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Original Scientific Paper

THE EFFECTIVENESS OF HIGH FLOW OXYGEN THERAPY AND NONINVASIVE MECHANICAL VENTILATION TREATMENT IN ACUTE RESPIRATORY FAILURE DUE TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE – A RANDOMIZED STUDY

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SUMMARY – Hypercapnic acute respiratory failure (ARF) is a common complication of chronic obstructive pulmonary disease (COPD). Respiratory support is required in ARF, which usually has a high mortality risk. The objective was to compare the effectiveness of noninvasive mechanical ventilation (NIV), which is the traditional treatment protocol for COPD, with high-flow nasal cannula oxygen therapy (HFNT) as an emerging treatment method. This study was performed between August 20, 2019 and December 20, 2019, as a prospective randomized controlled study. Patients who were admitted with ARF due to COPD were included in the study. With randomization, 30 patients were treated with HFNT, whereas 31 patients were treated with NIV. The pH value of the HFNT group was significantly higher at the 1st hour of treatment (p=0.001). While there were no significant differences in subsequent pH values in the HFNT group (p=0.130), the pH value in the NIV group was found to have changed significantly (p=0.030). Compared to the NIV group, the 1st hour PaCO2 value in the HFNT group was significantly higher (p<0.001). The PaCO2 value decreased and PaO2 value increased significantly during follow-up in both groups (p<0.001). There were no significant differences in intra-group lactate and HCO3 values in the HFNT group, whereas the corresponding changes in the NIV group were significant (p=0.002). Compared to the HFNT group, the NIV group length of stay in the intensive care unit (ICU) was significantly longer (p=0.039). The use of HFNT, especially in more serious COPD patients, can be described as an intervention that could be beneficial in the acute period and could reduce the frequency of nosocomial infections by shortening ICU stay.

Key words: *Chronic obstructive pulmonary disease; Acute respiratory failure; Noninvasive mechanical ventilation; High-flow nasal cannula oxygen therapy*

Introduction

Chronic obstructive pulmonary disease (COPD) ranks fourth on the list of the leading causes of death worldwide[1]. In addition, COPD has significant importance in the comorbidities of some diseases[2,3].

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COPD is a progressive disease with a chronic course and ultimately develops into respiratory failure with regard to predisposing and other factors[4]. In respiratory failure, hypoxemia and/or hypercapnia develops as a result of being unable to sustain external gas exchange at adequate level[5].

Hypercapnic acute respiratory failure (ARF) is a common complication of COPD. Respiratory support is required in ARF, which usually has a high mortality risk[4]. Alveolar ventilation is required for the correction of hypoxia and hypercapnia[6], and anatomic dead spaces need to be reduced. The first option for alveolar ventilation in ARF due to COPD is the application of treatment *via* a noninvasive mechanical ventilator (NIV)[7]. Additionally, high-flow nasal cannula oxygen therapy (HFNT), which is also amongst the treatment methods, has an advantage of decreasing dead space in addition to providing alveolar ventilation[6]. In the literature, a recent increase in the use of heated and humidified HFNT instead of conventional oxygen therapy has been reported in the treatment of patients with acute hypoxemic respiratory failure[8,9]. In a study of COPD patients, it is reported that HFNT reduced partial pressure of carbon dioxide (PaCO2) when compared to nasal oxygen treatment[10]. Some of the studies in the literature have emphasized that HFNT can be used instead of NIV, particularly after extubation[11-13].

Comparison of these two treatment protocols in the literature is limited in the case of ARF. In accordance with this purpose, in this study, it was intended to compare the effectiveness of NIV, which is the traditional treatment protocol for COPD, and HFNT as an emerging treatment method.

Patients and Methods

Study design

This study was performed between August 20, 2019 and December 20, 2019 as a prospective randomized controlled study. In order to carry out the study, local Ethics Committee Approval was obtained from Kanuni Sultan Suleyman Research and Training Hospital Clinical Research Ethics Committee (No: 2019/07/183 as of August 16, 2019). The conduct of this study complied with ethical principles of the Helsinki Declaration. Patients who were admitted to the Emergency Department, Health Sciences University, Kanuni Sultan Suleyman Research and Training Hospital with ARF due to COPD were enrolled in the study. The treatment methods were applied in the emergency Intensive Care Unit (ICU) to patients who met the criteria for the study. Treatment protocols and procedures to be performed were explained to all patients and their relatives, and a consent form was obtained. Before beginning the study, the minimal number of patients required in each group was determined through power analysis.

Patient characteristics

Patients who were previously diagnosed with COPD and were admitted to the Emergency Department with ARF were included in the study. The inclusion criteria of COPD patients for the study were determined as:

- patients who applied to the Emergency Department with ARF due to COPD during the study period;
- having respiratory acidosis (pH ≤7.35 and PaCO2 ≥50 mm Hg);
- using assistive respiratory muscles; and
- not having any mental disorders.

Exclusion criteria were determined as:

- severe respiratory failure requiring tracheal intubation (respiratory frequency ≥40 *per* minute, severe hypoxia, severe respiratory acidosis with pH <7.25, Glasgow score 8);
- oral or facial pathologies where NIV and HFNT treatments could not be applied;
- respiratory failure due to diseases other than COPD; and
- presence of additional or other organ failure.

After COPD patients with ARF were admitted to the emergency ICU, the patients were separated into two groups according to treatment, i.e., HFNT and NIV treatment groups. Those in the HFNT group received treatment with the following HFNT settings: 60% oxygen, 40% humidity at a temperature of 36-37 °C. The NIV group received treatment with 100% oxygen at PEEP 6 mm/water pressure in the CPAP-PSV mode. Age, gender, type of respiratory failure and clinical results of the patients were recorded. Starting from patient arrival, blood gas samples were obtained

at baseline (0 hours), and at the 1st, 2nd, 4th, and 8th hours. Vital symptoms, respiratory rate, and pulse oximetry results of the patients were recorded. The length of stay in the emergency ICU was recorded.

Throughout the scheduled dates of the study, 247 COPD patients were admitted to the emergency ward. Blood gas analysis of 103 patients was compatible with the aforementioned blood gas criteria. Thirty-three patients had additional diseases or organ failure that excluded them from the study. Another 9 patients refused to participate; thus, a total of 61 patients were included in the study. Among these participating patients, 30 were treated with HFNT and 31 were treated with NIV, randomly. Patients were divided into two groups (HFNT and NIV treatment) according to the pre-determined random number table (https://www.random.org/).

Statistical analysis

Data were analyzed using SPSS v. 20.0 for Windows. In order to evaluate normal distribution of all variables, the Kolmogorov-Smirnov test and skewness-kurtosis method were used. In addition to these, distribution of all variables was evaluated with histograms. Power analysis was based on PaCO2 level, due to being defined as one of the main outcome parameters in a previous similar study[14]. The required sample size in each group was calculated and showed that, with an alpha 0.05 error margin and 80% strength, each group should at least consist of 28 patients. In accordance with distribution of the data set, χ^2 compatibility test was applied to evaluate nominal data between the groups. Student's t-test was used to compare normally distributed parametric quantitative data. In order to evaluate changes within the groups (temporal data), the repeated measures analysis of variance (ANOVA) test was used. The Kaplan-Meier method was used to assess cumulative failure and survival rates with curves that were analyzed by log rank tests. The results were assessed with a $p<0.05$ significance level.

Results

The mean age of patients who underwent HFNT was 70±11.3 years, and the mean age of patients who received NIV was 74.19±10.3 years. There was no statistically significant difference between the patient groups participating in the study according to age (p=0.180). The median duration with COPD diagnosis was 7 (min=3 and max=10) years. Overall, 67.3% (n=37) of the patients were male and 32.7% (n=19) of them were female. The mean duration of ICU stay was 7.6±5 days. When patient respiratory types were evaluated, we found that 44.2% (n=27) of them had type 1 respiratory failure, and 55.8% (n=0.34) had type 2 respiratory failure. When the ultimate clinical results of the patients were evaluated, 78.1% (n=47) were discharged in good condition, 15.4% (n=10) were transferred from the ICU to an inpatient ward, while 6.5% (n=4) died.

In order to evaluate treatment efficacy in patients who were treated with HFNT and NIV, blood gases were measured at baseline (0 hours) and at the 1st, 2nd, 4th and 8th hours after treatment initiation. Evaluations comprised of pH, PaCO2, partial pressure of oxygen (PaO2), lactate, and bicarbonate (HCO3) measurements (Table 1).

While the pH value in the two groups was similar at baseline and at the 8th hour of treatment (p=0.289), the pH value in the HFNT group was significantly higher at the 1st hour of treatment (p=0.001). While there was no significant difference with regard to time-bound changes in pH values in the HFNT group (p=0.130), in the NIV group pH values changed significantly (p=0.030).

Compared to the NIV group, the 1st hour PaCO2 value in the HFNT group was also significantly higher ($p<0.001$). There was no significant difference between the groups with regard to the 8th hour PaCO2, 1st hour PaO2, and 8th hour PaO2 values. In temporal analyses, we found that there was a time-bound decrease in PaCO2 values and decrease in PaO2 values in both groups ($p<0.001$).

There was no significant difference between the 1st hour and 8th hour lactate values between the groups. While there was no significant difference in time-bound changes of lactate and HCO3 values in the HFNT group, temporal changes in the NIV group were significant (p=0.002).

When the length of stay in the ICU was compared, it was found that the HFNT group had a significantly shorter ICU stay that the NIV group (5.42±3.2 *vs.* 7.4±3.6 days; p=0.039). When 28-day mortality was

Table 1. Blood gas values in patients according to treatment groups

		Time					p**
		Initial	**1st hour**	**2nd hour**	**4th hour**	**8th hour**	
pH	HFNT (n=30)	7.3±0.4	7.35±0.5	7.35±0.5	7.35±0.5	7.35±0.7	0.130
	NIV (n=31)	7.28±0.7	7.32±0.6	7.32±0.6	7.31±0.7	7.34±0.9	**0.030**
	p*	0.289	**0.001**	0.102	0.071	0.622	
$PaCO_2$	HFNT (n=30)	70.5±2.8	69.5±1.8	59.54±1.6	59.3± 5.3	58.9±3.3	**<0.001**
	NIV (n=31)	74.8±2.66	66.8±3.04	64.6±3.14	62.12±2.7	58.6±2.2	**<0.001**
	p*	0.240	**<0.001**	0.162	0.499	0.351	
PaO_2	HFNT (n=30)	33.6±9.01	50.44±33.3	58.47±33.2	74.2±11.9	81.7±32.7	**<0.001**
	NIV (n=31)	31.7±2.9	47.4±4.5	55.3±6.6	57.1±7	71.4±6.9	**<0.001**
	p*	0.589	0.889	0.741	0.917	0.894	
Lactate	HFNT (n=30)	4.8±10.2	3.05±7.7	3.3±7.8	3.3±8.5	2.9±7.6	0.217
	NIV (n=31)	3.66±6.9	2.9±6.6	2.9±6.6	2.86±6.09	2.86±6.14	**0.002**
	p*	0.622	0.069	0.877	0.820	0.081	
HCO_3	HFNT (n=30)	32.3±1.5	32.8±1.4	32.1±1.4	33.03±1.5	32.9±1.6	0.130
	NIV (n=31)	30.4±1.6	30.6±1.2	31.6±1.5	31.9±1.5	32.9±1.3	**0.002**
	p*	0.418	0.790	0.845	0.624	0.526	

HFNT = high-flow nasal cannula oxygen therapy; NIV = noninvasive mechanical ventilator; data are expressed as mean ± standard deviation; *between groups; **within groups

evaluated, the mortality rate for HFNT recipients was 6.6%, while mortality rate was 6.4% in the NIV group. The Kaplan-Meier curve analysis did not reveal a statistically significant difference between the two treatment groups in terms of survival (log rank test 0.105; p=0.746) (Fig. 1).

Discussion

In this study, HFNT and NIV were compared in terms of their efficacy in the treatment of COPD patients presenting to the emergency ICU with ARF. The most prominent finding was higher pH and lower PaCO2 at the 1st hour of treatment, while these values were similar at the 8th hour of treatment. All values examined in both groups demonstrated positive changes at the end of the 8th hour. Concerning the length of stay in the ICU, it was found that HFNT recipients had shorter stay. Finally, we also found that there were no significant differences between the two treatment modalities in terms of 28-day mortality.

An important indicator of the patient well-being during COPD exacerbation is blood gas analysis. In our study, the two treatments were found to be similar at the end of the 8th hour. However, we found that HFNT had faster effect, whereas NIV induced gradual improvement. In other words, we found that both pH and PaCO2 values recovered more aggressively in HFNT recipients. Considering that the general vital functions of patients return to normal with rapid recovery of pH and PCO2 levels, it can be concluded that HFNT treatment is more effective than NIV, especially in the acute period of COPD exacerbation. Thus, it is likely that HFNT treatment could be more beneficial for patients, especially in hypercapnic respiratory failure. In a previous study, Fricke *et al.* have reported that HFNT could increase alveolar ventilation and reduce PaCO2 in patients with COPD *via* clearance of the anatomical dead space[15]. In a study somewhat similar to ours, it was found that the 6th and 24th hour treatment results were similar in recipients of either HFNT or NIV[16]. However, we performed a higher number of measurements within a shorter time period and found

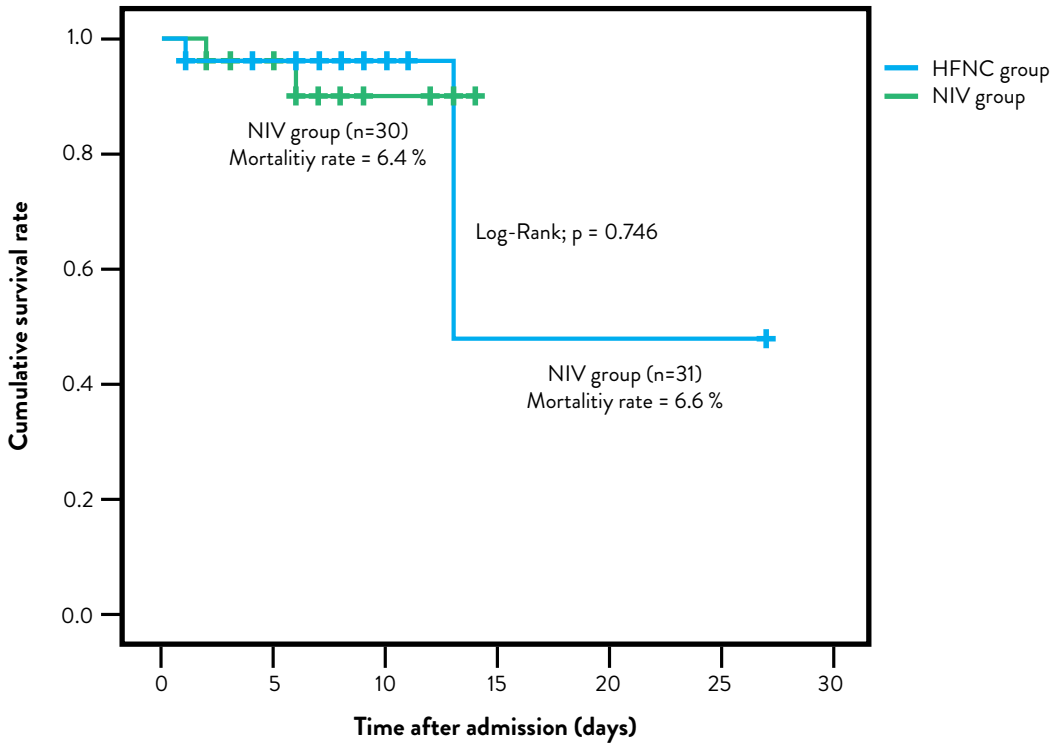

Fig 1. Kaplan-Meier survival curves for treatment groups.

that early response to HFNT was comparatively better than to NIV. However, at longer term, our results were similar to the findings of the abovementioned study.

There are several studies in the literature that examined the effects of NIV and HFNT treatment on blood gas parameters. In COPD patients with a pH value between 7.25 and 7.35, NIV treatment has been shown to affect pH and respiratory rate parameters positively in the first 4 hours[17-19] and decrease the level of PaCO2[20,21]. Similarly, it has been reported in several studies that HFNT lowers PaCO2 rapidly in COPD patients[22,23]. In our study, it was observed that both treatments had positive effects on blood gas parameters in accordance with the literature. The advantages and disadvantages of the two treatments have been studied relatively less frequently.

Sun *et al.* report that pH, PaO2, and PaCO2 values did not differ significantly between patients who received HFNT and NIV treatments at the 6th and 24th hours[24]. Jing *et al.*, in their study which assessed treatments applied to prevent respiratory failure after extubation in COPD patients, report that the 3rd hour pH value was significantly lower in the NIV group compared to the HFNT group. They showed that this difference was also present at the 24th hour of treatment, while it was absent at the 48th hour; furthermore, there was no significant difference between the groups in PaO2 and PaCO2 values; even though it was observed that the PaCO2 value was marginally better in the HFNT group, the difference was not significant[25]. In our study, it was observed that pH and PaCO2 values in patients who applied with COPD exacerbation improved in a shorter time in the HFNT group. Similar to our study, the benefits of HFNT were reported to be similar in patients with hypoxic respiratory failure[19]. In a previous study conducted on HFNT, it has been reported that the HFNT treatment decreased PCO2, reduced respiratory rate and increased tidal volume in COPD patients[20]. Roca *et al.* report that patients using HFNT found this method more comfortable, while also determining decreased respiratory rate and increased PaO2 levels[26]. Therefore, faster regression of abnormalities with HFNT application in our study seems to be in agreement with the

published literature. The HFNT treatment reduces nasopharyngeal dead space, improves oxygenation, decreases breathing effort and respiratory rate, provides a low level of positive airway pressure, and facilitates clearing of secretions by providing heated and humidified air[27]. In our study, these conditions were thought to be among the possible causes of better results with HFNT in the 1st hour of treatment.

Increased length of hospitalization and ICU stay during treatment may increase the risk of nosocomial infections in COPD patients. Therefore, it is important that the treatments shorten these periods as much as possible. In studies examining this relationship, it is reported that NIV significantly decreased the length of stay in the hospital and ICU[28,29]. In a study examining the effects of NIV and HFNT treatments on the length of hospitalization and ICU, both treatments were shown to have similar effect[24]. On the other hand, in the overall evaluation, it has been shown in several studies that both treatments shorten the length of hospital stay[24,28,29]. In our study, it was determined that HFNT was associated with a shorter ICU stay when compared with NIV treatment. This may have been due to improved effectiveness of HFNT therapy or relatively better patient compliance. In addition, the time required for well-being in COPD patients varies according to the type of treatment. Studies have shown that the duration of O2 treatment is significantly higher in patients treated with NIV than in patients treated with HFNT[24]. It is stated that this may be due to better treatment compliance in HFNT recipients. Treatment with NIV is often uncomfortable and it can decrease patient compliance, leading to increased treatment duration[24,28,29]. Therefore, the length of hospital stay may increase. In some recent studies, it has been revealed that NIV treatment is receiving less interest due to significant disadvantages, including possible side effects regarding the skin and lack of user-friendliness[24]. The HFNT treatment protects and moisturizes the respiratory mucosa. It has lower levels of side effects compared to NIV and has become a novel option in the treatment of various patients[27].

Effective treatment of COPD exacerbation will also decrease mortality. The NIV modality is the first-line treatment option when managing respiratory failure due to COPD. It has been revealed in previous studies that NIV treatments reduce endotracheal intubation and respiratory distress, and hence reduce mortality[21,29,30]. It must be noted that NIV has been shown to reduce mortality significantly; thus, it remains as an effective treatment option despite its disadvantages[31].

However, in the literature, the effects of both interventions on mortality have been studied, and both treatments have been shown to significantly reduce mortality[25,32,33]. By comparing interventions, Sun *et al.* report that there was no significant difference between these two modalities in terms of 28-day mortality[24]. In our study, in agreement with the literature, it was observed that the effects of both treatments on mortality in COPD exacerbation were similar. In another study examining the effect of NIV and HFNT treatments on mortality in ARF patients, the positive effect of HFNT treatment on survival compared to NIV treatment has been demonstrated. The authors of this study emphasize that HFNT treatment can be preferred as the first option in ARF patients[34]. Various studies have recommended the use of HFNT treatment in COPD patients, especially in ARF cases with severe clinical findings[35-38]. In agreement with our results, it has been shown that HFNT treatment quickly corrects PCO2 value and thus reduces respiratory rate and prevents increased need for O2[39,40]. In addition, it has been reported that the respiratory rate continued within normal limits for a certain period after treatment in COPD patients using HFNT after extubation, while the respiratory rate increased again in a short time with NIV treatment[41]. This suggests that the effect of HFNT treatment lasts longer.

The main limitation of this study was that it was single-centered and had a relatively small sample size. Considering the results of our study, especially the shorter length of stay in ICU, we believe that controlled randomized studies with larger samples are needed. Due to the nature of the interventions and the fact that the study was carried out in the emergency department, reliable blinding could not be performed, thus causing another limitation. Additionally, the lack of COPD history and lung function tests prior to inclusion in the study was also a limitation. Finally, we did not assess the presence/absence of pneumonia, compliance to therapy during hospital stay and breathing patterns, which have been shown to be associated with treatment failure[42].

Conclusion

Acute respiratory failure is a condition that requires urgent intervention, especially in patients with COPD. Today, NIV is used as the first option in the treatment of ARF, particularly in emergency wards and ICUs. In the treatment of COPD, both NIV and HFNT treatments positively affect the levels of pH, PaCO2, PaO2 and HCO3. The HFNT treatment was more effective than the NIV treatment in terms of pH value and PaCO2 level at the 1st hour of treatment; however, results were similar at the end of the 8th hour. In addition, HFNT recipients were found to have shorter length of stay in the ICU. Therefore, the use of HFNT, especially in severe COPD exacerbation, can be described as an intervention that could yield faster response and may reduce the frequency of nosocomial infections by shortening ICU stay.

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Sažetak

UČINKOVITOST TERAPIJE KISIKOM VISOKOG PROTOKA I NEINVAZIVNE MEHANIČKE VENTILACIJE KOD AKUTNOG ZATAJENJA DISANJA ZBOG KRONIČNE OPSTRUKTIVNE PLUĆNE BOLESTI – RANDOMIZIRANA STUDIJA

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Hiperkapnijsko akutno zatajenje disanja (*acute respiratory failure*, ARF) je česta komplikacija kronične opstruktivne plućne bolesti (KOPB). Kod ARF potrebna je respiracijska potpora koja obično ima visok rizik od smrtnosti. Cilj je bio usporediti učinkovitost neinvazivne mehaničke ventilacije (NIV) koja čini tradicionalni protokol liječenja KOPB i terapije kisikom visokog protoka pomoću nosne kanile (*high-flow nasal therapy*, HFNT) kao novije metode zbrinjavanja. Istraživanje je provedeno od 20. kolovoza 2019. do 20. prosinca 2019. godine kao prospektivna randomizirana kontrolirana studija. U istraživanje su bili uključeni bolesnici s ARF zbog KOPB. Procesom randomizacije 30 bolesnika liječeno je pomoću HFNT, a 31 bolesnik pomoću NIV. Vrijednost pH u prvom satu terapije bila je značajno viša u skupini HFNT (p=0,001). U skupini HFNT daljnje vrijednosti pH nisu pokazivale značajne razlike, dok su se u skupini NIV značajno mijenjale (p=0,030). Vrijednost PaCO2 u prvom satu u skupini HFNT bila je značajno viša u usporedbi sa skupinom NIV (p<0,001). Utvrđeno je da se vrijednost PaCO2 značajno snižavala, a vrijednost PaO2 rasla tijekom praćenja u objema skupinama (p<0,001). Nije bilo značajnih razlika unutar skupine u vrijednostima laktata i HCO3 u skupini HFNT, dok su odnosne promjene u skupini NIV bile značajne (p=0,002). U usporedbi sa skupinom HFNT, boravak u jedinici intenzivnog liječenja (JIL) bio je značajno duži u skupini NIV (p=0,039). Primjena HFNT, poglavito u težih bolesnika s KOPB, može se opisati kao intervencija koja može biti korisna u akutnom razdoblju i može smanjiti učestalost bolničkih infekcija kroz skraćivanje boravka u JIL.

Ključne riječi: *Kronična opstruktivna plućna bolest; Akutno zatajenje disanja; Neinvazivna mehanička ventilacija; Terapija kisikom visokog protoka pomoću nosne kanile*