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Noninvasive ventilation for acute hypercapnic respiratory failure: intubation rate in an experienced unit.

Damien Contou[1], M.D.; Chiara Fragnoli[1], M.D.; Ana Córdoba-Izquierdo[1], M.D.; Florence Boissier[1], M.D.; Christian Brun-Buisson[1], M.D. and Arnaud W. Thille[1, 2, 3], M.D., Ph.D.

Author's affiliations:

(1) Medical Intensive Care Unit, AP-HP, Henri Mondor Hospital, Créteil, France

(2) INSERM U955, Créteil, France

(3) Medical Intensive Care Unit, University Hospital of Poitiers, Poitiers, France.

Correspondingauthor: Damien Contou, Réanimation Médicale, Hôpital Henri Mondor, 51 avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France.

Mail: contou@club-internet.fr

Phone Number: +33 149 812 344; Fax number: +33 149 814 943

Running Head: Predictive factors for NIV failure in acute hypercapnic respiratory failure

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ABSTRACT

Background

Failure of noninvasive ventilation (NIV) is common in patients with chronic obstructive pulmonary disease (COPD) admitted to the intensive care unit (ICU) for acute hypercapnic respiratory failure (AHRF). We aimed to assess the rate of NIV failure and to identify early predictors of intubation under NIV in patients admitted for AHRF of all origins in an experienced unit.

Methods

Observational cohort study using data prospectively collected over a 3-year period after the implementation of a nurse-driven NIV protocol in a 24-bed medical ICU of a French university hospital.

Results

Among 242 patients receiving NIV for AHRF ($PaCO_2$ > 45mmHg), 67 had cardiogenic pulmonary edema (CPE), 146 had acute-on-chronic respiratory failure (AOCRF) - including patients with COPD (n=99) or another chronic respiratory disease (n=47) - and 29 had non-AOCRF (mostly pneumonia). Overall, the rates of intubation and ICU mortality were respectively 15% and 5%. Intubation rates were 4% in CPE, 15% in AOCRF and 38% in non-AOCRF (p<0.001). After adjustment, non-AOCRF was independently associated with NIV failure, as well as acidosis (pH <7.30) and severe hypoxemia (PaO_2/FiO_2 ≤ 200) after 1 hour of NIV initiation, whereas altered consciousness on admission and ventilatory settings had no influence on outcome.

Conclusion

Intubation rate could be reduced to 15% in patients receiving NIV for AHRF, with a mortality rate of only 5%. Whereas the risk of NIV failure is associated with hypoxemia and acidosis after initiation of NIV, it is also markedly influenced by the presence or absence of an underlying chronic respiratory disease.

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KEY WORDS

Non-invasive ventilation, acute respiratory failure, acute-on-chronic respiratory failure, cardiogenic pulmonary edema, chronic obstructive pulmonary disease, hypercapnic coma, endotracheal intubation.

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INTRODUCTION

Non-invasive ventilation (NIV) reduces the rates of intubation and mortality in patients with severe acute exacerbation of chronic obstructive pulmonary disease (COPD)[1, 2] or cardiogenic pulmonary edema (CPE).[3] In our intensive care unit (ICU), NIV has been used since the late 1980's and shown by Brochard et al.[4] to be beneficial in patients admitted with acute exacerbation of COPD. A subsequent prospective randomized study demonstrated that NIV was associated with reduced rates of endotracheal intubation and mortality in these patients.[5]

Several large surveys show that the use of NIV have become widespread in treatment of severe exacerbation of COPD in Europe and in the United States.[6-8] Despite the increasing experience with this technique, the rate of NIV failure remains high, between 20% to 30% in COPD patients admitted to ICUs.[2, 5, 9, 10] NIV may also be used as first-line management of non-COPD patients having acute hypercapnic respiratory failure (AHRF), but the rate of NIV failure and intubation can exceed 30% to 40% in this group.[8, 11, 12] In COPD patients, the severity of hypercapnia and/or acidosis after initiation of NIV is a major predictor of NIV failure.[11, 13-15] However, no study has evaluated the impact of ventilatory settings and respiratory parameters under NIV on outcome and little information is available on hypercapnic non-COPD patients treated with NIV.

The aims of this study were 1) to assess the rate of NIV failure in patients admitted for AHRF whatever the cause causes in an experienced unit, and 2) to identify early predictors of intubation under NIV.

Some of the results of this study have been previously reported in the form of an abstract at the 2012 meeting of the European Society of Intensive Care Medicine (ESICM) in Lisbon, Portugal.[16]

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PATIENTS AND METHODS

This observational cohort study was conducted in our 24-bed medical ICU at Henri Mondor University hospital in Créteil, France. The Institutional Review Board of the French Society for Respiratory Medicine approved this noninterventional study and waived the need for informed consent.

Patients

We prospectively included all consecutive patients admitted during a 3-year period (June 2008 – June 2011) and who received NIV as initial ventilatory support for AHRF. AHRF was defined as recent dyspnea with sternocleidomastoid muscle activation and a respiratory rate > 25 breaths/min and/or an arterial pH < 7.35, with a $PaCO_2$ above 45 mmHg. We excluded patients who were intubated before ICU admission or intubated upon ICU admission without prior NIV, and patients for whom NIV was used with a “do not intubate” order.

Non-invasive ventilation protocol and definitions

The study was conducted after the implementation, in June 2008, of a nurse-driven NIV protocol which included prospective daily collection of clinical data and ventilatory parameters on a specific NIV monitoring form. When the NIV form was unavailable or incomplete, data were retrieved from the patient’s records.

All stages of the protocol had been developed within a multidisciplinary working group including ICU physicians, nurses, and respiratory therapists. A daily NIV prescription by the physician indicated the duration of NIV sessions and targeted expiratory tidal volume (around 6-8 ml/kg) and SpO_2 (88-92% in patients with AOCRF and ≥ 94% in other patients). Given that respiratory therapists are not present every day and all day long in our unit, the protocol aimed at empowering nurses to adjust the ventilatory settings and to improve the patient's tolerance to NIV. Nurses are not as highly skilled in mechanical ventilation as respiratory therapists in the United States can be, and were not involved in the decision to intubate. The first objective was to reach the targeted expiratory tidal volume and SpO_2, and to improve the patient's tolerance to NIV following a simple decision algorithm (see the protocol and algorithm used in the supplementary material).

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Pressure-support (PS) ventilation was started using a pressure-support level of 8 cmH_2O, a positive end-expiratory pressure (PEEP) level of 0 cmH_2O, an inspiratory trigger of 3 L/min, and a maximal inspiratory time of 1 second. The nurses then adjusted the ventilatory parameters including pressure-support level and FiO_2 according to the protocol. Pressure-support level was gradually increased by 2 cmH_2O steps to reach the target expiratory tidal volume and PEEP level was then adjusted as prescribed. FiO_2 was gradually adjusted by 5% step to reach the targeted SpO_2. Non-invasive ventilation was applied intermittently for periods of at least 2 hours, with a minimal duration of 6 hours per day, or continuously in case of hypercapnic coma, and was maintained until signs of respiratory distress improved. An algorithm was used by nurses in case of leaks, which involved first repositioning of the mask, second reducing the PEEP level at 2 cmH_2O, third, reducing the pressure-support level by steps of 2 cmH_2O until the minimal expiratory volume was reached, and fourth changing the mask interface. Assist-control ventilation could be used transiently in patients with hypercapnic coma and triggering insufficient tidal volume despite high PS levels.

A mobile cart containing all types and sizes of interfaces was available at the bedside during initiation of NIV. NIV was performed via a non-vented full-face mask (FreeMotion™ RT041, Fisher and Paykel, Auckland, New Zealand or Ultra Mirage™, Resmed, CA, USA), with an ICU ventilator using a dedicated NIV mode (Evita XL, Dräger, Lübeck, Germany, or Engström Carestation, GE Healthcare, Fairfield, CT, USA), equipped with a heated humidifier (MR850, Fisher & Paykel, Auckland, New Zealand).

The following criteria were used for endotracheal intubation: hypercapnic coma with inability to deliver tidal volume, loss of consciousness or persistent hypercapnic coma under NIV, psychomotor agitation making nursing care impossible and requiring sedation, pronounced worsening in signs of respiratory distress with a respiratory rate above 40 breaths/min under NIV, SpO_2 remaining below 90% despite FiO_2 100%, and persistent hypotension despite fluid resuscitation requiring vasopressors. Worsening respiratory acidosis or absolute values of pH/PCO_2 were not used as criteria for intubation in the absence of other signs cited above.

Data collection

From the NIV monitoring forms, we analyzed the number and duration of NIV sessions, ventilator settings (pressure support level, positive end-expiratory pressure, FiO_2), ventilatory parameters (SpO_2,

respiratory rate, expiratory tidal volume), level of consciousness assessed using the Richmond Agitation-Sedation Scale (RASS),[17] NIV tolerance (scored from 0 for "poor" to 3 for "excellent"), amount of leaks (scored from 0 for "no leaks" to 3 for "major") and hemodynamic parameters (heart rate, blood pressure). Poor tolerance was considered as a score of 0 or 1, and major leaks as a score of 2 or 3. Altered consciousness was defined as a RASS < 0 and coma as a Glasgow coma score ≤ 8. Blood gases were routinely measured 1 hour after initiation of NIV. Clinical data (respiratory rate, SpO_2, blood pressure, heart rate, Glasgow coma score) and blood gases at admission before NIV initiation were retrospectively collected from the medical chart. An independent pulmonologist classified patients according to the underlying cause of AHRF into one of three subgroups: (1) cardiogenic pulmonary edema (CPE), (2) Acute-on-chronic respiratory failure (AOCRF) including patients having chronic respiratory failure associated with COPD or with other causes (non-COPD), and (3) non-AOCRF, which included patients without underlying chronic respiratory disease.

Statistical analysis

All data were expressed as mean (± standard deviation) or as median and interquartile ranges [25^{th}-75^{th} percentiles], and dichotomous variables were reported as number (percentage). Qualitative data were compared using the chi-square test, and quantitative data using the unpaired Student's *t*-test or Kruskall Wallis test.

To evaluate independent factors associated with NIV failure at admission, univariate risk factors with a p value <0.10 were examined using backward stepwise logistic regression analysis. Among related significant univariate factors, only the most clinically relevant were entered into the regression model in order to minimize the effect of colinearity. We therefore included the cause of AHRF, tachypnea and altered consciousness at admission, and hypoxemia and respiratory acidosis after NIV initiation whereas SAPS 2 was not entered into the model. We considered two-tailed *p* values <0.05 as significant. The statistical analysis was performed using the statistical software package STATA version 10.1 (Stata Corp., TX, USA).

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RESULTS

Patients

Over the 3-year period, 242 patients received NIV for AHRF, including 67 with cardiogenic pulmonary edema (CPE), 146 with acute-on-chronic respiratory failure (AOCRF) and 29 with non-AOCRF **(Figure 1)**. Prospective data collection of ventilatory parameters under NIV was available for 83% (201/242) of them. Among the 47 patients with non-COPD AOCRF, 30 had obesity and/or obstructive sleep apnea syndrome (median body mass index of 38 kg/m^2) while others had bronchiectasis (N=4), permanent ventilatory impairment due to asthma (N=4), pulmonary cancer (N=2), chest-wall disease (N=3), myopathy (N=2), and myasthenia gravis (N=2). Among the 29 patients having non-AOCRF and hypercapnia, 24 had pneumonia (including 8 patients with clinical criteria for acute respiratory distress syndrome), and 5 had drug intoxication. The patients' characteristics at admission and their outcome in ICU are reported **Table 1**. Overall, 31 patients were comatose either at admission (n=15) or during the first 24 hours (n=16).

Rates of NIV failure and ICU-mortality

The overall rates of intubation and mortality were respectively 15% (36/242) and 5% (13/242). Intubation rates were 4% (3/67) in CPE, 15% (22/146) in AOCRF – with an identical rate in COPD and non-COPD patients - and 38% (11/29) in non-AOCRF ($p<0.001$) (**Figure 2**); corresponding ICU mortality rates were 3% (2/67), 5% (7/146) and 14% (4/29) ($p=0.08$) (**Figure 3**); Intubation rates were 11% (13/115) in patients having a pH on admission ≥ 7.30 and 18% (23/128) in those having a pH < 7.30 ($p=0.15$). In-ICU mortality rate of intubated patients was 36% (13/36).

Factors associated with NIV failure

Among variables recorded on ICU admission, the etiology of AHRF and tachypnea (> 30 breaths/min) were independently associated with NIV failure **(Table 2)**. Non-AOCRF was an independent predictor of NIV failure as compared to patients with AOCRF and CPE.

Pressure-support level adjusted by nurses was significantly greater 1 hour after NIV initiation than at NIV initiation (9.5±3.0 cmH_2O vs. 9.2±2.6, $p=0.036$) while tidal volume remained similar (468±144 ml

vs. 465±135, p=0.64). Although not significantly different, expiratory tidal volume 1 hour after NIV initiation tended to be lower in patients who failed NIV compared to those who succeeded in NIV.

Among variables recorded at one hour after NIV initiation, ventilatory settings and patient's tolerance to NIV or amount of leaks had no influence on outcome, whereas severe hypoxemia ($PaO_2/FiO_2 \leq 200$ mmHg) and severe acidosis (pH<7.30) were independently associated with NIV failure.

After adjustment, altered consciousness at admission was not associated with NIV failure and only 23% (14/60) of patients who had encephalopathy were intubated. Among the 31 comatose patients, 15 (48%) succeeded in NIV without need for endotracheal intubation.

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DISCUSSION

In hypercapnic patients receiving NIV as first-line ventilatory support for acute respiratory failure of various origins, we found that the overall rate of intubation was only 15%. However, this rate differed markedly according to the underlying cause of acute respiratory failure and reached 38% in patients without chronic respiratory disease (non-AOCRF). Among patients with AOCRF, no difference was found between COPD and non-COPD patients.

Rate of NIV failure according to the cause for acute hypercapnic respiratory failure

The intubation rate of only 4% in patients receiving NIV for CPE compares favorably with the 14% rate reported in a meta-analysis[3] and the 18% rate reported in a survey from the United States.[12] Some studies have even reported intubation rates exceeding 20% in the subset of hypercapnic patients.[18] Our results are, however, consistent with those of Nava et al.[19] who reported an intubation rate of only 6% in hypercapnic patients with CPE treated in an ICU having extensive experience with NIV.

The 15% intubation rate we recorded in patients with AOCRF is also lower than the 20% to 30% rates usually reported in studies evaluating NIV in COPD patients.[5, 8-10, 12] Plant et al. reported an overall intubation rate of only 15% in patients receiving NIV in respiratory wards but this rate reached 36% in patients with a pH<7.30[20] whereas only 18% of our patients with a pH<7.30 needed intubation. A recent study reported a rate of NIV failure of only 11% in severe COPD patients admitted to a specialized respiratory ICU,[21] with an ICU mortality rate of 8%, which is close to the 5% recorded in our study. In this large observational study, rates of NIV failure and mortality were significantly lower in patients with obesity-hypoventilation syndrome than in those with COPD.[21] We found a similarly low risk of NIV failure (15%) in patients having COPD or another underlying chronic respiratory disease. Indeed, NIV has been successfully used in obese patients with severe obstructive sleep apnea syndrome[21-23] or bronchiectasis,[24] and may also be effective, despite mixed results, in patients with restrictive pulmonary disease,[25] myasthenia gravis,[26] or neuromuscular disease.[27] So as, identification of an underlying chronic respiratory disease other than COPD could be of major interest to better assess the risk of NIV failure in hypercapnic patients.

By contrast, we found a markedly higher rate (38%) of NIV failure in hypercapnic patients with non-AOCRF, mostly associated with pneumonia. High intubation rates of 38%[12] or 47%[11] have already

been reported in non-COPD patients receiving NIV for AHRF when including patients with and without underlying chronic respiratory disease.[11, 12] In patients having "de novo" acute hypoxemic (non-hypercapnic) respiratory failure and no chronic respiratory disease, even higher intubation rates of up to 60% have been reported.[8, 12] It is noteworthy that the intubation rate in our subgroup of patients having "de novo" acute hypercapnic respiratory failure was only 38%, and that, although significantly less hypercapnic, they were not more hypoxemic than the others 2 subgroups.

Predictive factors for NIV failure after NIV initiation

A higher severity score is usually associated with NIV failure in hypercapnic patients.[11, 15, 28] However, using the SAPS2 is clinically impractical since this score is computed only at 24h after admission, therefore taking into account any potential complications of intubation in patients who failed NIV within the first 24 hours.

The severity of hypercapnia and/or respiratory acidosis after initiation of NIV is a well-known predictor of NIV failure.[11, 13-15, 29] Probably because we included AHRF of all origin, we also found that severe hypoxemia (P/F ratio ≤ 200) was an independent predictor of intubation in hypercapnic patients.

By contrast, tolerance to NIV and amount of leaks had no impact on NIV failure. In a survey from 70 ICUs, poor NIV tolerance was a strong predictor of NIV failure.[8] However, this study reported good NIV tolerance in only 27% of patients and 57% had high levels of leaks. In our series, 86% of patients had good NIV tolerance and only 10% had high levels of leaks probably due to our NIV protocol. Pressure-support level was significantly increased during the first hour of NIV suggesting that the protocol was correctly applied by nurses. With such good NIV tolerance during the first hour of NIV, the ventilatory parameters or ventilator settings had no influence on outcome. However, the trend towards a lower tidal volume in patients who failed NIV as compared to patients who avoided intubation might suggest the need to increase the targeted tidal volume in patients at high risk of failure.

Clinical implications

In a general ICU using a protocolized care and monitoring of NIV by nurses, the overall rate of intubation in hypercapnic patients receiving NIV for acute respiratory failure could be maintained below 15%. This rate can be used as an upper limit, both for COPD patients and for other patients having a

chronic underlying respiratory disease. These results are probably due first to our NIV protocol optimizing the patients' tolerance to NIV, and second to our conservative intubation criteria enabling continuation of NIV under close monitoring in some patients with altered consciousness. As expected, the rate of intubation was particularly high in patients with persistently or newly occurring severe altered consciousness. Nevertheless, 48% of our comatose patients succeeded ~~in~~ NIV without the need for intubation. Several studies have already shown that NIV could be successful in patients with hypercapnic coma.[30, 31] Moreover, it has been shown that NIV failure was not associated with an increased mortality rate in hypercapnic patients;[28] thus, delayed intubation in some patients likely did not worsen their outcome. In our study, the ICU mortality rate for intubated patients was 36%, which is in line with the 30% to 40% rate reported in large surveys.[12, 28] Our results also suggest that, similarly to protocols for weaning from mechanical ventilation[32] or sedation[33] which enabled reduction of the time to extubation, NIV protocols involving nurses and/or respiratory therapists might reduce the intubation rate.

Limitations

Our study was conducted in a single unit with a long-standing experience in the practice of NIV, and therefore our results may not be applicable to other centers with less extensive experience. Experience and nurse-driven protocols may improve tolerance to NIV and we report a poor tolerance rate of only 14% after 1 hour of NIV. Another limitation is the retrospective nature of the study. However, prospective data collection of ventilatory parameters under NIV was available for a vast majority of our patients and, because of the availability of computerized medical charts for all patients, all those receiving NIV for AHRF could be analyzed.

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CONCLUSION

While the rate of NIV failure is usually around 20 to 30% for acute hypercapnic respiratory failure, we found that the intubation rate could be maintained below 15% in a highly experienced unit, with an overall ICU mortality of only 5%. Our study suggests that a NIV trial should be considered in all hypercapnic patients presenting with acute respiratory failure, even when the risk of failure is high because of coma, whether in patients with AOCRF or in patients without underlying respiratory disease. Interestingly, severe hypoxemia was an independent predictor of NIV failure in hypercapnic patients of all origins, whereas altered consciousness at admission and ventilatory settings had no influence on outcome.

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FIGURE LEGENDS

Figure 1: Flow-Chart of selection of patients for inclusion in this study

Among the 1163 patients admitted for acute respiratory failure, 465 patients received NIV, of which 35 were excluded because of a "do-no-intubate" order. Among the 430 remaining patients, 242 had acute hypercapnic respiratory failure and were included in the study, including 67 patients with cardiogenic pulmonary edema (CPE), 146 having acute-on-chronic respiratory failure (AOCRF) - including 99 having chronic obstructive pulmonary disease (COPD) and 47 other causes of chronic respiratory failure (non-COPD patients) - and 29 having non-AOCRF.

Figure 2

Intubation rates (%) in patients receiving NIV for acute hypercapnic respiratory failure (AHRF), overall and according to the reason for admission, including CPE, COPD, AOCRF not due to COPD and non-AOCRF. (NIV: Non-invasive ventilation, CPE: cardiogenic pulmonary edema, AOCRF: Acute-On-Chronic Respiratory Failure, COPD: Chronic Obstructive Pulmonary Disease)

Figure 3

ICU mortality rates (%) in patients receiving NIV for acute hypercapnic respiratory failure (AHRF), overall and according to the reason for admission, including CPE, AOCRF and non-AOCRF. (NIV: Non-Invasive Ventilation, CPE: Cardiogenic Pulmonary Edema, AOCRF: Acute-On-Chronic Respiratory Failure)

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Table 1: Characteristics and outcomes of 242 patients receiving non-invasive ventilation (NIV) for acute hypercapnic respiratory failure (AHRF) of all origin.

	All AHRF	**CPE**	**AOCRF**	**Non-AOCRF**	
	N=242	**N=67**	**N=146**	**N=29**	***p* value**
Age, mean (±SD), years	70 (±15)	76 ±11) **	70 (±12)	56 (±21) **	p<0.001
Male sex, n (%)	144 (60%)	36 (54%)	88 (60%)	20 (69%)	p=0.36
SAPS II, mean (±SD)	35 (±14)	38 (±14) *	33 (±12) **	37 (±18)	p<0.05
Characteristics at admission					
Systolic arterial pressure, mean (±SD), mmHg	143 (±50)	165 (±81) **	136 (±28) **	130 (±25)	p<0.001
Heart rate, mean (±SD), beats/min	99 (±21)	95 (±20)	100 (±21)	105 (±25)	p=0.11
Respiratory rate, mean (±SD), cycles/min	29 ±8)	32 (±7) *	28 (±8) **	30 (±10)	p=0.01
Glasgow coma score, mean (±SD)	14 (±2	14 (±2)	14 (±2)	14 (±3)	p=0.06
SpO_2, mean (±SD), %	91 (±10)	90 (±12)	91 (±9)	94 (±5)	p=0.17
pH, mean (±SD), units	7.28 (±0.09)	7.26 (±0.10) *	7.28 (±0.07)	7.31 (±0.10) *	p=0.02
$PaCO_2$, mean (±SD), mm Hg	68 (±17)	62 (±15) **	72 (±16) **	59 (±16) **	p<0.001
PaO_2, mean (±SD), mm Hg	99 (±65)	118 (±77) **	91 (±62) *	96 (±38)	p<0.001
Bicarbonates, mean (±SD), mmol/L	33 (±7)	29 (±6) **	35 (±6) **	29 (±7) **	p<0.001
PaO_2/FiO_2 at NIV initiation, mean (±SD), mm Hg	229 (±86)	235 (±88)	233 (±79)	199 (±107)	p=0.10
Outcomes					
Duration of NIV the first day, median [IQR], hours	8 [4-11]	7 [4-8] *	9 [4-12] **	6 [4-10]	p=0.01
Total duration of NIV, median [IQR], days	2 [1-4]	2 [1-3] **	3 [1-5] **	1 [1-3]	p<0.001
Rate of NIV Failure, n (%)	36 (14%)	3 (4%) **	22 (15%)	11 (38%) **	p<0.001
ICU Length of stay, median [IQR], days	6 [4-9]	4 [3-6] **	7 [5-9]	8 [6-14] *	p<0.001
ICU mortality, n (%)	13 (5%)	2 (3%)	7 (5%)	4 (14%)	p=0.087

Values are given in mean (± standard deviation, SD), median [interquartiles range, IQR] or proportion (%) and compared using Kruskall Wallis test or Chi 2 between the three groups.
* $p < 0.05$ as compared to all others patients using Student's *t*-test
** $p < 0.01$ as compared to all others patients using Student's *t*-test
Abbreviations: AHRF: Acute Hypercapnic Respiratory Failure, NIV: Non-Invasive Ventilation, CPE: Cardiogenic Pulmonary Edema, AOCRF: Acute-On-Chronic Respiratory Failure, SAPS II: Simplified Acute Physiology Score II, ICU: Intensive Care Unit

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Table 2: Predictors of endotracheal intubation in patients admitted for acute hypercapnic respiratory failure (AHRF) receiving non-invasive ventilation (NIV).

	NIV Success N= 206	**NIV Failure N= 36**	**Bivariate Tests p value**	**Multivariate Logistic regression OR [95%CI], p value**
Age, mean (±SD), years	71 (±15)	65 (±14)	**p=0.04**	Not significant
SAPS II, mean (±SD), points	34 (±14)	42 (±12)	p<0.0001	Not included
Underlying cause of ARF			***p <0.001***	
CPE, n (%)	64 (31%)	3 (8%)	**p=0.026**	0.29 [0.07-1.07] p=0.064
AOCRF, n (%)	124 (60%)	22 (61%)	1 (reference)	
Non-AOCRF, (%)	18 (9%)	11 (31%)	**p=0.004**	**3.94 [1.44-10.7] p=0.007**
At Admission before VNI				
Altered consciousness (RASS<0), n (%)	46 (22%)	14 (39%)	**p=0.034**	Not significant
Respiratory Rate, mean (±SD), breaths/min	29 (±8)	32 (±7)	p=0.08	
Respiratory Rate > 30 breaths/min, n (%)	76 (37%)	20 (56%)	**p=0.025**	**2.72 [1.17-6.31] p=0.02**
pH, mean (±SD), units	7.28 (±0.09)	7.27 (±0.08)	p=0.76	
pH < 7.30, n (%)	105 (51%)	23 (64%)	p=0.15	
$PaCO_2$, mean (±SD), mm Hg	68 (±17)	69 (±15)	p=0.60	
Bicarbonates, mean (±SD), mmol/L	33 (±7)	32 (±8)	p=0.82	
Systolic arterial pressure, mean (±SD), mmHg	143 (±33)	132 (±24)	p=0.06	Not significant
Heart rate, mean (±SD), beats/min	98 (±21)	104 (±24)	p=0.12	
Ventilatory settings under NIV	**N=177**	**N=22**		
FiO_2, mean (±SD), %	50 (±24)	56 (±26)	p=0.31	
PEEP level, mean (±SD), cmH_2O	4.8 (±1.6)	4.2 (±1.2)	p=0.09	Not significant
PS level, mean (±SD), cmH_2O	9.2 ±2.6)	9.4 (±2.8)	p=0.74	
Tidal Volume, mean (±SD), ml	475 (±140)	415 (±166)	p=0.06	Not significant
Respiratory rate, mean (±SD), breaths/min	27 (±8)	29 (±7)	p=0.25	
Important leaks, n (%)	8 (4.5%)	2 (8%)	p=0.33	
Poor tolerance, n (%)	27 (15%)	1 (4%)	p=0.21	
Blood gases after 1h of NIV	**N=188**	**N=33**		
PaO_2/FiO_2, mean (±SD), mm Hg	237 (±86)	192 (±72)	**p=0.006**	
$PaO_2/FiO_2 \leq 200$ mm Hg, n (%)	60/188 (32%)	20/33 (61%)	**p=0.002**	**2.85 [1.24-6.55] p=0.01**
pH, mean (±SD), units	7.33 (±0.08)	7.30 (±0.12)	**p=0.028**	
pH < 7.30, n (%)	53/188 (28%)	16/33 (48%)	**p=0.025**	**2.48 [1.06-5.77] p=0.035**
Lack of increase in pH, n (%)	39 (21%)	13/33 (39%)	**p=0.026**	
$PaCO_2$, mm Hg	61 (±18)	68 (±21)	p=0.059	
Decrease in $PaCO_2$, n (%)	131 (70%)	18 (55%)	p=0.10	

Abbreviations: CPE: Cardiogenic Pulmonary Edema, AOCRF: Acute-On-Chronic Respiratory Failure, RASS: Richmond Agitation-Sedation Scale, PEEP: Positive End-Expiratory Pressure, OR: Odds Ratio, CI: 95% Confidence Interval.

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Logistic regression was performed using 219 observations with an area under ROC curve of 0.791: sensitivity=66%; specificity=76%; positive predictive value=32%; negative predictive value=93%; correctly classified = 75%

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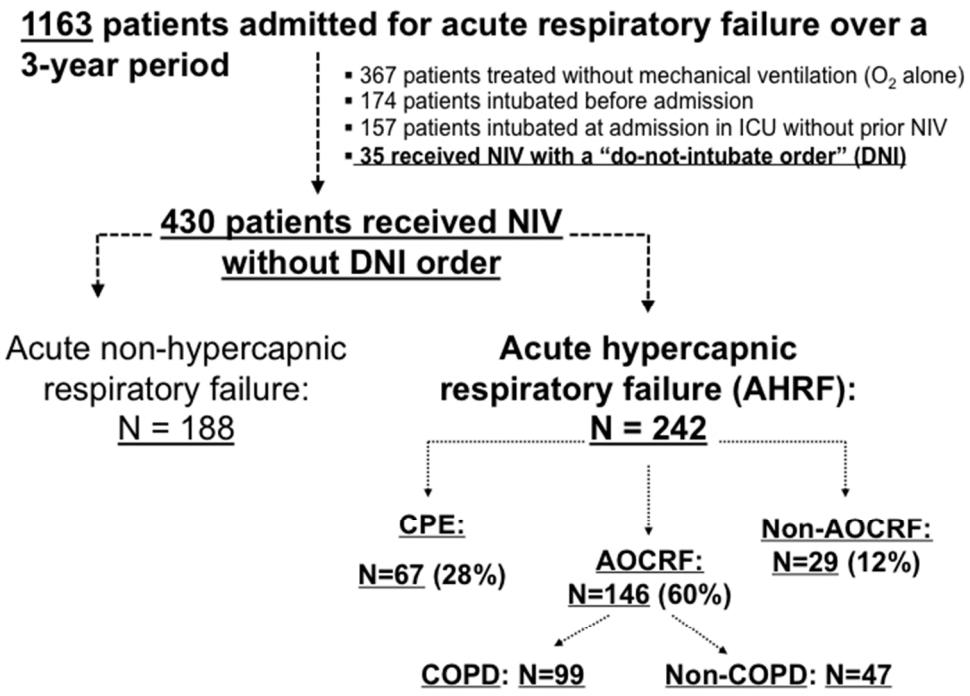

Flow-Chart of selection of patients for inclusion in this study
Among the 1163 patients admitted for acute respiratory failure, 465 patients received NIV, of which 35 were excluded because of a "do-no-intubate" order. Among the 430 remaining patients, 242 had acute hypercapnic respiratory failure and were included in the study, including 67 patients with cardiogenic pulmonary edema (CPE), 146 having acute-on-chronic respiratory failure (AOCRF) - including 99 having chronic obstructive pulmonary disease (COPD) and 47 other causes of chronic respiratory failure (non-COPD patients) - and 29 having non-AOCRF.
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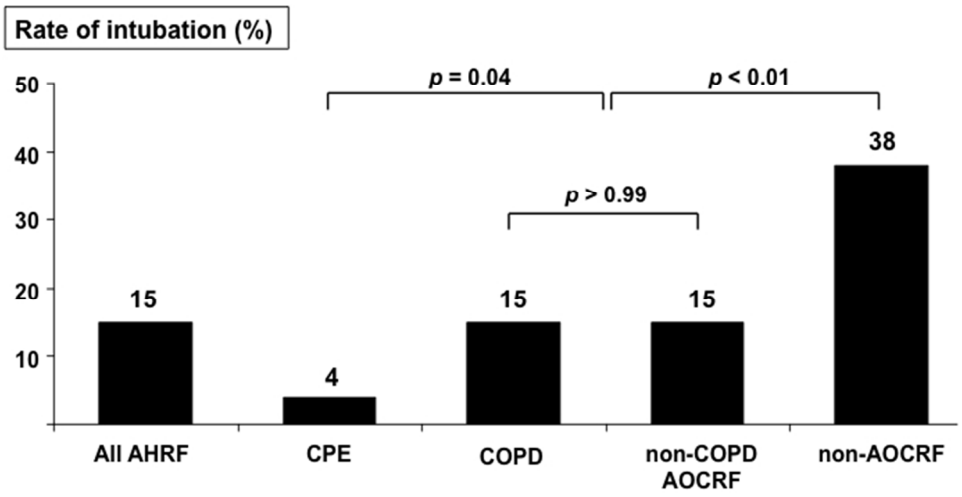

Intubation rates (%) in patients receiving NIV for acute hypercapnic respiratory failure (AHRF), overall and according to the reason for admission, including CPE, COPD, AOCRF not due to COPD and non-AOCRF. (NIV: Non-invasive ventilation, CPE: cardiogenic pulmonary edema, AOCRF: Acute-On-Chronic Respiratory Failure, COPD: Chronic Obstructive Pulmonary Disease)
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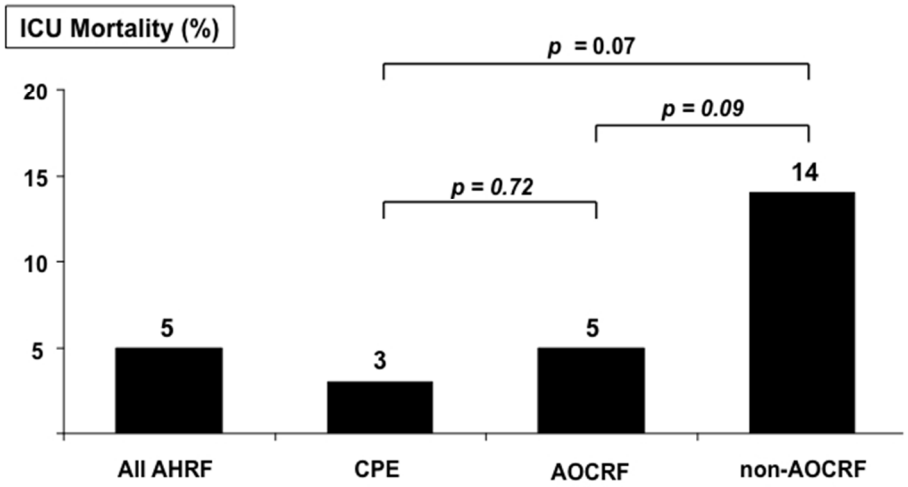

ICU mortality rates (%) in patients receiving NIV for acute hypercapnic respiratory failure (AHRF), overall and according to the reason for admission, including CPE, AOCRF and non-AOCRF. (NIV: Non-Invasive Ventilation, CPE: Cardiogenic Pulmonary Edema, AOCRF: Acute-On-Chronic Respiratory Failure)
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