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FACTORS OF NON-INVASIVE VENTILATION (NIV) FAILURE IN PATIENTS WITH ACUTE HYPOXEMIC RESPIRATORY FAILURE DUE TO SEVERE COMMUNITY ACQUIRED PNEUMONIA (CAP)

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Abstract: Background: NIV is recommended as a first line of treatment for acute hypercapnic respiratory failure even in patients with acidosis. On the other hand, experts have a controversial opinion when it comes to a NIV trial for acute hypoxemic respiratory failure. Most of them don't recommend NIV in severely hypoxemic patients because many studies report failure rates from 20 to 70,3% in this particular setting. Over the years, the use of NIV for acute hypoxemic respiratory failure has increased and the failure rates have dropped, mainly because clinicians make better patient selection and they are more aware of the factors, indicating pending NIV failure.
Aim: The aim of our study is do determine the NIV failure rate in a cohort of patients with severe CAP, treated in an intensive care unit (ICU) of a specialized center for pulmonary diseases and to study the factors that are associated with NIV failure.
Materials and methods: We studied a prospective cohort of 56 patients with severe CAP that developed acute hypoxemic respiratory failure and were put on NIV. 15 of them had pneumonia without ARDS; 9 – mild, 24 – moderate and 8 – severe ARDS. All of them were ventilated with pressure-supported modes (S, S/T, AVAPS) or CPAP only, taking into account the protective ventilation strategy. We recorded the patients' age, CURB 65 and SAPS II score on admission and their heart rate (HR), respiratory rate (RR) and parameters of oxygenation, obtained from an arterial blood-gas analysis (ABG) on admission, 1 h and 24 h after initiation of NIV. Then we compared those parameters between patients that succeeded and those that failed an initial NIV trial.
Results: Of all 56 patients, undergoing a NIV trial, only 8 (14%) failed and were intubated. 5 of them died in the ICU and the other 3 were extubated successfully. The reasons for NIV failure were: insufficient correction of hypoxemia in 6 patients, large leak in 1 and delirium in 2. After conducting a Mann-Whitney U test, we found statistically significant differences in age (median: 56,5; IQR: 18,5 vs. median: 67,5; IQR: 26,5; p=0,027), PaO_2/FiO_2 on the 1st (median: 161; IQR: 81,47 vs. median: 120,88; IQR: 50,13; p=0,039) and 24th hour (median: 183,56; IQR: 71,45 vs. median: 118,18; IQR: 56,47; p=0,011) after ventilation onset and HCO_3 on admission (median: 23,59; IQR: 5,23 vs. median: 18,6; IQR: 7,15;p=0,006), on the 1st (median: 24,5; IQR: 5,33 vs. median: 20,35; IQR: 6,78, p=0,013) and 24th hour (median: 25,45; IQR: 7,13 vs. median: 21,6; IQR: 4,4; p=0,01) after ventilation onset between the groups of NIV success and failure. To investigate the strength of association between these parameters and NIV failure, we conducted a Kruskal-Wallis H statistical analysis and computed the correlation coefficient of Cohen W. It showed that all of the above listed factors have a strong association with NIV failure.
Conclusion: In severe CAP with or without ARDS, causing acute hypoxemic respiratory failure, NIV can be a safe option for respiratory support with close monitoring of PaO_2/FiO_2 and HCO_3, which may indicate upcoming failure.
Keywords: non-invasive ventilation, failure, risk factors, community acquired pneumonia, acute respiratory failure.

1.BACKGROUND

NIV failure is defined as worsening of respiratory failure with endotracheal intubation and invasive mechanical ventilation (IMV) or death of the patient during a NIV trial. A lot of factors contribute to NIV failure and different trials report NIV failure rate between 20 and 70,3% in the setting of acute hypoxemic respiratory failure. NIV failure per se is an independent risk factor, associated with increased mortality, especially in acute hypoxemic respiratory

failure. [26] Data from a French study, conducted in 2016, show, that the use of NIV in acute hypoxemic respiratory failure in the last years increases, and its failure rates drop as well. These results may be due to improved awareness of the factors, associated with NIV failure and better patient selection. Clinicians make better patient selection and they are more aware of the factors, indicating pending NIV failure. [17]

NIV failure can be classified in immediate, early or late NIV failure.

Immediate is the NIV failure that occurs in the first hour after ventilation onset. It is caused mainly by psychomotor agitation instead of a physiological impediment to ventilation or worsening patient condition. [26] The main reasons for its occurrence are: weak cough reflex, hypercapnic encephalopathy or coma (Some studies suggest that an NIV trial can be conducted even in severely hypercapnic patients with neurologic decrement with the aim of rapid $PaCO_2$ reduction. [28]), agitation and patient-ventilator asynchrony, caused by a large leak.

Early is the NIV failure between the 1st and the 24th hour after ventilation onset. It is the most common type of NIV failure and the major risk factors for its occurrence are associated with the underlying disease, causing acute respiratory failure. [26] According to several studies the NIV failure rate is larger in acute hypoxemic then in acute hypercapnic respiratory failure. [2,4,5,7,11,15,19,21] The main reasons the occurrence of early NIV failure are: pneumonia [26,31], poor ABG on admission [5], SAPS II score > 35 on admission [3,4,24,34], inability to correct the hypoxemia in the first hours [3,4,8,12,16,18,24], respiratory rate > 25/min one hour after ventilation onset [18,23,26,34], tidal volume > 9.5 ml/kg [10], late initiation of the NIV trial [26], worsening radiological scores in the first 24 hours [26], shock [12,16,22,27], increased alveolo-arterial gradient ($A\text{-}aDO_2$) 24 hours after ventilation onset [9,23].

Late NIV failure occurs after the first 24 hours after an initial good response to therapy. In the acute setting it is associated with fluctuations of the patient's general condition during the course of the disease [26], inadequate ventilation settings with patient-ventilator asynchrony [33] or inappropriate interface selection causing leakage [6] or decubital wounds [26] and lack of humidification [26].

2. AIM

The aim of our study is do determine the NIV failure rate in a cohort of patients with severe CAP, treated in an ICU of a specialized center for pulmonary diseases and to study the factors that are associated with NIV failure.

3. MATERIALS AND METHODS

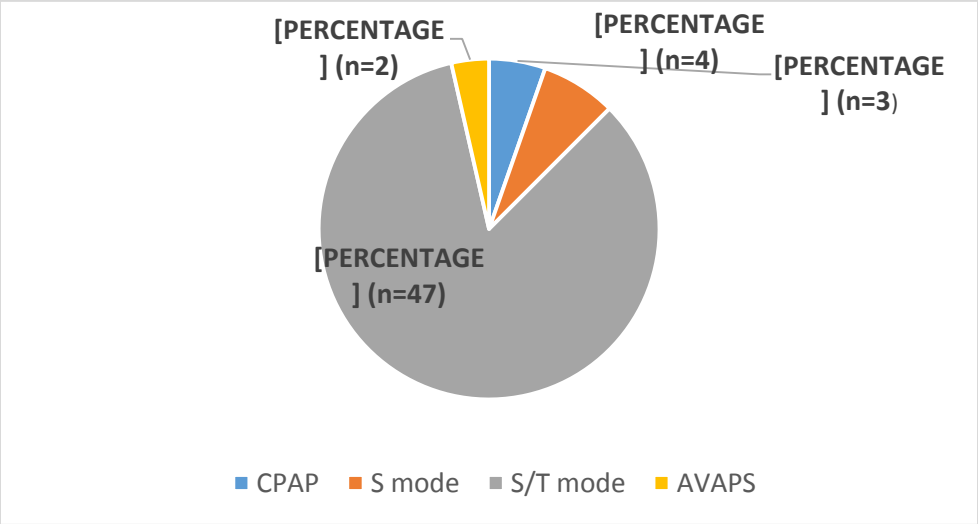
We studied a prospective cohort of 56 patients with severe CAP that developed acute hypoxemic respiratory failure and were put on NIV not later than two hours after hypoxemia verification (PaO_2 < 60 mmHg in ABG while breathing room air or low flow oxygen) and inability to correct it with oxygen therapy alone. The diagnosis of severe CAP was made according to the criteria of the American Thoracic Society. [20] Patients under 18 years of age, pregnant women, those with cardiogenic pulmonary edema, lung carcinoma, active tuberculosis, coma, agitation or encephalopathy, cardiac or respiratory arrest, hemodynamic instability, acute myocardial infarction, inability to clear secretions, hematemesis or hemoptysis, head trauma, uncontrollable vomiting and significant pleural effusion were excluded from the study.

After inclusion we classified the patients according to their disease severity assessed by the criteria of the Berlin definition for ARDS. [30] 15 of them had pneumonia without ARDS, 9 – mild, 24 – moderate and 8 – severe ARDS. All patients were ventilated with pressure-supported modes (S, S/T, AVAPS) or CPAP only (Fig. 1), taking into account the protective ventilation strategy: EPAP, assuring alveolar recruitment and satisfactory oxygenation without a subjective feeling of discomfort with a minimum of 4 cmH_2O; IPAP, assuring a tidal volume of 6-7 ml/kg with a maximum of 25 cmH_2O; RR between 20 and 25/min and an initial FiO_2 between 0,6 and 1q which was tailored according to an ABG follow up. The decision which ventilation mode will be chosen in the individual patient was made by the attending physician on admission.

During the first few days of treatment the patients spent more than 16 hours a day on ventilation (intensive NIV) and after improvement of condition the period without ventilation was extended.

NIV was discontinued on the following circumstances: 1. Clinical improvement with adequate oxygenation, maintained with oxygen therapy only; 2. Clinical deterioration and need for tracheal intubation and IMV; 3. Patient refusal. We defined the following intubation criteria: 1. Refractory hypoxemia, unresponsive to NIV for 24 hours; 2. Worsening of oxygenation after he 24th hour, unresponsive to changes in ventilator settings; 3. Disturbed consciousness, making the patient uncooperative; 4. Unstable hemodynamics, acute myocardial infarction; 5. Inability to protect the airways; 6. Increased sputum production or uncontrollable vomiting.

Fig. 1 NIV modes used in the study in percentage and absolute number of patients



During the treatment we recorded the patients' age, history of fever, smoking and co-existing disease, laboratory tests, CURB 65 and SAPS II score on admission and their HR, RR and parameters of oxygenation, obtained from an ABG, on admission, 1 h and 24 h after initiation of NIV. Then we compared those parameters between patients that succeeded and those that failed an initial NIV trial.

The statistical analysis was conducted with the IBM SPSS package v. 25. Due to the non-parametric nature of the data we used the Mann-Whitney U and Kruskal-Wallis H statistical tests.

4. RESULTS

The initial characteristics of the patients are showed in table 1.

Table 1 Demographic characteristics, case history, physical examination and ABG data on admission

Variable	Median value	Co-existing disease	Number of patients
Age	Median: 58,5; IQR: 18	**Without co-ecisting disease**	n=14
Male/ Female	31/25	**Systemic arterial hypertension**	n=30
Packyears	Median: 20; IQR: 34,25	**Diabetes melitus**	n=16
Highest fever in the last week (^{o}C)	Median: 38.6; IQR: 1	**COPD (without exacerbation)**	n=10
HR	Median: 100; IQR: 27,5	**Obesity hypoventilation syndrome**	n=8
Systolic blood pressure	Median: 125,5; IQR: 37,5	**Obstructive sleep apnea**	n=5
RR	Median: 34; IQR: 6	**Obesity**	n=11
CURB 65	Median: 2; IQR: 1	**Cor pulmonale**	n=14
SAPS	Median: 35,5; IQR: 19,75	**Heart failure**	n=12
pH	Median: 7,48; IQR: 0,08	**Ischamic heart disease**	n=11
$PaCO_2$	Median: 31,3; IQR: 9,4	**History of stroke**	n=1

PaO_2	Median: 47,6; IQR: 13,97	**Other**	n=18
PaO_2/FiO_2	Median: 153,81; IQR: 87,73		
HCO_3	Median: 23,4; IQR: 6,5		
Sat %	Median: 86,5; IQR: 12,23		

Of all 56 patients, undergoing a NIV trial, only 8 (14%) failed and were intubated. 5 of them (8,9% from the whole group and 62,5% of the NIV failure group) died in the ICU and the other 3 were extubated successfully. Of these 8 patients 2 had early and the other 6 – late NIV failure. The reasons for NIV failure were: insufficient correction of hypoxemia in 6 patients, large leak in 1 and delirium in 2. Amongst the diseased 3 were with mild, 3 – with moderate and 2 – with severe ARDS (Fig. 3).

Age, CURB 65 and SAPS II score on admission, as well as the physical examination parameters and the results from the ABGs on admission, the 1st and the 24th hour were compared between the two groups (Table 2).

From all of the studied parameters, we found statistically significant differences in age (p=0,027), PaO_2/FiO_2 on the 1st (p=0,039) and 24th hour (p=0,011) after ventilation onset and HCO_3 on admission (p=0,006), on the 1st (p=0,013) and 24th hour (p=0,01) after ventilation onset between the groups of NIV success and failure.

Table 2 Comparison of age, CURB 65 and SAPS II scores, physical examination and ABG results

	NIV success (n=48)	**NIV failure (n=8)**	**p**
Age	Median: 56,5; IQR: 18,5	Median: 67,5; IQR: 26,5	**0,027**
CURB 65 on admission	Median: 2; IQR: 2	Median: 3; IQR: 1,5	0,052
SAPS II on admission	Median: 33; IQR: 19,75	Median: 40; IQR: 23,75	0,069
RR on admission	Median: 33,5; IQR: 5,75	Median: 35; IQR: 9,25	0,133
HR on admission	Median: 100; IQR: 16,5	Median: 115; IQR: 60,75	0,413
pH on admission	Median: 7,49; IQR: 0,09	Median: 7,45; IQR: 0,09	0,146
$PaCO_2$ on admission	Median: 31,95; IQR: 9,53	Median: 28,2; IQR: 9,05	0,065
PaO_2 on admission	Median: 47,7; IQR: 14,03	Median: 46,3; IQR: 20,83	0,326
PaO_2/FiO_2 on admission	Median: 153,97; IQR: 74,4	Median: 153,33; IQR: 120,37	0,845
HCO_3 on admission	Median: 23,59; IQR: 5,23	Median: 18,6; IQR: 7,15	**0,006**
Sat % on admission	Median: 86,6; IQR: 12,28	Median: 23,7; IQR: 17,03	0,146
RR on the 1st hour	Median: 25,5; IQR: 6	Median: 29; IQR: 11,5	0,206
HR on the 1st hour	Median: 90; IQR: 15,75	Median: 95; IQR: 41,25	0,454
pH on the 1st hour	Median: 7,46; IQR: 0,09	Median: 7,39; IQR: 0,2	0,099
$PaCO_2$ on the 1st hour	Median: 34,35; IQR: 9,28	Median: 32,95; IQR: 7	0,739
PaO_2 on the 1st hour	Median: 84,2; IQR: 29,4	Median: 76,5; IQR: 39,55	0,605
PaO_2/FiO_2 on the 1st hour	Median: 161; IQR: 81,47	Median: 120,88; IQR: 50,13	**0,039**
HCO_3 on the 1st hour	Median: 24,5; IQR: 5,33	Median: 20,35; IQR: 6,78	**0,013**
Sat % on the 1st hour	Median: 96,95; IQR: 3	Median: 96,2; IQR: 7,23	0,374
RR on the 24th hour	Median: 24; IQR: 5	Median: 30; IQR: 20	0,115
HR on the 24th hour	Median: 85; IQR: 10	Median: 100; IQR: 42,5	0,095
pH on the 24th hour	Median: 7,45; IQR: 0,07	Median: 7,44; IQR: 0,06	0,326
$PaCO_2$ on the 24th hour	Median: 36,15; IQR: 8,88	Median: 34,3; IQR: 9,9	0,351
PaO_2 on the 24th hour	Median: 83,7; IQR: 23,95	Median: 65,2; IQR: 22,8	0,063
PaO_2/FiO_2 on the 24th hour	Median: 183,56; IQR: 71,45	Median: 118,18; IQR: 56,47	**0,011**
HCO_3 on the 24th hour	Median: 25,45; IQR: 7,13	Median: 21,6; IQR: 4,4	**0,01**
Sat % on the 24th hour	Median: 96,8; IQR: 2,5	Median: 94; IQR: 7,5	0,7

Table 3 Cohen W coefficient of those variables, that are significantly different between the NIV success and NIV failure groups

Variable	Cohen W coefficient
Age	0,64
PaO_2/FiO_2 on the 1st hour	0,57
PaO_2/FiO_2 on the 24th hour	0,84
HCO_3 on admission	0,96
HCO_3 on the 1st hour	0,79
HCO_3 on the 24th hour	0,84

To investigate the strength of association between these parameters and NIV failure, we conducted a Kruskal-Wallis H statistical analysis and computed the correlation coefficient of Cohen W (Table 3). The Cohen W coefficient is being interpreted in the same way as Pearson's coefficient. With values ≥0,1, there is a weak association, ≥0,3 – moderate association and ≥0,5 – strong association between the independent and depending variables. [14] In our case the independent variable is NIV failure and the dependent – the various factors, causing it. After conducting this statistical analysis, in becomes clear that all of the above listed factors have a strong association with NIV failure.

5. DISCUSSION

The NIV failure rate in our study (14%) is lower compared to previous studies (20 – 70,3%). The most frequently mentioned reasons for NIV failure in cases of acute hypoxemic respiratory failure with lung origin are the low PaO_2/FiO_2 on admission and 1 hour after ventilation onset, high APACHE II and SAPS II scores, the need for continuous vasopressor therapy and worsening of the radiological findings. [1,4,9,22,27]

Antoneli et al. suggest 34 to be the cutoff point of the SAPS II score, after which there is a sharp increase of NIV failure risk. Nikolini et al. even lower the bar to 29 points in patients with H1N1 influenza pneumonia. [3,25] The median SAPS II score on admission in our study is 35,5 – slightly higher than that, proposed by Antoneli. Of all 56 patients that underwent an NIV trial 29 (51,79%) had SAPS II > 34. We found no statistically significant difference in the SAPS II score between the NIV success and NIV failure groups.

According to Carron et al. a $PaO_2/FiO_2 \leq 115$ is an indicator of pending NIV failure in patients with severe pneumonia. [9] In his study on H1N1 influenza pneumonia reports an increase of the rate of NIV failure even by $PaO_2/FiO_2 \leq 127$ on admission. [25] In our study we conducted a NIV trial in 12 (21,43%) with $PaO_2/FiO_2 \leq 115$ on admission. The difference in the median values of PaO_2/FiO_2 between the NIV success and NIV failure groups is minimal and doesn't reach statistical significance. These results are consistent with those of Uçgun et al., who denies the role of PaO_2/FiO_2 and APACHE II score on admission as risk factors for NIV failure. [32]

Actually PaO_2/FiO_2 an admission is rarely cited in studies. Most of the trials use the dynamic of PaO_2/FiO_2 in the first hours after initiation of therapy to predict NIV failure. In his study Carron defines $PaO_2/FiO_2 \leq 140$ one hour after ventilation onset in patients with severe CAP and $PaO_2/FiO_2 \leq 175$ in ARDS as risk factors for NIV failure. [9] Sehgal et al. determine a cutoff value of $PaO_2/FiO_2 < 150$ in mild to moderate ARDS. [29] Nikolini suggests almost the same cutoff point ($PaO_2/FiO_2 \leq 149$) in H1N1 influenza pneumonia. Antoneli also agrees with Sehgal and Nikolini. In his study he issues a statement that patients with $PaO_2/FiO_2 < 146$ 1 hour after ventilation onset and de novo acute hypoxemic respiratory failure are at high risk of NIV failure. [4] other studies report lower values of PaO_2/FiO_2 after the first few hours of NIV, but don't cite exact cut off points after which endotracheal intubation is recommended. [8,18,23,27,32] Like the studies quoted above, we found out that PaO_2/FiO_2 on the 1st and 24th hour after ventilation onset are lower in the NIV failure than in the NIV success group. Due to the small cohort we couldn't determine a cutoff value of the respiratory quotient, predictive for NIV failure.

Regarding the other ABG values - pH, PaO_2, $PaCO_2$ and HCO_3^-, only the difference in HCO_3^- is statistically significant between the two study groups. The HCO_3^- is lower in the NIV failure group on admission, as well as on the 1st and the 24th hour after ventilation onset. Similar observation is made by Carillo et al., who report that a low HCO_3^- 1 hour after initiation of treatment is a risk factor for NIV failure. [8]

Some studies point out improvement of the HR and RR in NIV success patients. [1,8,13,18] Although this seems to be a logical finding, we didn't find any association between HR and RR with NIV failure in our cohort. This discrepancy can be due to the adequate relief of the symptoms of respiratory distress by the ventilation. Also the number of patients in the NIV failure group is too small to reach statistical significance.

6. CONCLUSION

In severe CAP with or without ARDS, causing acute hypoxemic respiratory failure, NIV can be a safe option for respiratory support with close monitoring of PaO_2/FiO_2 and HCO_3^-, which may indicate an upcoming failure.

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