

Determinants of immediate failure of noninvasive mechanical ventilation outside the intensive care unit

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Abstract

Background: This study aimed to characterize which are the early determinants of immediate failure of the use of noninvasive mechanical ventilation (NIMV) outside the ICU.

Methods: This prospective study included patients who were admitted to the Military Hospital in Guayaquil, Ecuador. Each variable was analyzed independently by using a multiple logistic regression model toward establishing an association with the event.

Results: A total of 249 cases of NIMV over a 10 year period of its application outside the ICU was included in the study. Fifty-five (22.10%) patients were transferred to the ICU. A multivariate analysis showed that the determinants of immediate NIMV failure outside the ICU were the following: age (OR: 1.12; $P = 0.03$); SBP (OR: 1.04; $P = 0.001$); HR (OR: 1.66; $P < 0.0001$); $p\text{CO}_2$ (OR: 1.16; $P = 0.007$); PO_2 (OR: 1.35; $P = 0.003$); levels of IPAP (OR: 1.35; $P < 0.0001$); and the number of quadrants affected, as shown in a chest X-ray (OR: 1.40; $P < 0.0001$).

Conclusions: The number of affected quadrants in a chest X-ray, tachyarrhythmia and hypoxemia may be useful in the initial decision in the use of NIMV outside the ICU. High values of IPAP, the persistence of elevated $p\text{CO}_2$, arterial hypotension, and age could be useful as a second screening associated with immediate NIMV failure outside the ICU.

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Noninvasive mechanical ventilation (NIMV) has been proven to be an effective treatment for acute respiratory failure of various etiologies [1–3]. As a result of several studies that evaluated the safety and efficacy of NIMV, recommendations have been made emphasizing that this method should be made available in all hospitals supporting patients with acute respiratory failure [4, 5]. The use of NIMV for respiratory failure has traditionally been carried out in the intensive care unit (ICU) environment [6, 7], which has more capable staff and better monitoring than a general ward, emergency department, postoperative unit, or other areas of hospitalization. Outside

the ICU, the emergency room and general wards are the most frequent sites of NIMV initiation; under such conditions, the treatment can be sustained for hours or days [8–10].

There are several obstacles in administering NIMV in the ICU, such as the numbers of beds, high costs and lack of resources. Thus, the use of NIMV outside the ICU is an attractive and necessary option. Studies have shown the feasibility of applying this technique in different regions of the world [11–16]. Additionally, data have shown a positive association between the early implementation of NIMV and its success in patients with acute respiratory failure of different aetiolo-

gies, especially in those treated at an early stage since the following the onset of mild ARF (acute respiratory failure). In these settings, it is important to determine what variables are associated with the early success or failure of NIMV in order to guide physicians in the safe implementation and management of this life-saving strategy outside the ICU.

Of the studies that have looked into the use of NIMV outside the ICU, mostly in general wards, even fewer have investigated what the determinants of using NIMV are in such settings. More importantly, these studies had several limitations, including small sample sizes, primary objectives that did not properly evaluate a real "failure" of treatment (i.e., percentage of intubation and death), as well as patient samples that did not represent the general population (i.e. patients who refused advanced therapies and underwent NIMV for palliation, comfort, or relief of dyspnoea) [11, 12].

Accordingly, the aim of the present study is to establish what the determinants of immediate failure are in the use of NIMV in patients with respiratory failure. We also evaluate data on mortality, length of hospital stay, and length of mechanical ventilation in those patients who received NIMV.

METHODS

This prospective study included patients admitted to the Military Hospital in Guayaquil, Ecuador, between December 1, 2004 and January 1, 2014. Written informed consent was obtained from the patients or, if the patients were incapable of giving such consent, from their families. The study was approved by the Ethics Committee of the School of Medicine of the University San Francisco de Quito and of the Military Hospital in Guayaquil, Ecuador.

INCLUSION AND EXCLUSION CRITERIA

The criteria for inclusion in the study were: (a) patients with ventilatory failure secondary to hypercapnia ($\text{PaCO}_2 > 45$ mm Hg, pH 7.35 or less); (b) patients with inadequate oxygenation ($\text{PaO}_2 < 60$ mm Hg) breathing ambient air ($\text{SaO}_2 < 92\%$) with severe dyspnoea ($\text{RR} > 25$ breaths per minute) with the use of accessory muscles, during hospitalization.

Patients were excluded if they had haemodynamic instability, were non-cooperative or agitated, were unable to use the interface device, had recent surgery of the upper airway tract, or were using NIMV with a do-not-resuscitate (DNR) order.

PROTOCOL OF NONINVASIVE MECHANICAL VENTILATION FOR TREATMENT OF ACUTE RESPIRATORY FAILURE

When the patient had been diagnosed with acute respiratory failure in the pulmonology department, a senior physician was consulted for assessment and management. The senior specialist made the decision on the initiation and parameters of NIMV. Patients were observed and evalu-

ated by respiratory therapists, resident doctors, and nurses trained in NIMV.

The first phase of NIMV therapy was carried out for an uninterrupted period of 3 hours, which was strictly supervised by a respiratory therapist, an NIMV-trained medical resident, or the primary care doctor. After the initial phase, NIMV was provided in an alternative form for a 3-hour duration, after the patient's tolerance had been determined and according to the guidance of the respiratory therapist or nurse.

In our institution, each room had 4 beds that were not separated by partitions. The monitoring in each ward consisted of taking the patient's vital signs 3 or 4 times daily, depending on the condition of the patient and the resources of the ward. Throughout 2004 until 2014, the following mechanical ventilators used were: from 2004–2006, the VPAP II auto-adjustable system for titration (ResMed) and BiPAP Duet Lx with Auto-Trak; 2006–2008, BiPAP Pro 2 with Auto-Trak (Bi-Flex) and Knightstar 330–335; and 2008–2014, BiPAP Synchrony and BiPAP Vision.

Patients were placed in the spontaneous (S), spontaneous/timed (S/T), and spontaneous/timed with AVAPS modes, depending on the case, the duration and the progression of disease. The IPAP and EPAP levels were started and established at 12 cm H_2O and 6 cm H_2O , respectively, to reach a maximum of 20 cm H_2O according to RR, inspiratory times, while ramp (symbols) were set on a case-to-case basis and according to the patient's progression. Two types of interface devices were used, namely: the Resironics Comfort, Comfort Full, Comfort Select, and Full Face Mask (Resironics Inc., Murrysville, Pennsylvania, USA); and the Mirage II and Ultra Mirage II or III series (ResMed). Weaning started after the stabilization of clinical variables and gasometric patients.

MEASUREMENTS

Clinical stability was defined as: (a) $\text{RR} < 25$ rpm, (b) $\text{HR} < 100$ bpm, and (c) normal arterial pH with $\text{SaO}_2 > 90\%$ with ambient air or low oxygen flow (< 3 L min^{-1}).

The independent variables analyzed were as follows: age; sex; length of NIMV; length of hospital stay; diagnostics of hospitalization (exacerbation COPD, status asthmaticus, cardiogenic APE, community-acquired pneumonia, and other pathologies); geometric parameters (pH, PaO_2 , PaO_2 , HCO_3 , excess base, and SaO_2) collected before the start of NIMV; vital signs (SBP, DBP, RR, and HB); ventilator mode (spontaneous, spontaneous/timed, BiPAP S/T + AVAPS); levels of IPAP and EPAP; and the effect shown on the chest X-ray (1, 2, 3, or 4 quadrants). Arterial blood gas measurements were made before admission to the medical ward, and before and during NIMV. Mask Interface complications, such as excessive discomfort, nasal ulcer, gastric distention, and claustrophobia related to the mask, were also evaluated.

MEASUREMENT OF RESULTS

The primary outcome measured was the effectiveness of NIMV, defined as the need for transfer to the ICU setting for access to sophisticated monitoring software. The secondary outcomes measured were length of hospitalization, endotracheal intubation, and death.

IMMEDIATE FAILURE OF NIMV

This refers to failure within minutes and not beyond the first hour.

NEED TO TRANSFER TO THE ICU

We define NIMV failure outside the ICU as the need to transfer the patient to the ICU by one of the following causes:

1. Endotracheal intubation.
2. Requirement of sophisticated monitoring in ICU (presence of cardiac arrhythmia, use of infusion of vasodilators or inotropic agents).

CRITERIA FOR NIMV FAILURE IN GENERAL WARDS

The following are the criteria for the failure of NIMV in general wards: (a) persistence of hypercapnic ventilatory failure as evidenced by an increase in basal PaCO₂ and persistence of low pH despite the use of NIMV; (b) persistent hypoxemia as evidenced by PaO₂ < 70 mm Hg with SaO₂ < 90%, despite the use of NIMV; (c) severe dyspnoea (RR, 30–40 breaths per minute) with the use of accessory muscles, and bronchospasm despite the use of NIMV; and (d) presence of cardiac arrhythmia (atrial fibrillation or atrial flutter) during NIMV. The decision on the waiting time to transfer the patient to the ICU and the cessation of NIMV was made by senior physicians who were experts in NIMV.

STATISTICAL ANALYSIS

All data were expressed as means ± standard deviation for continuous variables and as percentages for categorical variables. Each variable was analyzed independently in order to find any association with an event defined as failure of NIMV (transfer to ICU). The *t* test for independent samples was used on data with a Gaussian distribution and similar variance (determined through homogeneity of variance or the Levene test). A nonparametric test (chi-square or Fisher's exact test) was used on data with a non-normal distribution for categorical variables. A *P*-value of < 0.05 was considered statistically significant. In order to determine the variables that are predictors of the failure of NIMV, a multiple logistic regression model was made with transfer to the ICU as the dependent variable (the variable was dichotomous). The independent variables in the bivariate analysis (*P* < 0.15) were considered in the multivariate analysis. All analyses were carried out by using MedCalc version 16.1 (1993–2016 MedCalc Software bvba).

CALCULATION OF THE SAMPLE SIZE

As ten patients were considered for each variable in the multiple logistic regression analysis, a total of 240 patients were required. Thus far, two of the largest studies on this subject include that by Plant *et al.* [8], which considered 236 patients, and that by Harrell *et al.* [acc. 17], which set forth within its theoretical framework the criterion of a minimum of 10–20 cases for each variable. In a simulation, Freedman and Pee [17] showed that type I errors increased when the ratio of the number of variables to the number of observations was greater than 0.25, corresponding to a rate of less than 4 events per variable.

RESULTS

During its 10 years of applying NIMV outside the ICU, the hospital in this study admitted 3,136 patients diagnosed with respiratory disease. A total of 706 patients presented with acute respiratory failure; 381 were managed with conventional treatment, and 325 were deemed candidates for NIMV. Of these candidates, 249 met the inclusion criteria for starting NIMV outside the ICU, whereas 76 did not (Fig. 1).

The mean age of the final study population was 70.6 ± 15.5 (95% CI: 68.4–72.8) years; males accounted for 143 patients (57.4%), and females for 106 (42.6%). The mean length of hospitalization was 9.8 ± 10.5 (95% CI: 8.5–11.1) days while the mean length of NIMV was 5.6 ± 3.5 (95% CI: 5.1–6) days. The vital signs of the patients were as follows: SBP, 128.7 ± 24.3 (95% CI: 125.7–131.7) mm Hg; DBP, 90.7 ± 20.8 (95% CI: 88.1–93.3) mm Hg; HR, 100.2 ± 16 (95% CI: 98.2–102.2) beat/min; RR, 32.8 ± 7 (95% CI: 31.8–33.6) breath/min; and SO₂, 90% (95% CI: 80%–90%). The arterial blood gas measurements were as follows: pH, 7.34 ± 0.06 (95% CI: 7.33–7.35); pCO₂, 47.3 ± 16 (95% CI: 45.2–49.2) mm Hg; PO₂, 71.7 ± 15.7 (95% CI: 69.7–73.6) mm Hg; HCO₃⁻, 25.4 ± 6.7 (95% CI: 24.2–25.9), mmol L⁻¹; and BE, 1 ± 6.9 (95% CI: 0.1–1.8) mmol L⁻¹. The levels of EPAP were 6.1 ± 0.7 (95% CI: 6–6.2) cm H₂O, while those of IPAP were 14 ± 2.7 (95% CI: 13.6–14.3) cm H₂O. The number of quadrants affected, as shown in the chest X-ray, were: 0 quadrants, 23.2%; one quadrant, 31.7%; two quadrants, 38.1%; and three quadrants, 6.8% (Table 1).

Fifty-five patients (22.1%) were transferred to the ICU, whereas 194 (77.9%) were not. The reasons for using NIMV were as follows: COPD exacerbation due to an infectious process (93 patients, 37.3%); community-acquired pneumonia (74 patients, 29.7%); status asthmaticus (27 patients, 10.8%); cardiogenic APE (27 patients, 10.8%); pulmonary fibrosis (17 patients, 6.8%); COPD plus + pneumonia (6 patients, 2.4%); status post tuberculosis (2 patients, 0.8%); interstitial pneumonitis (1 patient, 0.4%); OSA (1 patient, 0.4%); and pulmonary tuberculosis (1 patient, 0.4%).

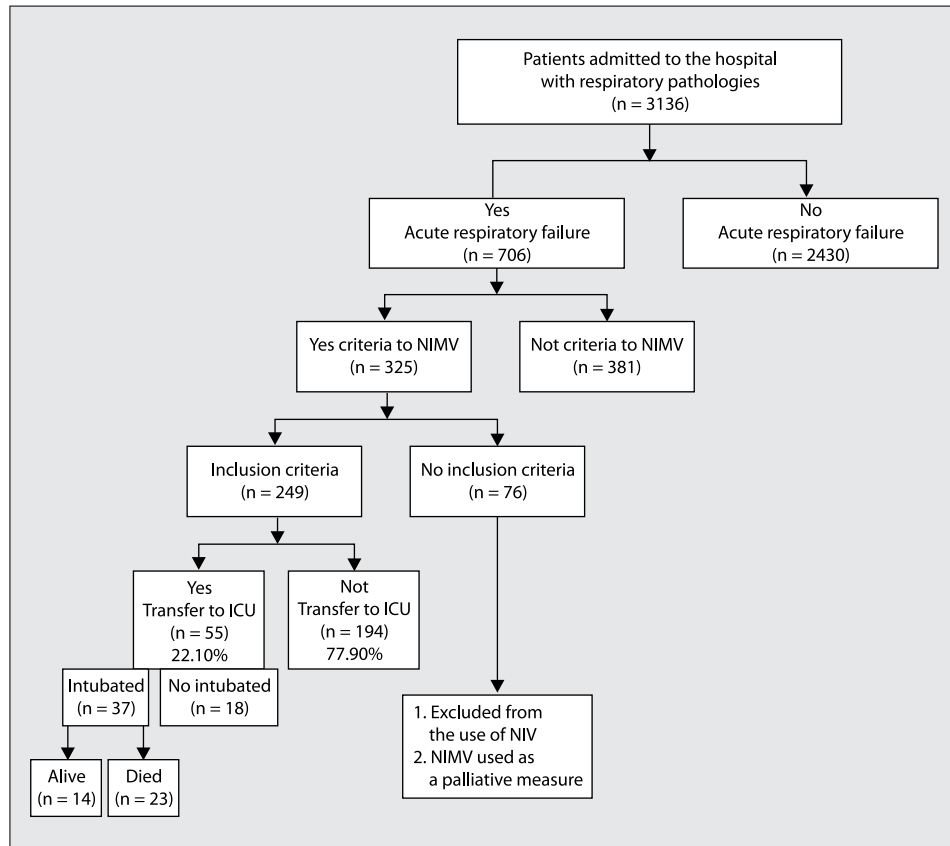


Figure 1. Patient selection for noninvasive ventilation (NIMV)

Table 1. Baseline characteristics of the study population

VARIABLE	MEAN	SD	CI	Range
APACHE II	14.7	2.94	14.0–15.3	12–20
Age (years)	70.6	17.5	68.4–72.8	15–102
Length of hospitalization (days)	9.8	10.5	8.5–11.1	1–120
Length of NIMV (days)	5.6	3.5	5.1–6	1–22
SBP, mm Hg	128.7	24.3	125.7–131.7	80–223
DBP, mm Hg	90.7	20.8	88.1–93.3	49–175
HR, beat min ⁻¹	100.2	16.0	98.2–102.2	62–140
RR, breath min ⁻¹	32.8	7.0	31.8–33.6	10–56
SO ₂ oximeter, %	90%	10%	89–90%	71–99%
pH	7.34	0.06	7.33–7.35	7.25–7.48
pCO ₂ , mm Hg	47.3	16.0	45.2–49.2	15.9–108.9
PO ₂ , mm Hg	71.7	15.7	69.7–73.6	38.6–115.5
HCO ₃ , mmol L ⁻¹	25.4	6.7	24.2–25.9	11.3–43.3
EB mmol L ⁻¹	1.0	6.9	0.1–1.8	-19–21.4
SaO ₂ , %	0.90	0.05	0.89–0.90	0.64–0.99
Levels of EPAP, cm H ₂ O	6.1	0.7	6–6.2	5–8
Levels of IPAP, cm H ₂ O	14.0	2.7	13.6–14.3	11–20
Number of quadrants affected in the chest X-ray	1.2	0.8	1.1–1.3	0–3

Abbreviations in the text

Table 2. Multivariate analysis based on primary outcome of noninvasive mechanical ventilation (NIMV) failure

Independent Variables	OR	Std Error	P
Age	1.12	0.0011	0.0383
HR	1.65	0.0014	< 0,0001
Levels of IPAP	1.35	0.0081	< 0,0001
SBP	1.04	0.0008	0.0012
PCO ₂	1.16	0.0012	0.0007
PO ₂	1.35	0.0013	0.0032
Number of quadrants affected in the chest X-ray	1.39	0.0245	< 0.0001

Statistical significance at $P < 0,05$; abbreviations in the text

The types of ventilators used outside the ICU setting were as follows: the BiPAP Duet System with Auto-Trak (120 patients, 48.2%); BiPAP Pro with Auto-Trak (22 patients, 8.8%); BiPAP Synchrony (30 patients, 12%); BiPAP Vision (1 patient, 0.4%); Knightstar 335 (50 patients, 20.1%); Quantum PSV (4 patients, 1.6%); and ResMed Vpap II (22 patients, 8.8%). The ventilation settings applied were as follows: spontaneous (196 patients, 78.7%); S/T (49 patients, 19.7%); S/T + AVAPS (3 patients, 1.2%); and PAV (1 patient, 0.4%). Of the 249 total cases, 55 patients (22.10%) were transferred to the ICU, 37 (14.9%) required endotracheal intubation, and 23 died (9.2%).

The multivariate analysis showed that the variables predictive of transfer to the ICU were as follows: age (OR: 1.12; $P = 0.0383$); SBP (OR: 1.04; $P = 0.0012$); HR (OR: 1.66; $P < 0.0001$); PCO₂ (OR: 1.16; $P = 0.0032$); PO₂ (OR: 1.35; $P = 0.0032$); levels of IPAP (OR: 1.35; $P < 0.0001$); and number of quadrants affected in the chest X-ray (OR: 1.40; $P < 0.0001$) (Table 2).

The multivariate analysis showed that the variables that were predictive of transfer to the ICU: Table 2 summarizes the outcomes

DISCUSSION

Our study shows that over a period of ten years, NIMV was administered outside the ICU with a high percentage of success (77.9 %). In "real life," the monitoring of patients receiving NIMV in general wards or outside the ICU in most hospitals is similar to that in the ICU setting.

We determined variables that could help identify early patients who would benefit from NIMV outside the ICU from its initial administration and after the initial screening, starting from certain basic parameters of easy accessibility that lead to an improvement in the outcomes of ARF patients.

Our findings could be useful for the appropriate selection of patients, which should be treated from the start in the ICU due to its high probability of failure.

In patients with hypoxemia affecting more than 2 lung quadrants, tachyarrhythmia may be useful in the initial decision in the use of NIMV out of the ICU as a first screening, while a high level of inspiratory pressure, the persistence of elevated PaCO₂, arterial hypotension, and age could be useful as a second screening associated with the immediate failure of NIMV.

The data of this study may indicate that patients complicated by ARF with these conditions should be managed in the ICU from the first moment of admission. After the initial screening physical parameters showing statistical significance should be applied for the second screening of the other high-risk patients. We determined the variables that were determinants of NIMV failure among patients with heterogeneous causes of ARF in this setting commonly found in daily practice, in order to help physicians identify patients that could potentially benefit from this treatment.

Our structure and management in ordinary wards comprising basic monitoring with the taking of vital signs 3 to 4 times a day depending on the conditions of the patient and the resources on the room, resembles more the daily practice of the management of patients in this setting. The scientific literature reports an increasing number of scientific papers that report the early identification of such patients and the rapid use of NIMV outside the ICU [18–21].

Although the patients treated with NIMV in the general ward are less severely ill than those treated in the ICU, there is growing interest in the use of NIMV outside the ICU due to its associated positive outcomes and ease of use compared with the ICU setting [22–24]. Most studies determined the rates of intubation and death as primary objectives and included patients who refused advanced support strategies, with NIMV used only for palliation, comfort, or relief of dyspnoea. The present research used a defined study population that included only patients with respiratory failure (ARF) and specified a primary outcome of transfer to the ICU, and more accurate assessment of the failure of treatment.

Other authors have also shown that the presence of certain variables can be determining factors in the success of the NIMV outside of the ICU. Pacilli *et al.* [25] found that the predictive variables were age, pH, albumin, quality of life as measured on the Barthel scale, and the SPAS II score. Khalid *et al.* [26] prospectively evaluated 238 patients with SaO₂ < 90 % and RR > 28 identified by an emergency medical group. Forty-five patients received NIMV, and 75 did not; both groups were managed in the general ward. The authors concluded that the application of NIMV in a select group of patients, such as those with COPD exacerbation, asthma exacerbation, and cardiogenic APE, could be done in the general ward under monitoring by an MET (medical emergency team). However, the main weakness of this study was that the authors suggested that no monitoring should

be done in the ward, whereas the BiPAP Vision device has sophisticated software for the close monitoring of patients. On the other hand, they did not identify immediate, early or late factors that would allow the appropriate selection of patients and planning in use of NIMV in this setting, which would therefore constitute the strength of our study. The types of ventilation equipment and modes used in our study were as specified in the standard protocols in our centre. With technological advances that include newer interfaces and ventilators, along with the associated learning curves, both ourselves and others have found improved results over time with the use of NIMV in different clinical scenarios

Delayed endotracheal intubation should be avoided as studies have shown that such a delay could increase the rates of hypotension, desaturation, and aspiration, with subsequent risk of increased mortality [27, 28]. The location of treatment is one of the major determinants of the success of NIMV. Although the ICU is considered a safe place in which to apply this method, the presence of several obstacles has encouraged the use of NIMV outside this setting. Numerous studies have shown the efficacy of NIMV applied outside the ICU in different parts of the world, including Canada [19], the United States [14], the United Kingdom [8], China [15], Saudi Arabia [16], Australia [18], and Italy [24, 29, 30]. Nonetheless, no similar studies have been carried out in South American countries. There are certain considerations in the use of NIMV outside the ICU, such as strict surveillance in the initiation phase and the experience of the healthcare team in identifying predictors of the success or failure of NIMV.

The present study has several limitations. Firstly, it was carried out in only one hospital, which may not be representative of the region while the monitoring capability outside the ICU may also vary depending on the training and expertise of the teams in different hospitals [32]. Secondly, although baseline PO₂ data are provided, data on PaO₂/FiO₂ are not as most of the patients were ventilated with the use of BiPAP devices without a FiO₂ blender, meaning their determination could not be exact. Thirdly, the majority of patients had COPD exacerbation and cardiogenic APE, in which the use of NIMV has been shown to attain favourable results; however, the outcomes could differ in patients with other clinical entities. Fourthly, different types of ventilators were used during various periods, with completely different performances; the NIMV success rate may thus be dependent on these differences. Finally, the pCO₂ levels obtained herein could be lower than those typically reported because many of our patients came from regions of high altitude in Ecuador.

Finally, we only detected the determinants of immediate failure of NIMV during the first hour of its use. Early and late failures were not analyzed in this study.

CONCLUSIONS

NIMV can be used outside the ICU with good outcomes, especially in facilities in which the shortage of beds is a significant problem in the ICU. In particular, certain predictors of the event could help doctors in their choice of site of care (ICU or general ward). However, until standardized protocols for the effective application of NIMV outside the ICU have been established by institutions, we do not promote the unjustified use of NIV outside the ICU.

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