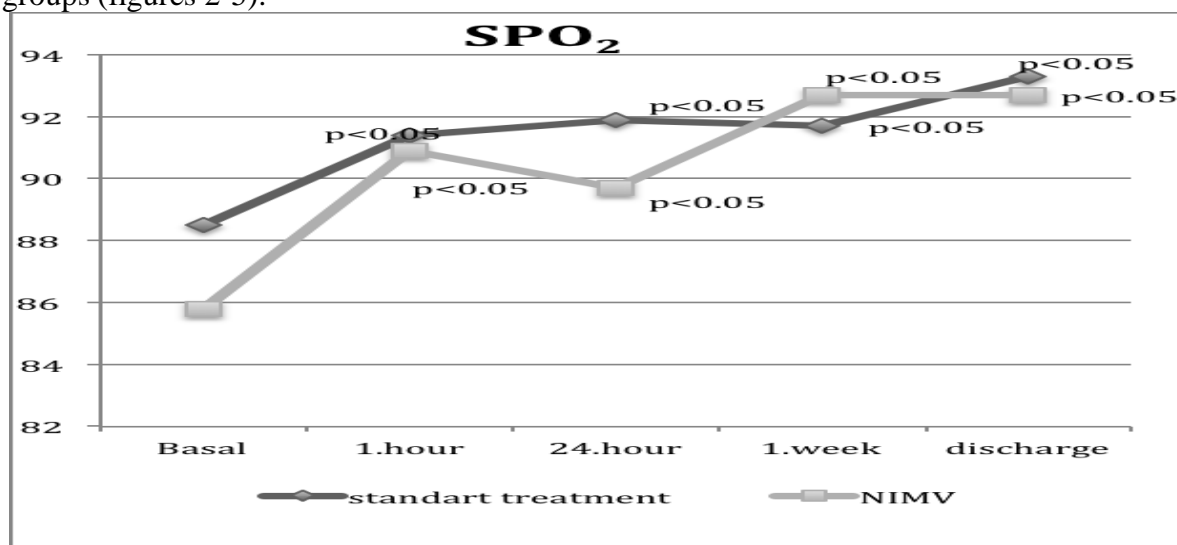


Figure 2 - SPO₂ trend in both treatment arm

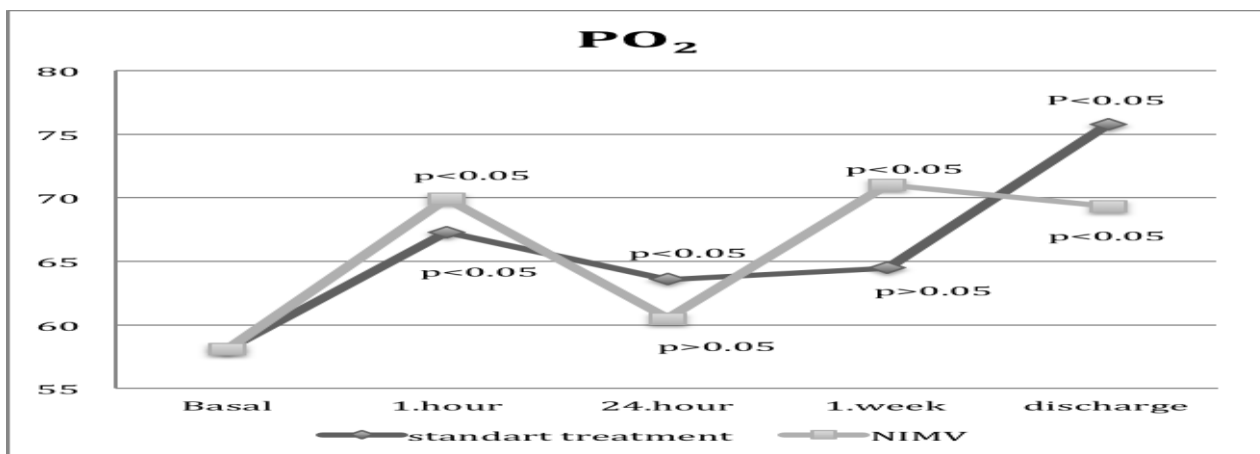


Figure 3 - PO₂ trend in both treatment arm

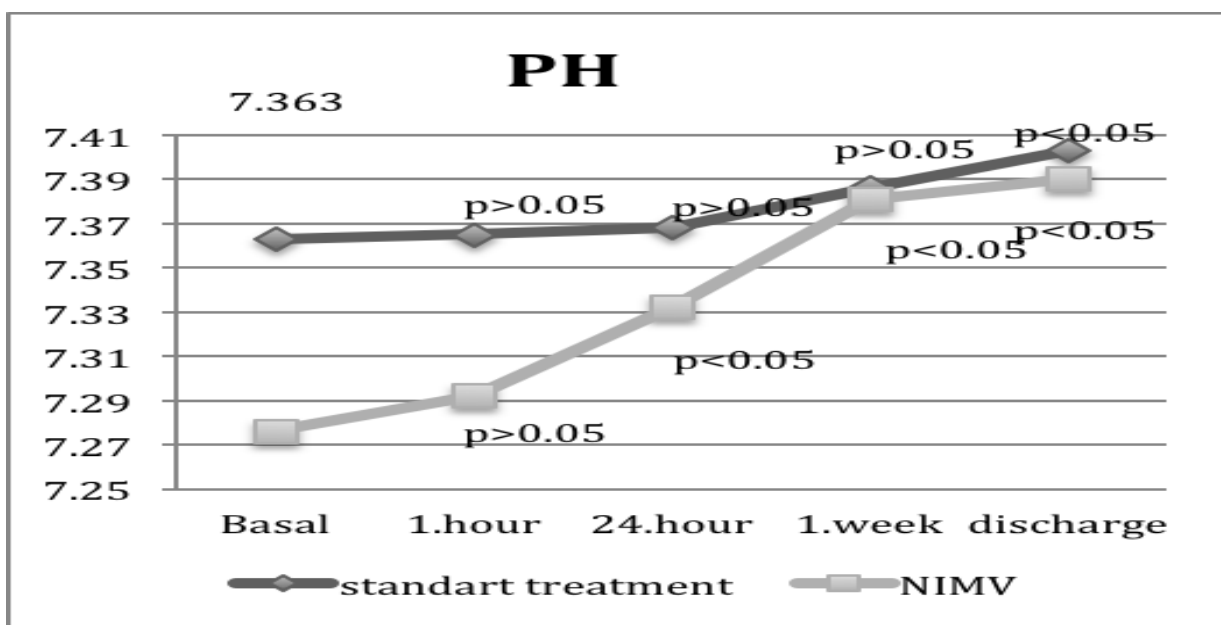


Figure 4 - pH trend in both treatment arm

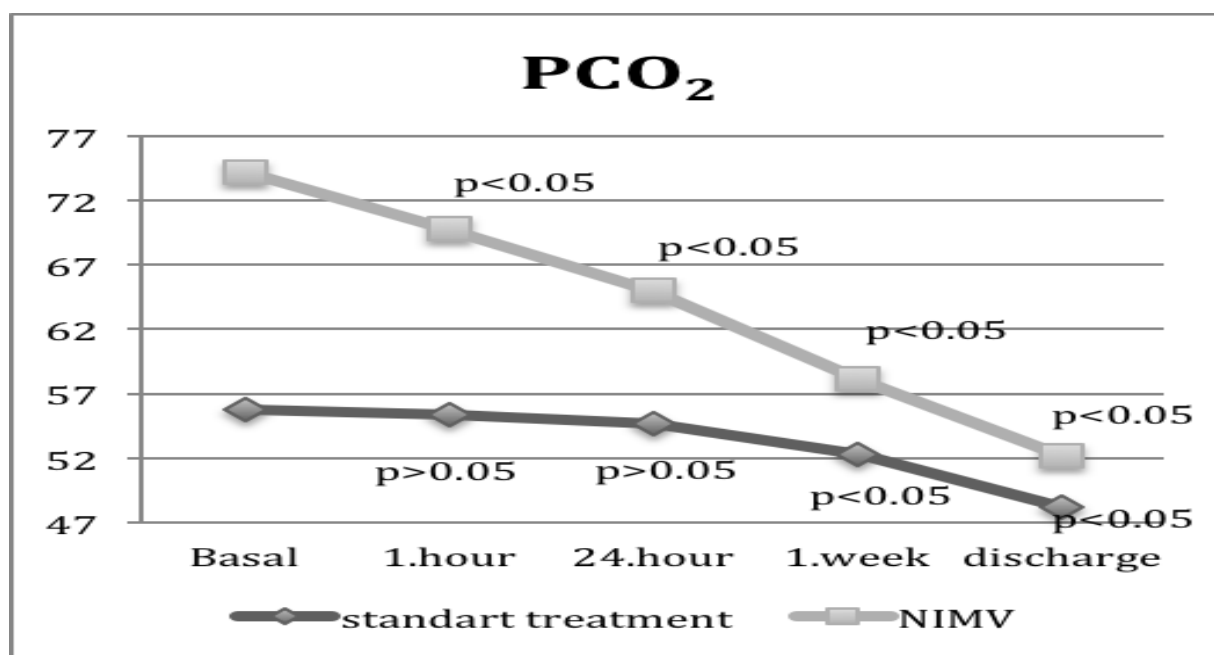


Figure 5 - PCO₂ trend in Both Treatment Arm

PaO₂ increased in medical treatment group (from 58.1±11.1 to 75.8±31.2 mmHg (p<0.05)) and in NIMV group (from 58.1±1.8 to 69.3±18.1 mmHg (p<0.05)). However PaCO₂ were significantly improved from baseline to the first hour only in NIMV group (from 73.5 ± 4.7 mmHg to 69.8±12 mmHg (p<0.05)) and this improvement continued until discharge (from 73.5 ± 4.7 mmHg to 52.1±7.6 mmHg p<0.05). Although there was no difference in medical treatment group in the first hour (55.8±5.1mmHg to 55.3±5.4mmHg, p>0.05 and), PaCO₂ improved on discharge (55.8±5.1mmHg to 48.2±6.6 mmHg). Figure 2 to 5 show physiological parameters in both groups .

The respiratory rate improved in both groups. Even though there was no statistically significant difference in the respiratory rate improvements in both groups, there was a clear trend in favor of NIMV group (figure 6).

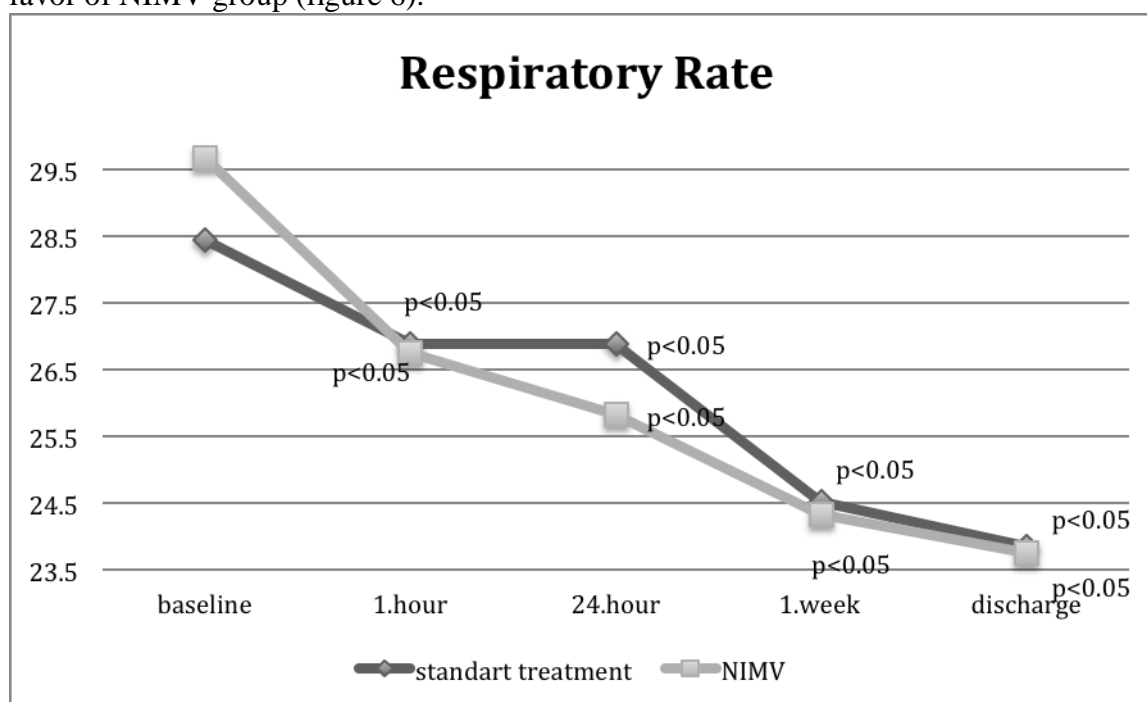


Figure 6 Respiratory rate trend in both treatment arm

Pulmonary function test (PFT) done one day after hospitalization was accepted as baseline PFT. PFT improvement trend was in the same way during the first week and on discharge in both treatment arms (figure 7).

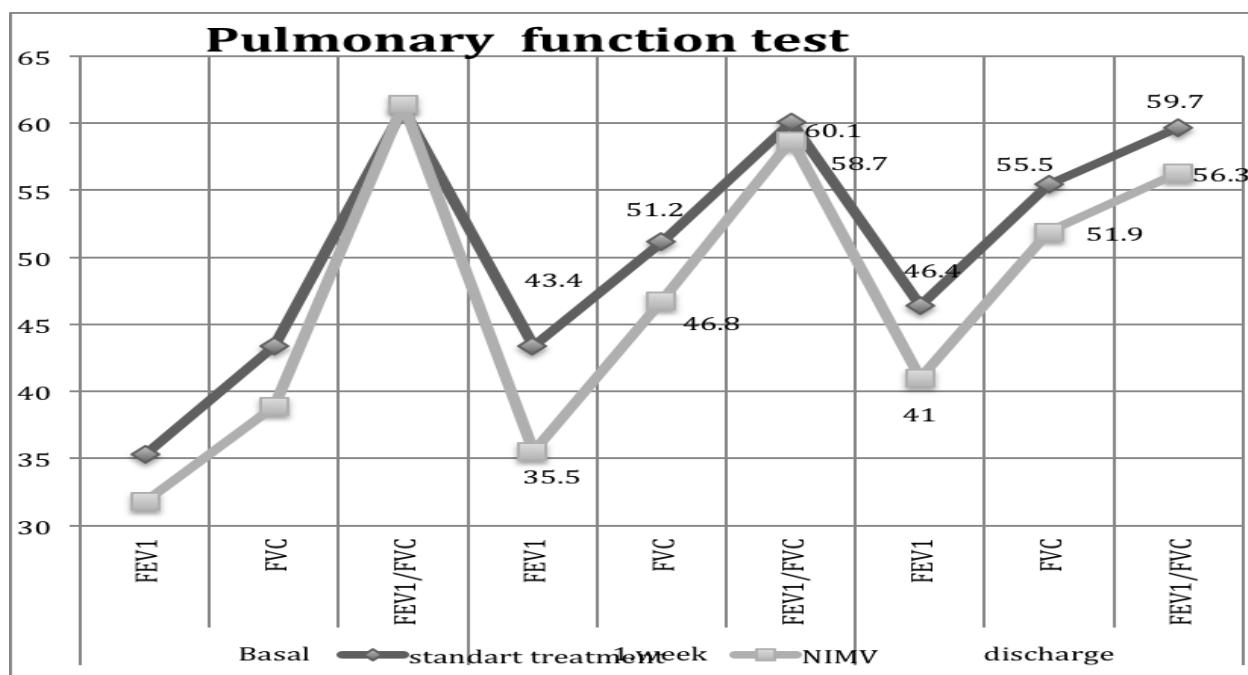


Figure 7 - Pulmonary function test in both treatment arm

Hospital Stay. Hospital stay was significantly shorter for patients receiving noninvasive ventilation (16 ± 8 days vs. 25 ± 10 days, $P = 0.005$).

Entubation and Mortality rate. Nine (35%) of the 26 patients in the standard-treatment group required NIMV because of the worsened arterial blood gases, 8 of them were discharged with success however one of them required endotracheal intubation. In NIMV group 3 patients required intubation, 1 patient was discharged with a success however 2 patients died. There was statistically no difference in both group in terms of treatment success rate, intubation and mortality rate ($p > 0.05$).

Complications. There was no complication developed in medical treatment group, however in NIMV group, 6 patients could not tolerate NIMV, one patient had abdominal distension, 2 patients had red eye due to mask leakage and one patient had nasal ulcer due to mask pressure.

Discussion. The aim of this study was to assess the effects of NIMV in the routine management of COPD patients recovering from acute respiratory failure (ARF). To this end, we designed a prospective, controlled study, which was carried out entirely in an emergency room. Our investigation provides information on the evaluation of several important physiological variables during recovery from ARF in COPD. We found evidence that NIV facilitates recovery in these patients.

In the study, while the intervention group received standard medical treatment plus NIMV, the control group received only standard medical treatment. Both groups were similar in terms of age, BMI, however sicker patients with worse arterial blood gases were assigned to NIMV group since NIMV is considered the standard of care in the management of acute hypercapnic respiratory failure secondary to COPD [10]. Our enrollment criteria were designed to select patients who were likely to need endotracheal intubation. Patients who required immediate intubation were not included.

The aim of ventilatory support is to “gain time” by unloading respiratory muscles,

increasing ventilation and thus reducing dyspnea and respiratory rate, and improving arterial oxygenation and, eventually, hypercapnia and related respiratory acidosis [11]. Bott and coworkers performed a prospective, randomized study of the effects of nasal positive-pressure ventilation in patients with acute exacerbations of COPD [12]. In their study several physiologic measures and the degree of breathlessness were significantly improved in the NIMV group, as compared with the baseline values and with the data in the control group. This study suggests that benefits can be expected from noninvasive ventilation. Accordingly, in our study, PaO₂ and oxygen saturation values were improved in both treatment arm however Indeed, only patients treated with NIMV had a significant improvement of arterial pH, paCO₂ within first and 24 hours, even this group had worse baseline values than control group. Antonelli and coworkers showed that improvements in pH, PaCO₂ and lung capacity values are associated with successful responses to NIMV in COPD patients with acute hypercapnic respiratory failure so that earlier studies, including the current study showed that NIMV has a strong and early effects on arterial blood gases and vital signs [13,14].

Respiratory rate was reduced significantly by the treatment in both group however given the respiratory rate at presentation was higher in NIMV than medical treatment group, we may speculate that NIMV with medical treatment is better treatment option especially reducing respiratory rate in the first hour. The data by Castillo et al. supports our observation by showing that the use of NIMV significantly reduced the respiratory rate and improved conscious level within the first 2 hours [15].

At variance with other studies [4,9,12], in our study, there was no significant difference in early mortality, need for ET intubation in patients treated with NIMV in addition to medical therapy and medical therapy alone. In a prospective multicenter randomized controlled study, 236 patients with acute exacerbation of COPD with mild to moderate acidosis were randomized to medical therapy and medical therapy plus NIMV on respiratory ward [16]. In this study, the failure criteria was the need for intubation, and the authors found that the use of NIMV significantly reduced the need for intubation and in-hospital mortality. The success rate was 85% in NIMV group. Brochard et al, suggested that after adjustment, the main factor explaining the difference in mortality was the number of patients requiring intubation [9]. In our study, the number of patients underwent ET intubation were not different in both groups, it may explain why there was no difference in terms of mortality rates. However, a clear trend in favor of patients who received NIMV in addition to medical therapy was clear from the data that baseline arterial blood gases values and clinical conditions of patients were worse in NIMV group and also the data that a number of patients in the medical treatment group had to receive NIMV because of clinical deterioration. Differences with the studies published earlier may be due to a shorter period of observational follow-up or, to the relatively small sample size of most studies, the present one included. To show advantages of NIMV on mortality, long term randomized controlled, multicenter studies are needed.

The duration of hospitalization was significantly lower in NIMV group (16 versus 25 days), the result in accordance with the findings of previous studies [9,17,18]. It is difficult to assess exacerbation rates on account that current study was not designed and powered for long term follow-up however taking exacerbation rates and hospitalization rates into account, NIMV may be a cost-saving measure in terms of socio-economical burden and nosocomial infections owing to decreased length of hospital stay.

Nasocomial pneumonia rate was reported up to 30% in ET intubated patients [19] compared with invasive mechanical ventilation, NIMV decreases risks of ventilator-associated pneumonia and sinusitis, especially in patients who are immunosuppressed or with comorbidities [7]. Accordingly in our study, pneumonia or serious complications were not developed during noninvasive ventilation. This study was not powered to compare NIMV with mechanical ventilation. However comparing with other study [19], NIMV has added advantages in terms of decreasing infectious complication of mechanical ventilation.

As a consequence, this study shows that the use of noninvasive ventilation, in selected patients admitted for acute respiratory failure due to COPD achieves physiological benefits of reduced work of breathing and improved gas exchange. We may postulate that NIMV can obviate

the need for intubation and thus reduce complications of ET intubation and mortality and shorten the hospital stay.

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