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Changes in the practice of non-invasive ventilation in treating COPD patients over 8 years

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Abstract *Objective:* We reviewed data of 208 episodes of acute respiratory failure due to chronic obstructive pulmonary disease treated by non-invasive ventilation (NIV) in our Respiratory Intensive Care Unit (RICU) from its opening in 1992 to 1999. *Material and methods:* We assessed whether the rate of NIV success, the severity of the disease, and the associated costs changed in this period during which the staff and the equipment did not change. *Results:* The failure rate was constant over the years (17.2% on average). The severity of the episodes of ARF, defined by pH and APACHE II at admission, worsened during the years. The statistical change point test allowed us to identify 1997 as the year of a significant change in the severity of admission pH and therefore to identify two different periods: 1992–1996 (mean pH = 7.25 ± 0.07) and 1997–1999

(7.20 ± 0.08 ; $P < 0.001$). In this latter period the risk of failure for a patient with a pH < 7.25 was threefold lower than in 1992–1996. In 1997–1999 an increasing number of episodes of ARF with a pH > 7.28 were treated in the Medical Ward (20% vs 60%). This allowed a significant reduction of daily cost per patient treated with NIV (558 ± 8 Euros vs 470 ± 14 Euros, respectively; $P < 0.01$). *Conclusions:* We conclude that, over time, experience with NIV may progressively allow more severely ill patients to be treated without changing the rate of success. The daily cost of NIV per patient can be reduced by treating less severely ill patients outside the RICU.

Keywords Non-invasive ventilation (NIV) · Chronic obstructive pulmonary disease (COPD) · Acute respiratory failure (ARF)

Introduction

There is now strong evidence and many consolidated data to support the use of non-invasive ventilation (NIV) in the management of acute exacerbations of chronic obstructive pulmonary disease (COPD) [1, 2, 3] and in selected patients with hypoxaemic respiratory failure [4], but this ventilatory technique seems not to be very largely employed (i.e., $< 3\%$ of mechanically ventilated patients, according to a multinational survey) in the “real world” of the Intensive Care Unit (ICU) [5]. It was, however, recently shown in a French survey [6] that in 35%

of patients ventilated in ICU, NIV represents the first attempt of mechanical ventilation. Interestingly, the first controlled studies on the use of NIV in the ICU, published in the early 1990s, were also carried out in France [7], suggesting that the now relatively greater use of NIV in that country may be a consequence of the familiarity with this technique that the medical and paramedical staff has gained throughout these years. The success of NIV largely depends on the acceptance and compliance of the patient, and these are likely to be associated with the way that this method of ventilation is applied by the operator. The learning and training process that a hospi-

tal team gains throughout the years may be important in this respect. Literature data indirectly raise this suspicion.

For example, in 1992, Foglio et al. [8] concluded, from a retrospective study, that the use of NIV was not more effective than standard medical treatment alone in an acute respiratory failure (ARF) due to COPD, but the same group sometime later showed opposite results [9], so that in an accompanying editorial Brochard [10] stated that "it was possible that some learning effects explained part of the improvement in the success rate".

It is, therefore, possible that the progressively increasing experience of medical and paramedical personnel, deriving from the systematic use of NIV over the years, may modify clinical practice (i.e., the severity of patients treated) and patients' outcome, but this issue has never been systematically addressed.

The opening, 10 years ago, of a Respiratory Intensive Care Unit (RICU) largely devoted to non-invasive treatment of acute respiratory failure, gave us the unique opportunity to collect data prospectively on patients being treated with NIV and, therefore, to evaluate this issue.

The primary aims of the study were to assess whether the rate of NIV success, the severity of disease treated, and the costs associated with NIV changed during an 8-year period. A secondary outcome was to assess if among the collected data some variables could predict the success of NIV and if their predictive power could change throughout time.

Methods

Between January 1992 and December 1999 we prospectively collected data relative to COPD patients [11] undergoing an episode of ARF and treated with NIV in our Respiratory Unit, both in the RICU (5 monitored beds) and in the medical ward (70 beds). The RICU is equipped for intensive but non-invasive monitoring; there are either ventilators specifically designed for NIV (BiPAP ST/D Respironics, USA; O'NYX, Nellcor-Puritan-Bennett, USA; Helia, Saime, France; Vential, Saime, France; 335 Nellcor-Puritan-Bennett, USA; VPAP II Sullivan, ResMed, Australia) or ICU ventilators (Cesar, Taema, France; Amadeus, Hamilton, Switzerland; 8400 Bird, USA; Vision BiPAP, Respironics, USA) so that it is possible to switch from NIV to conventional mechanical ventilation at any moment that endotracheal intubation becomes mandatory [12]. The application of NIV was approved by our local Ethics Committee and oral consent was given by the patients or their next-of-kin. Criteria for starting NIV were: pH <7.35 and PaCO₂ >65 mmHg, plus one of the following: severe dyspnoea, respiratory rate >25 b/m, and accessory muscle recruitment. Absolute exclusion criteria were considered: 1) coma, 2) respiratory gasping, 3) inability to remove secretions, and 4) need to protect the airways. Throughout the overall period of the study, however, other variables such as the severity of illness and, in particular, the presence of co-morbidity (APACHE II score) and impaired sensorium, may have varied according to the different attitude of the physicians during the entire period (see results). Throughout the overall period, the individual physicians and respiratory therapists remained the same, while approximately 20% of the nursing team was substituted. The nurse/patient ratio did not change: this ratio

was 1/3 during daytime shifts, and 1/6 during the night shift. Likewise, the size of the medical team (three physicians in rotation during the daytime, one physician on duty at night) remained constant during the period of the study as did that of the Respiratory Therapists (1/5 from 8 a.m. to 4 p.m.). A face mask was always used.

Data relative to age, severity of illness assessed by APACHE II score [13], as well as arterial blood gases (ABG) before and after 1 h of ventilation were analysed. PaCO₂ and pH values were also calculated as percentage of variation from the baseline after 1 h of treatment. Failure of NIV was defined as death or the need for intubation. This latter was defined a priori in 1992, when the first clinical study was performed in our Unit as a worsening in pH and/or a pH = 7.25 after 1 h of NIV, deterioration in the sensorium (Kelly score >3 [14]) or respiratory arrest. Clearly the "time of intubation" based on the pH may have varied in the last few years, due to a better confidence with the technique gained throughout the years. However, this is a matter of this study.

Information relative to the costs of care of a patient treated by NIV was obtained from a computer-based system developed by our Institution that allowed us to calculate all the direct and indirect costs, according to the yearly inflation rate of the currency [15]. The data are expressed in Euros. The daily cost of each patient undergoing NIV was calculated according to the location in which the NIV was applied (see results).

Statistical analysis

Continuous variables were analysed using a Student's test for independent variables or the Mann Whitney test if the distribution of the variables was not normal. Nominal variables were compared using the chi-square test or Fisher's exact test as appropriate. A $P < 0.05$ was considered statistically significant. The change point test [16] was used to determine whether there was a change in pH and APACHE II at admission according to the year of treatment. A χ^2 for linear trend analysis was used to assess any changes with time in the proportion of patients with pH >7.28 treated outside the RICU and to assess the relative risk of failure judged at enrolment throughout the study period.

A stepwise logistic regression was used to identify the variables associated with failure of NIV. First, the available data on success and failure of NIV were compared in a univariate analysis. Second, variables found to be associated with failure (P value 0.10 in the previous analysis) were entered into a logistic regression model according to the "forced entry" method.

Results

Between 1992 to 1999, a total number of 248 episodes of ARF were treated by NIV (Fig. 1), 208 (84%) of them were treated in RICU and so were considered for analysis. Their outcomes are reported in Fig. 1. Patients' characteristics are listed in Table 1. As shown in Fig. 2, keeping constant the number of patients ventilated by NIV per bed per year, the failure rate was constant and not statistically significant throughout the years, being on average 17.2%. However, as illustrated in Fig. 3, the severity of the episodes of acute respiratory failure, defined by pH at admission, worsened significantly during the study period. In particular, the change point statistical test showed a significant decrease in pH at admission in 1997 (Fig. 3, lower part), thus allowing us to identify

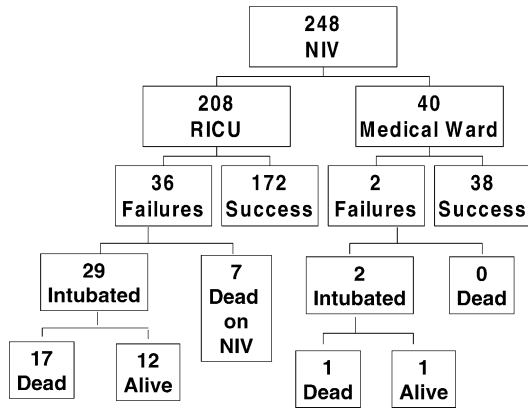


Fig. 1 Distribution of the study population according to the outcome of the NIV trial

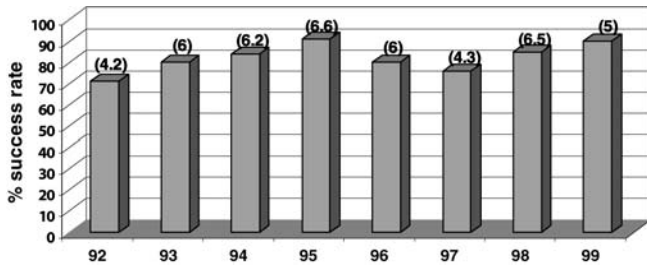


Fig. 2 Success rate of the patients treated with NIV in the 8 years of the study. Numbers in brackets are the numbers of patients ventilated with NIV for a single RICU bed per year. *P* = ns

Table 1 Patients' characteristics at enrolment. Data are mean±SD

Patients = 208	Mean value±SD
Age (years)	71±8
Apache II	23±6
ABG at admission	
pH	7.23±0.08
PCO ₂ (mmHg)	86±17
PO ₂ /F _i O ₂	256±57
Origin	
Medical ward	77%
Other hospitals	15%
Home	8%

two different periods: 1992–1996 (first period) in which the mean pH at admission was 7.25±0.07, and 1997–1999 (second period) during which the mean pH at admission was significantly lower (7.20±0.08, *P*<0.0001). APACHE II score at admission did not show any statistical change point (Fig. 3, upper part), but its mean value was statistically higher in the second period than before (25±6 vs 22±6, respectively, *P*<0.01). RICU mortality did not significantly change during the study

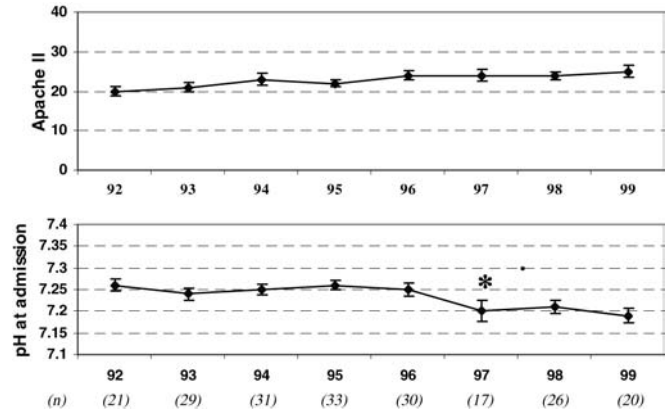


Fig. 3 Severity score at admission, as assessed by the APACHE II, and pH at admission in the 8 years of the study. Symbols are mean±standard error (SE). In 1997, a significant decrease in admission pH (change point statistical test) was observed. No significant change point was shown for APACHE II. (*n*) = number of patients treated each year. * = *P*<0.01

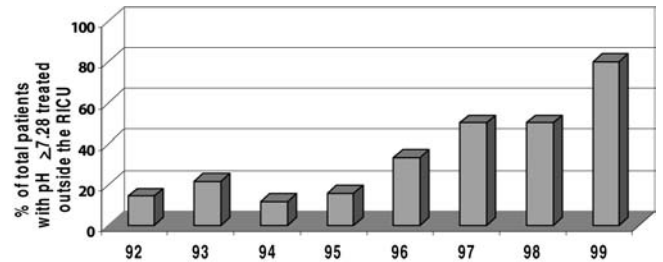


Fig. 4 Percentage of patients with pH >7.28 treated outside the RICU, in the medical ward, in the 8 years of the study. *P*<0.001 in the χ^2 Hf for linear trend analysis

period (from 19% in 1992 to 5% in 1999, *P* = ns). NIV was delivered usually in Pressure Support mode or eventually in Pressure Controlled mode in the case of patient ventilator mismatching due to air leaks.

NIV was performed for 5.2±1.8 days and the daily application lasted usually more than 18 h for the first 24 h and then gradually reduced until weaning was achieved. NIV was definitively withdrawn when patients reached levels of pH >7.35 in spontaneous breathing without further neurological worsening for at least 24 h. ICU ventilators were always used in the first 24–48 h, while later on most of the patients were switched to home care ventilation.

With time, the less severely ill patients (i.e., pH>7.28) were progressively treated outside the RICU, in the medical ward (MW) so that, as illustrated in Fig. 4, there was a significant progressive increase (χ^2 for linear trend = 17.8; *P*<0.001) in the number of patients treated in the medical ward. Among these patients, those admitted to RICU had a significantly higher APACHE II at admis-

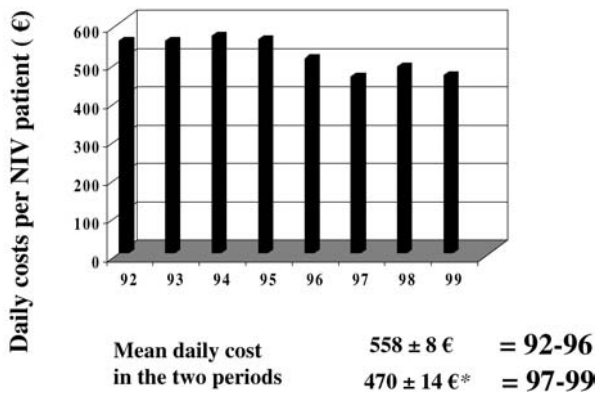


Fig. 5 Mean daily cost calculated for a single patients treated with NIV is shown for each year of the study. * $P < 0.01$

sion (20 ± 4 vs 15 ± 2 when compared with patients treated in the MW; $P < 0.01$).

The cost of each patient undergoing NIV in the two periods of the study was calculated and expressed as a mean daily cost per patient. Figure 5 shows that the total costs were significantly lower in the years 1997–1999 ($P < 0.01$). The mean daily cost in the period 1992–1996 was 558 ± 8 Euros vs 470 ± 14 Euros in the years 1997–1999. This was, in particular, due to the increased patient/personnel ratio in the subset of patients treated in the medical ward, so that the expenses due to staff salaries were decreased.

Secondary outcome

The clinical characteristics of the patients treated in the RICU, at admission, and ABGs before NIV and after 1 h of NIV, are summarized in Table 2. In the first period (1992–1996) among the variables recorded at admission, the severity of acidosis (pH and PaCO₂) and of illness (APACHE II), were significantly worst in the patients

who failed NIV. In the second period (1997–1999) NIV failures differed only for an higher APACHE II ($P < 0.006$).

After 1 h of treatment two additional variables were associated with a successful treatment, irrespective of the study period: an improvement in pH and PaCO₂ value (either in terms of absolute value or as a change since admission time). Interestingly, failures in the first period had the same pH at admission as the successes in the second period (7.21 ± 0.06 vs 7.21 ± 0.08 , respectively).

Therefore, we calculated the relative risk of failure of patients treated by NIV according to the severity of the respiratory failure at admission and the period of the study. Due to the paucity of patients with pH > 7.30 treated in RICU in the second period, the risk was calculated only for a pH of 7.30 and 7.25. Compared with a patient with a pH of 7.30 treated in the second period, a patient with a pH of 7.25 has a 1.5-fold (95%, CI 1–3.8) higher risk of failure if treated in the years 1997–1999 vs a 3.3-fold (95%, CI 2.2–5.1) higher when treated in the years 1992–1996 ($P = 0.03$).

The stepwise regression model including the factors used in the univariate analyses found that APACHE II score, the change in PaCO₂, and pH after 1 h of NIV as well as the absolute value of pH after 1 h were independent predictive factors for success (Table 3) in the overall period of the study.

Table 3 The independent predictive factors for failure as highlighted by the stepwise regression model. (Δ = percentage changes from baseline after 1 h of ventilation)

Variable	95% CI lower limit	OR	95% CI upper limit	P value
Apache II	1.00	1.13	1.28	0.007
Δ PCO ₂	1.19	1.30	1.43	0.004
pH 1 h	0.36	0.46	0.59	<0.001
Δ pH	0.00	0.02	0.07	<0.001

Table 2 Characteristics of the patients who succeeded or failed NIV in the two periods (1992–1996 and 1997–1999). Data are mean \pm SD, Δ = change after 1 h since admission time

	First period (n = 145)			Second period (n = 63)		
	Success (n = 119)	Failure (n = 26)	P value	Success (n = 53)	Failure (n = 10)	P value
Age (years)	71 \pm 9	73 \pm 5	0.35	70 \pm 7	72 \pm 5	0.41
Apache II	21 \pm 6	25 \pm 6	0.005	24 \pm 5	29 \pm 7	0.006
pH adm	7.26 \pm 0.07	7.21 \pm 0.06	0.003	7.21 \pm 0.08	7.18 \pm 0.10	0.24
pH h	7.31 \pm 0.06	7.20 \pm 0.09	<0.0001	7.30 \pm 0.06	7.18 \pm 0.08	<0.001
Δ pH	0.06 \pm 0.03	-0.01 \pm 0.04	<0.0001	0.09 \pm 0.04	0.002 \pm 0.06	<0.0001
PCO ₂ adm (mmHg)	83 \pm 17	91 \pm 14	0.03	88 \pm 16	99 \pm 22	0.06
PCO ₂ h (mmHg)	75 \pm 14	95 \pm 18	<0.0001	77 \pm 13	100 \pm 22	<0.0001
Δ PCO ₂	-8.3 \pm 8	4.3 \pm 6.2	<0.0001	-9.7 \pm 7.4	1.9 \pm 9.3	<0.0001
PO ₂ adm (mmHg)	55.1 \pm 11	53.2 \pm 11	0.43	52.9 \pm 12.3	51.5 \pm 13.6	0.74

Discussion

The analysis of data relative to the activity of our RICU, from its opening in 1992 through 1999, shows that NIV was employed to treat progressively more severe episodes of COPD exacerbation, while the rate of treatment success remained constant; furthermore, the calculated risk of failure for the more severe patients was threefold higher in the first years (1992–1996) compared to the last years of activity (1997–1999). Indeed with time, a larger number of patients in a less severe condition were treated outside the RICU so that we recorded a significant reduction in the daily costs for patients treated with NIV.

Even if it is very difficult to quantify these variables, there is some indirect evidence which supports the hypothesis that the progressive training and familiarity with the technique could mainly explain our findings. The numbers of medical doctors, respiratory therapists and nurses, the kind of equipment used, and the structural environment remained constant throughout the whole period, and indeed the individual members of staff changed very little.

Even if a trend in an increase in the severity of acute respiratory failure treated was clearly shown, the analysis of this trend, by the changing point test, reveals a significant change in attitude regarding treating more severely ill patients 5 years after the opening of the unit. This period may be considered too long to reach a “plateau” in the practice of and familiarity with NIV. It is nevertheless interesting to note that during these first few years a systematic training program was conducted in the hospital. In particular, all the nurses working inside and outside the RICU underwent educational courses twice a year, including not only the practice of NIV delivery, but also the basis of cardiopulmonary resuscitation, and the management of life-threatening emergencies. The respiratory therapists were also progressively taught the basics of mechanical ventilation, and the practice of NIV delivery in the acute setting. A specific protocol, both for nursing and respiratory therapists, was not implemented except for the prevention of skin breaks of the nose. However, in the last 5 years, the introduction of a clinical diary for the monitoring and collection of vital signs and ventilatory settings may have improved and standardised the approach to NIV by paramedics. Both medical and paramedical personnel participated in courses outside the hospital and attended major national and international meetings; the number of publications from our Institution also progressively increased, so that the motivational aspect of the medical and paramedical staff also may have improved. On the other hand, the nursing workload did not seem to have increased through the years, so that the change in our practice was not likely to have been related to more time spent at the patients’ bedside. This information was not

systematically recorded for each patient, although it was for a few cases [15], since in itself this is a very “time-consuming” clinical practice. Indeed, while in an uncontrolled study Chevrolet et al. [17] demonstrated that NIV may be a very time-consuming procedure for nurses and so may be very difficult to apply, 10 years later they concluded that this technique, in experienced hands, appears not to influence the nurses’ workload in the ICU significantly [18].

ICU ventilators and monitors were not changed in the study period, but we should recognise that the technology used in NIV has altered in the last decade and may have influenced the typology of the patients treated, since the success of NIV may depend on its acceptance. In particular, home care ventilators are now equipped with software developed to compensate for air-leaks, with new non-rebreathing devices [19] and systems of triggering [20], so that the patient-ventilator interaction and carbon-dioxide clearance may be better. While this new products were employed for the subset of patients treated in the medical ward, the patients treated in the RICU were always ventilated (at least in the first 24 h) with ICU ventilators, that at that time were not specifically designed for NIV, and indeed patient-ventilator dyssynchrony was sometimes a problem [21]. On the other hand, the materials and the shape of facial masks used for NIV have dramatically improved over time so that the newer and more sophisticated interfaces may have influenced the tolerance of NIV and therefore the possibility to treat more severely ill patients with the same good outcomes [22]. However, we have to recognise the possibility that new treatment strategies such as the latest antibiotics or new bronchodilators and new interventions such as PC program updates may have improved the patients’ outcomes in the second period.

As illustrated in Table 2, during the first period we used NIV to treat less severe cases, judged by both pH and APACHE II score at admission, so that patients with sensorial abnormalities, inability to clear secretions, and a high APACHE II score were not admitted to a NIV trial and were, therefore, intubated and/or transferred to the ICU. Standardised clinical guidelines were not developed or applied in our Institution until very recently, so that the change in the severity of clinical conditions accepted for NIV treatment did not depend on an “objective” statement, but rather on a more “aggressive attitude” that was perhaps influenced not only by our own clinical experience but also by growing evidence from literature in this field. The first few studies performed outside the ICU enrolled patients with a mean pH of approximately 7.32 [2, 23], while in more recent studies this value dropped to approximately 7.28 [24, 25]. Based on our own experience and on literature data, we began to treat less severely ill patients (i.e., pH>7.28) outside the RICU, in the medical ward. A pH of approximately

7.30 was also recently shown, in a large multicentre randomised study, to be a clinical threshold value, discriminating between success and failure, for patients treated with NIV in a medical ward [3]. In the event of haemodynamic stability and a normal sensorium we started to treat this subset of patients, most of whom were already admitted to the hospital for a rehabilitation program and underwent an acute exacerbation once there, directly in their room to avoid any psychological decompensation related to a more aggressive environment. This strategy produced a substantial financial benefit, an issue that is currently very important. As a matter of fact, in the last 3 years we were able to save about 90 Euros a day per patient treated with NIV, while keeping the rate of success constant. The major saving was related to direct costs and in particular staff salaries, which in Italy, as in most European countries, represent a consistent percentage of total costs. The different nurse/patient ratio (1/3 during the daytime in the RICU vs 1/10 in the medical ward) may explain this difference, together with a higher number of medical doctors present in the unit during the day. Overall, the mean costs in the two periods of time were much lower than we reported in US dollars in a 1997 study [15]. This is largely due to the fact that at that time the exchange rate between the US dollar and the Italian Lira was much higher than now (1 US \$ = 1,590 Lira in 1997 vs 2,210 Lira in 2001).

These findings may highlight the fact that the less severely ill patients (pH = 7.28) should be treated outside the RICU for a better cost-effectiveness. A general recommendation is not, however, easy to be made. A recent review on this topic, has stated that "the ideal allocation for NIV will vary from country to country and, indeed, from hospital to hospital, depending upon local factors" [26].

A secondary outcome of the study was to assess if among the recorded variables, some of them could predict the success of NIV. Up to now a number of studies have looked for predictors of outcome for NIV [27, 28,

29, 30, 31]. All these agree on finding an important predictive role of the change in ABGs, particularly pH and PaCO₂ after a short period of NIV. They also found that patients in whom NIV treatment failed were significantly more acidaemic at enrolment than those successfully treated [27, 28, 29, 30, 31].

In his study, Plant et al. [29] showed that, compared with patients with a pH of 7.30 and a PaCO₂ of about 75 mmHg at admission and treated by NIV, the risk of failure of a patient with a same PaCO₂ and a pH of 7.25 was more than threefold higher. Interestingly, in our study we found a similar result in patients treated in the first period, while in the second period the same kind of patients were treated with a much lower risk.

The stepwise regression analysis performed on the entire period of observation largely confirmed what has so far been published, i.e., that the changes in pH, and to a lesser extent in PaCO₂, after 1 h of NIV are strongly associated with NIV success or failure.

Thus, we may say that even if the severity of acidosis at enrolment represents a possibility to stratify the relative risk of failure in a given time and for a given setting of operating staff, familiarity with the technique and amelioration in the performance could affect the predictive value of this variable allowing a further improvement in the rate of success for a given pH at admission.

In conclusion, we have shown that the clinical practice of applying NIV for an acute exacerbation of COPD may change over time, so that with increased staff training, more severely ill patients may be treated with a reduced risk of failure. In the meantime, increased confidence with the technique may allow the same team to treat less severely ill patients outside the RICU, so that the total NIV cost per year decreases significantly. Future studies are needed to prospectively assess if the implementation of practical guidelines in delivering NIV may result in better outcomes for the patients and less energy expenditure for the medical and paramedical staff.

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