Original Article

Factors associated with noninvasive ventilation response in the first day of therapy in patients with hypercapnic respiratory failure

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Abstract:

BACKGROUND AND AIM: Noninvasive ventilation (NIV) decreases mechanical ventilation indication in the early period of acute hypercapnic respiratory failure (AHcRF) and factors for success have been studied well. But, less is known about the factors influencing the NIV response in the subacute period. This study was aimed to determine the factors influencing the reduction of $PaCO_2$ levels within first 24 hours of therapy.

METHODS: NIV response was defined as reduction of $PaCO_2$ level below 50 mmHg within first 24 hours. Patients with AHcRF, treated with NIV, were divided into 2 groups according to this criterion; group 1 as the nonresponsive, group 2 as the responsive. The differences in NIV methods and characteristics of the two groups were evaluated and compared in this retrospective study.

RESULTS: A total of 100 patients were included in the study; 66 of them in group 1 and 34 in group 2. No significant differences were identified between the length of NIV application and intensive care unit (ICU) stay, intubation and mortality rates, across the groups. Ninety-one percent of the patients in group 2 had received all night long NIV therapy; this was just 74% in group 1 (P=0.036). Results of multivariate analysis showed that while nocturnal application was significantly associated with better response, prior home ventilation and requirement of higher pressure support (PS) levels significantly and independently associated with poorer response to NIV therapy.

CONCLUSION: In patients with AHcRF, all night long use of NIV may accelerate healing by improving $PaCO_2$ reduction within the first 24 hours. A rapid response in $PaCO_2$ levels should not be expected in patients requiring higher PS levels and using prior home ventilation.

Key words:

Chronic obstructive pulmonary disease, first day, hypercapnic respiratory failure, noninvasive ventilation, response

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Randomized controlled trials show successful use of noninvasive ventilation (NIV) in the management of acute hypercapnic respiratory failure (AHcRF) to prevent endotracheal intubation in patients with chronic obstructive pulmonary disease (COPD) exacerbations or acute cardiogenic pulmonary edema and in immunocompromised patients, as well as to facilitate extubation in patients with COPD.[1,2]

Patient selection is one of the most important factors in determining the NIV success. Although patients with hypoxemic respiratory failure have poorer response to NIV, patients with hypercapnic respiratory failure, particularly with COPD exacerbations, have a better response.[3] However, all hypercapnic COPD patients are not responsive to NIV. A higher APACHE II score (>29), lower Glascow Coma Score (<11), pH<7.25, respiratory rate >35/min, air leakage, copious secretions, asynchrony, and lack of compliance or tolerance are found to be predictors for failure of NIV in these patients. If pH is <7.25 in COPD acute attack, then failure rate varies between 52 and 65%.[1]

Technical aspects such as choice of interface and ventilator settings are clearly important for NIV success.

The optimal location for NIV application is still a matter of debate. There are many reports supporting the use of NIV in intensive care units (ICUs).[4,5] But, in recent years, there are also some studies recommending the initiation of NIV in emergency departments and in general wards.[6] On the other hand, patients with chronic respiratory failure and using home mechanical ventilation are increasing. According to Eurovent survey, the estimated prevalence of home mechanical ventilation in Europe is 6.6 per 100 000 people.[7] There are no clear data how these patients respond to NIV therapy during their AHcRF attack.

Studies evaluating the NIV success generally assessed the patients' response within the early

period such as within the first hours.[8-11] The aim of this evaluation is to determine if it decreases intubation indication or mortality. To decrease the intubation indication is one of the most important contributions of NIV to patient outcome. On the other hand, to treat hypercapnia as soon as possible and discharge the patient to the wards might be another important contribution. By achieving this aim, it is possible to decrease costs and occupancy rates of the ICUs. Because of these reasons, it is important to know potential factors associated with the success rates of the NIV therapy within the first 24 hours. In our previous study in which we investigated the influence of obesity on the NIV strategies and outcomes, we saw that severe obesity was associated with late response during hypercapnic respiratory failure attacks.[12] In this study, we aimed to assess the other factors influencing NIV response such as etiology of hypercapnia, chronicity of underlying disease, total length of daily, or nocturnal NIV (NNIV) use in the first day of the therapy in patients with AHcRF.

Methods

This retrospective study was performed by reevaluating the medical records of patients with AHcRF who were treated with NIV in an ICU of a university hospital between the years 2006 and 2009.

Inclusion criteria

All hypercapnic adult patients (older than 18 years) who were admitted to ICU with a $PaCO_2$ level of ≥60 mmHg, who were conscious, and who did not have any one of the exclusion criteria were included in the study.

Exclusion criteria

Patients who had severe hemodynamic instability and inability to protect airway; who have facial deformity and/or trauma, pure hypoxemic respiratory failure, and end-stage disease; who need immediate endotracheal intubation, i.e., being in a coma state (decreased level of consciousness, GCS of <8), progression to cardiac or respiratory arrest were excluded from the study.

The medical records of the patients with respiratory failure requiring NIV were screened. Following data were recorded from the files to the database of the patients; gender, age, diagnosis, pulmonary function test results (performed during stable period), APACHE II scores, body mass index, home ventilation, and long-term oxygen therapy (LTOT) usage rates, admission (emergency department) and baseline (pre-NIV application) arterial blood gas (ABG) measurements.

The time period of NIV application (more than 6 hours or less than 6 hours in a day, or between 6 to 12 hours), whether the patient was ventilated whole night long or not (between 24.00 p.m to 06.00 a.m), discharge ABG measurements, length of NIV application (how many days?), length of hospital stay, and the outcome of the patient (intubated, died, or discharged) were also recorded.

Parameters related to noninvasive ventilation application

Necessary pressures (pressure support [PS] and positive end expiratory pressure [PEEP] values), respiratory rate, tidal volume (VT), and time period to reduce $PaCO_2$ levels below 50 mmHg were recorded.

Definitions

Hypercapnic respiratory failure: $PaCO_2$>60 mmHg while PaO_2>60 mmHg.

Sleep- or obesity-related hypoventilation syndromes: Patients with obstructive sleep apnea syndrome (OSAS) and Obesity Hypoventilation syndrome (OHS), and overlap syndrome included in this group.

Obstructive sleep apnea syndrome: The patient suspected of OSAS must fulfill the criterion A or B, plus criterion C.

A. Excessive daytime sleepiness that is not better explained by other factors.
B. Two or more of the following that are not better explained by other factors:
   Choking or gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, impaired concentration.
C. Overnight monitoring demonstrates five or more obstructed breathing events per hour during sleep.[13]

If patient did not have polysomnography, then they were diagnosed clinically as likely to have OSAS with the criterion of A and B.

Obesity hypoventilation syndrome: Is characterized by obesity (BMI>30 kg/m^2), daytime hypercapnia ($PaCO_2$>45 mmHg), and sleep-disordered breathing in the absence of other known causes of hypercapnia.[13]

Overlap syndrome: The combination of COPD and sleep apnea-hypopnea syndrome.[14]

Noninvasive ventilation response was defined as reduction of $PaCO_2$ level below 50 mmHg within the first 24 hours. Patients were divided into 2 groups according to this criterion. First group (group 1) was nonresponsive group and the second one (group 2) was the responsive group.

Noninvasive ventilation protocol of the ICU

All patients were ventilated with a full face mask and ICU or portable ventilators were used for NIV. If a single circuit is used, it was equipped with an expiratory valve.

The inspiratory and expiratory pressures were initially set as 15 and 5 cmH_2O, respectively, in PS (or Bi-level-S with portable ventilators) mode. The pressure settings were increased gradually to the patient's tolerance with the aim of achieving a respiratory rate <25 breaths/min, saturation of oxygen ($SatO_2$)>90%, $PaCO_2$<50 mmHg, and VT between 450 to 500 ml. The fractional concentration of oxygen was also titrated to maintain $SatO_2$>90%. If patients had apneas, first mode was switched to pressure control with the minimum rate of 16/minute and if apnea continued, end-expiratory pressure levels increased gradually. Ventilator settings were adjusted on the basis of continuous monitoring of $SatO_2$, clinical data, and measurements of ABGs. After the initiation of NIV therapy, patients were first evaluated with ABG analysis for early response at the end of the first hour. If $PaCO_2$ level decreased, pH improved and if the patient was clinically stable, then NIV was ordered to be applied continuously for the first 24 hours as much as possible.

The Evita 4 (Drager Medical, Lubeck, Germany), Vela (Viasys Healthcare France SAS, Plaisir, France), and BiPAP Synchrony (Respironics) ventilators were used for the NIV therapy.

Medical treatments of the patients for obstructive lung disease, infections, and heart failure were also planned according to the guidelines.

Statistical analyses

SPSS for Windows 15.0 software was used for the statistical analysis of the results (SPSS for Windows; Chicago, IL, USA). Results are presented as mean±SD and percentiles. Continuous variables were compared using the Student *t* test for normally distributed variables and the Mann Whitney *U* test for not normally distributed variables. The Chi-square test or the Fisher exact test was used to compare categorical variables. A difference was considered statistically significant when $P<0.05$. To determine any independent factor associated with NIV response, a multivariate analysis (logistic regression test) was performed among the significant parameters of univariate analysis.

Results

Baseline characteristics

Hundred patients met the inclusion criteria and were included in the study. Table 1 shows baseline characteristics of the patients. There were no significant difference between the age, gender, APACHE II scores, pulmonary function test results, LTOT usage rates, and diagnosis of the two groups [Table 1]. There were also no significant difference in admission and baseline ABG values of the two groups ($P>0.05$) [Figure 1]. Figure 2 shows the distribution of the patients according to the baseline $PaCO_2$ levels before the NIV application. Home ventilation usage rate was significantly higher in group 1 (nonresponsive group) [Table 1]. More than 53% of the patients had BMI>30 kg/m^2.

Noninvasive ventilation applications

Ninety-one percent of the patients in group 2 had received all night long NIV therapy; this was just 74% in group 1 ($P=0.036$) [Table 2].

Table 2 shows mean necessary PS, PEEP, VT, and respiratory rates of the groups to reduce the $PaCO_2$ levels to below

Table 1: Comparison of the demographic characteristics, pulmonary function tests, and admission diagnosis of the group 1 (non responsive) and group 2 (responsive) patients

Parameter	Group 1 (n:66) Mean±sd (%)	Group 2 (n:34) Mean±sd (%)	*P*
Age (years)	66±13	68±11	0.635
Gender, female, *n* (%)	39 (59)	16 (47)	0.252
APACHE II	18±4	18±3	0.881
BMI, kg/m^2	34±10	32±11	0.137
Home ventilation, *n* (%)	26 (39)	5 (15)	0.009*
FEV1, % predicted	46±19	42±19	0.270
FEV1/FVC,%	71±16	67±18	0.251
LTOT, *n* (%)	34 (52)	14 (41)	0.422
Diagnosis			
COPD	37 (56)	23 (68)	0.207
SORHS	28 (42)	14 (41)	0.905
NMD	2 (3)	1 (3)	0.980
Kyphoscoliosis	10 (15)	2 (6)	0.169
PERF	4 (6)	6 (18)	0.071

*Parameters with a *P* value <0.05 were evaluated with multivariate analysis. BMI = Body mass index; COPD = Chronic obstructive pulmonary diseases; SORHS = Sleep or obesity related hypoventilation syndromes (OSAS, OHS, Overlap syndrome); NMD = Neuromuscular diseases; PERF = Postextubation respiratory failure; FVC = Force vital capacity; FEV1 = Force expiratory volume in 1 second; LTOT = Long-term oxygen therapy

Table 2: Comparison of the necessary settings and measurements of noninvasive ventilation between the groups

Parameter	Group 1 (n:66) Mean±sd (%)	Group 2 (n:34) Mean±sd (%)	*P*
Level of pressure support, cm H_2O	18±5	16±3	0.010*
Level of PEEP, cmH_2O	7±2	6±2	0.323
Tidal volume, ml	529±130	513±181	0.330
Respiratory rate/min	20±5	22±7	0.319
Duration of total daily use >6 hrs, *n* (%)	50 (76)	29 (85)	0.199
Duration of total daily use >12 hrs, *n* (%)	17 (26)	6 (18)	0.257
Duration of total daily use between 6-12 hrs, *n* (%)	33 (50)	23 (68)	0.136
Nocturnal NIV use, *n* (%)	49 (74)	31 (91)	0.036*

*Parameters with a *P* value <0.05 were evaluated with multivariate analysis

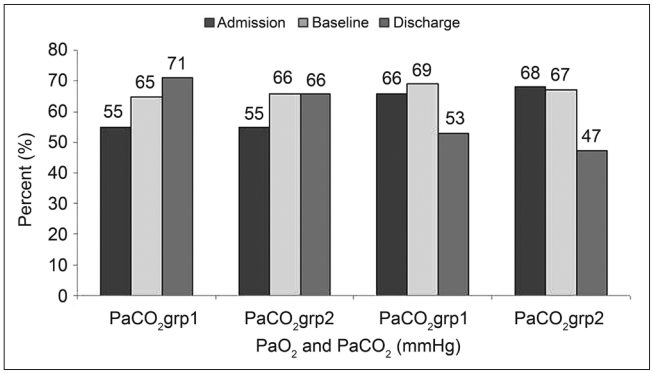

Figure 1: Comparison of the arterial blood gas values of the two groups (group 1 and group 2) at admission, baseline, and discharge

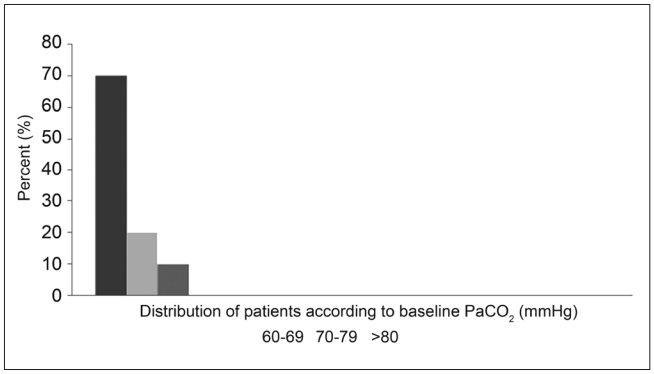

Figure 2: Distribution of the patients according to baseline $PaCO_2$ levels before NIV application; 60-69 mmHg, 70-79 mmHg, >80 mmHg

50 mmHg. According to results, despite a significantly higher level of PS usage in group 1 than in group 2, the higher PS levels did not increase VT and $PaCO_2$ failed to reduce below 50 mmHg within the first 24 hours in group 1.

In the 23% of group 1 and 15% of group 2, portable ventilators were used (P=0.265).

Outcomes

In 34% of the whole study population, $PaCO_2$ level was reduced to below 50 mmHg within the first 24 hours (composing the group 2 patients). In 22% of the whole study population, $PaCO_2$ levels never reduced to below 50 mmHg during their ICU stay and they were discharged with a $PaCO_2$>50 mmHg. No significant difference was identified in the length of NIV application and ICU stay of group 1 and 2 (8±5 *vs* 7±4 days and 9±5 *vs* 8±4 days, respectively) (P>0.05). Intubation and mortality rates were not different for the two groups (%1.5 *vs* %0 and %5 *vs* %0, respectively) (P>0.05). Responsive group (group 2) was discharged with significantly lower $PaCO_2$ levels than the nonresponsive group (group 1), i.e., 47±5 *vs* 53±8 mmHg, respectively (P=0.001) [Figure 1].

Results of risk factor analysis for response

Results of multivariate analysis showed that although nocturnal application significantly and independently is associated with a better response to NIV, the use of home ventilation therapy and requirement of higher PS levels significantly and independently is associated with poorer response to NIV therapy [Table 3].

Table 3: Multivariate analyses for the factors affecting NIV response within the first 24 hours

Variable	OR* (CI 99%)	*P*
Nocturnal application	6.6 (1.3-33)	0.022
Home ventilation	0.149 (0.041-0.55)	0.004
Higher pressure support level	0.81 (0.70-0.94)	0.005

*OR = Odds ratio; for the reduction of $PaCO_2$ below 50 mmHg within the first 24 hours

Discussion

Results of this study showed that although nocturnal application of NIV is associated with faster reduction in the $PaCO_2$ levels, higher PS requirement and prior home ventilation usage are predictors for late and poorer response to NIV in AHcRF.

In this study, although there were no significant differences in the total durations of daily NIV application of nonresponsive and responsive groups, significantly higher percentage of patients in the responsive group received NNIV than the nonresponsive group. These results suggest that nocturnal usage of NIV may have an additional effect or benefit on $PaCO_2$ control independently from the total daily usage time even during acute exacerbations.

Studies have shown that patients with neuromuscular disease (NMD), severe kyphoscoliosis, COPD, and OHSs are at risk for nocturnal hypoventilation and they are frequently good responsive to nocturnal ventilation.[15-18] Probably, because of this reason, all night long use of NIV was an independent predictor for NIV response in the first 24 hours in our study group.

A mild CO_2 retention normally occurs with the onset of sleep and increases further during the rapid eye movement (REM) sleep. Respiratory muscle weakness as seen in NMDs or increased work of breathing as seen in obese and COPD patients exacerbates this normally occurring mild CO_2 retention.[15] The mechanical disadvantages caused by severe COPD predispose to ventilatory hyporesponsiveness to CO_2 and nocturnal hypoventilation, especially during REM sleep. This further blunts central drive, promotes more CO_2 retention.

Ballard *et al*. showed that upper airway resistance rises by 164% and 263% and VT falls by 20% and 35% during non-REM and REM sleep, respectively.[19] The evidence suggests that at least for restrictive thoracic disorders and COPD, NNIV acts mainly by ameliorating nocturnal hypoventilation, stabilizing gas exchange, and enhancing CO_2 ventilatory responsiveness.[16-18]

In our study, mean BMI is higher than 30 kg/m^2 in both groups, nearly 40% of the patients had sleep- or obesity-related hypoventilation syndromes and more than 50% of the patients had COPD. OHS is the combination of hypercapnia and obesity (body mass index ≥30 kg/m^2). Approximately 80 to 90% of OHS patients have underlying OSAS and mechanisms of action of NNIV in these patients include reducing the respiratory load, increasing minute volume for a given breathing effort, and providing ventilation during central apneic events (if a backup rate is used).[20,21] A prospective cohort study about OHS patients revealed that low ventilatory responsiveness to CO_2 was associated with more hypoventilation during REM sleep and greater daytime sleepiness, abnormalities that were ameliorated by short-term therapy with NNIV.[22]

Another finding of the study is that patients using home mechanical ventilation or in other words with chronic hypercapnia were significantly associated with slower and lower response rates to NIV therapy in the ICU during acute attacks. This result is very important because in recent years, the number of patients with chronic respiratory failure using home mechanical ventilation is progressively increasing.[7] We do not have national data showing home mechanical ventilation usage rates, but at least our previous studies (16% and 21%) and this study (31%) revealed that these patients are also increasing with years in our country probably due to increasing smoking and obesity rates.[12,23] Studies performed with stable chronic hypercapnic patients and investigating the effect of home mechanical ventilation on $PaCO_2$ levels show that even under this therapy, $PaCO_2$ levels of the patients are around 55 to 60 mmHg.[24-28] Probably for this reason, we could not decrease $PaCO_2$ level below 50 mmHg, particularly in group 1. Supporting these findings of our study, group 1 was discharged as more hypercapnic than group 2 also. It is impossible to know or guess the baseline $PaCO_2$ levels of the patients during admission to emergency department in patients with AHcRF. But, if the information of home ventilation usage can be obtained, then the intensivist can predict that hypercapnia is chronic and can be resistant.

Results of this study showed that to increase PS levels may not be the only and the best solution to decrease $PaCO_2$ levels and if the patient does not respond to higher inspiratory pressures, intensivist should consider other choices. In our study, we could not achieve to reduce $PaCO_2$ below 50 mmHg level, despite we use higher level of PS in group 1. According to protocol of our

study, we targeted a VT between 450 and 500 ml considering the body weights of patients and increase PS levels to reach this target VT. Results showed that mean VT of the both groups is around 500 ml and group 1 required significantly higher levels of PS. But still, reduction in the $PaCO_2$ level was lower in group 1 than in group 2. A possible explanation of this result is the increase in air leakage by increasing the PS level and worsening patient ventilator synchrony. Studies performed in mechanically ventilated patients have shown that higher PS levels may cause ineffective triggering and cycling off asynchronies. In a study where assistance was varied between 0% and 100%, Leung *et al*. found that there were almost no ineffective efforts below 60% of assistance, but ineffective efforts increased gradually when assistance was 60 to 100%.[29] In a cohort of 62 intubated patients, Thille *et al*. recently found that ineffective triggering represented almost 90% of all asynchronies during PS ventilation (PSV) and COPD was a risk factor for asynchrony. Patients with ineffective triggering had a higher VT and higher PS.[30] This asynchrony has been described with different diseases but is observed mainly in patients with expiratory flow limitation leading to the development of intrinsic PEEP.[27] Another asynchrony caused by higher levels of PS and seen frequently during NIV due to leaks is prolonged inspiration as part of a cycling of asynchrony.[31,32]

There are some important limitations of this study. First of all, it is a retrospective study, so we could not assess some important parameters like amount of leak or asynchronies. But we believe that it was a good representative of current status about the use of NIV therapy in acute hypercapnic patients in ICU. Secondly, this study was made with a heterogeneous group of the patients. Since we had a few number of patients with NMD, kyphoscoliosis, and postextubation respiratory failure, we could not evaluate separately the differences in the NIV response in these patients. A future prospective study with selected patient groups evaluating more parameters during NIV would be more effective in clarifying other factors associated with the NIV response in the first day of AHcRF.

Conclusion

Results of this study suggests that during AHcRF attacks, an intensive use of NIV, even during all night long, may shorten the $PaCO_2$ reducing time and may accelerate the discharge of the patients to the wards. And in chronic hypercapnic patients, to struggle to reduce $PaCO_2$ below 50 mmHg by increasing PS levels may not be helpful to reduce $PaCO_2$ earlier. A rapid response in $PaCO_2$ levels should not be expected in patients requiring higher PS levels and using prior home ventilation.

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