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Noninvasive ventilation for the treatment of acute respiratory failure in patients with hematologic malignancies: a pilot study

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Abstract *Objective*: To evaluate treatment with noninvasive ventilation (NIV) by nasal mask as an alternative to endotracheal intubation and conventional mechanical ventilation in patients with hematologic malignancies complicated by acute respiratory failure to decrease the risk of hemorrhagic complications and increase clinical tolerance.
Design: Prospective clinical study.
Setting: Hematologic and general intensive care unit (ICU), University of Rome "La Sapienza".
Patients: 16 consecutive patients with acute respiratory failure complicating hematologic malignancies.
Interventions: NIV was delivered via nasal mask by means of a BiPAP ventilator (Respironics, USA); we evaluated the effects on blood gases, respiratory rate, and hemodynamics along with tolerance, complications, and outcome.
Measurements and results: 15 of the 16 patients showed a significant improvement in blood gases and respiratory rate within the first 24 h of treatment. Arterial oxygen tension (PaO_2), PaO_2/FIO_2 (fractional inspired oxygen) ratio, and arterial oxygen saturation significantly improved after 1 h of treatment (43 ± 10 vs 88 ± 37 mmHg; 87 ± 22 vs 175 ± 64; 81 ± 9 vs 95 ± 4 %, respectively) and continued to improve in the following 24 h ($p < 0.01$). Five patients died in the ICU following complications independent of the respiratory failure, while 11 were discharged from the ICU in stable condition after a mean stay of 4.3 ± 2.4 days and were discharged in good condition from the hospital.
Conclusions: NIV by nasal mask proved to be feasible and appropriate for the treatment of respiratory failure in hematologic patients who were at high risk of intubation – related complications.

Key words Acute respiratory failure · Leukemia · Noninvasive ventilation

Introduction

Noninvasive mechanical ventilation by face mask is currently used to treat acute episodes in chronic respiratory failure (ARF) [1–5]. In ARF (hypoxemia associated with hypercapnia or not) it may be useful as well, as standard O_2 therapy and drug administration often show little benefit in improving the patient's clinical condition. In this case, traditional mechanical ventilation after tracheal intubation is usually the first choice, even though it often has disadvantages which conflict with the clinical condition of patients [6]. By contrast, noninvasive ventilation appears to be more comfortable for the patient and to cause less anxiety. It does not require sedation and could be of great interest for treating immunocompromised patients such as those with hematologic malignancies. Moreover, noninvasive ventilation reduces the risk of

Table 1 Clinical details of the 16 patients (*SAPS* simplified acute physiology score, *NHL* non-Hodgkin lymphoma, *AML* acute myelocytic leukemia, *ALL* acute lymphoblastic leukemia, *CML* chronic myelocytic leukemia, *NCPE* noncardiogenic pulmonary edema, *CPE* cardiogenic pulmonary edema, *BP* bacterial pneumonia, *VP* viral pneumonia, *FP* fungal pneumonia)

Patient	Age (years)	Sex	Diagnosis	Cause	SAPS	Length of treatment	Outcome
1	56	M	NHL	BP	14	8 (days)	Died
2	23	M	AML	NCPE	13	8	Survived
3	29	M	AML	CPE	17	1	Died
4	27	M	AML	BP	18	2	Died
5	51	F	AML	VP	10	5	Died
6	64	M	NHL	FP	10	5	Survived
7	64	M	NHL	FP	16	3	Died
8	38	M	CML	BP	14	3	Survived
9	68	M	NHL	VP	12	5	Survived
10	19	M	NHL	FP	10	6	Survived
11	26	F	AML	FP	12	3	Survived
12	14	F	ALL	BP	14	3	Survived
13	23	F	CML	VP	16	2	Survived
14	62	F	AML	FP	14	9	Survived
15	23	F	CML	BP	12	2	Survived
16	25	M	ALL	FP	12	4	Survived

hemorrhage due to intubation in thrombocytopenic subjects.

Up to now very little has been reported on this application of noninvasive ventilation. Tognet et al. [7] recently reported the successful treatment of respiratory failure in patients with hematologic malignancies with noninvasive ventilation through a face mask. The aim of our pilot study was to evaluate the feasibility and efficacy of noninvasive ventilatory support by utilizing pressure support ventilation (PSV) and positive expiratory pressure (PEEP) delivered by a nasal mask in patients with hematologic malignancies complicated by ARF.

Patients and methods

After obtaining approval from our institutional Ethics Committee and informed consent from patients, 16 consecutive patients affected by ARF complicating hematologic malignancies were enrolled. The main clinical data are given in Table 1. ARF was precipitated in 14 patients by pneumonia (bacterial 5, viral 3, fungal 6 patients) diagnosed on the clinical history, chest X-ray, hypothermia or hyperthermia (temperature < 36 °C or > 38.2 °C), and rapid worsening of gas exchange, and confirmed by bronchoalveolar lavage, blood cultures, and serologic tests. Of the 2 remaining patients 1 had cardiogenic pulmonary edema and 1 noncardiogenic pulmonary edema due to an allergic reaction to iodate contrast media. Enrollment conditions were: (A) arterial oxygen tension (PaO_2) ≤ 60 mmHg during standard O_2 therapy with a Venturi face mask delivering a fractional inspired oxygen (FiO_2) ≥ 0.5, (B)increased respiratory muscle workload suggested by tachypnea [respiration rate (RR) ≥ 35 breath per min], involvement of accessory muscles and/or paradoxical breathing with patient reporting subjective distress. These are the intubation criteria for ARF patients usually adopted in our intensive care unit (ICU). Exclusion criteria were: presence of neurological disease, failure of more than two organs, facial deformities, lack of cooperation, and preexisting chronic obstructive lung disease (COPD).

At entry to the study, 6 of 16 patients were neutropenic and 14 were thrombocytopenic. For ventilatory support we utilized a BiPAP ventilator (Respironics, Murreysville, Pennsylvania, USA) [8]. This is based on a flow generator for nasal continuous positive airway pressure (CPAP). A pressure control valve maintains airway pressure at one of two levels: expiratory positive airway pressure (EPAP, equivalent to PEEP) or inspiratory positive airway pressure (IPAP, equivalent to pressure support level). This is possible even with rapid changes of flow. In the spontaneous mode, the device cycles from EPAP to IPAP when the inspiratory flow exceeds 40 ml/s for more than 30 ms. The IPAP level is kept steady for longer than 180 ms and reverts to EPAP: when inspiratory flow decreases below a threshold level, when the start of expiration is detected, or if IPAP lasts more than 3 s.

The nasal mask (Respironics, Murreysville, Pennsylvania, USA) is manufactured in flexible, nontraumatic silicon rubber and fits the face of the patient well. We chose to start with a nasal mask for better comfort, as recently reported by Lapinsky et al. [12] and for other considerations that are detailed in the discussion.

To avoid the risk of hemorrhages and air leaks, no patient had a nasogastric tube. Ventilation was set starting with values of EPAP = 4 cmH_2O and IPAP = 10 cmH_2O. Subsequently, rapid increases in PSV values were made until respiratory discomfort lessened, with $PaO_2 \geq 60$ mmHg with the administration of additional O_2 ($FIO_{2 \leq} 0.5$). Mean values for EPAP and IPAP during the study were 5 ± 0.3 cmH_2O and 16 ± 2 cmH_2O, respectively. Approximate values of FIO_2 were obtained by drawing a sample of inspiratory gas (50 ml) from the nasal mask, then analyzing this by a gas analyzer (Radiometer, Copenaghen, Denmark).

During the first 24 h, noninvasive ventilation was maintained continuously until oxygenation and clinical status improved; then, it was administered discontinuously with 15–30 min intervals every 3–6 h, according to the patient's clinical condition. During these interrupted periods, the patients breathed through FIO_2 0.5 Venturi masks. The length of noninvasive ventilation cycles was progressively reduced to 4 h/day, and it was withdrawn completely in cases of stable improvement of blood gas values along with the clinical

Table 2 Changes in arterial blood gases, PaO_2/FIO_2, respiratory rate *RR,* mean arterial pressure *MAP* and heart rate *HR* during the study. Values are mean ± SD (*T0* baseline, *T1* after 1 h, *T2* after 3 h, *T3* after 12 h, *T4* after 24 h)

	T0	T1	T2	T3	T4
pH	7.5 ± 0.04	7.43 ± 0.03	7.44 ± 0.04	7.44 ± 0.03	7.40 ± 0.01
PaO_2 (mmHg)	43 ± 10	88 ± 37	91 ± 25	96 ± 26	90 ± 26*
$PaCO_2$ (mmHg)	32 ± 4	35 ± 8	35 ± 4	33 ± 3	38 ± 7
SaO_2 (%)	81 ± 9	95 ± 4	96 ± 3	97 ± 2	96 ± 4*
PaO_2/FIO_2 (breaths/min)	87 ± 22	175 ± 60	203 ± 91	210 ± 90	185 ± 84*
RR	42 ± 7	34 ± 10	34 ± 10	33 ± 8	33 ± 7
MAP (mmHg)	89 ± 11	78 ± 11	81 ± 11	85 ± 15	75 ± 12
HR (beats/min)	112 ± 17	102 ± 14	97 ± 10	99 ± 16	96 ± 22

* $p < 0.01$

Table 3 Complications during the study

Complications	*n*	Leading to death
Septic shock	3	3
Gastrointestinal hemorrhage	1	1
Acute myocardial infarction	2	1
Skin necrosis	5	0

condition ($PaO_2 \geq 80$ mmHg breathing FIO_2 0.5; RR ≤ 30 bpm and normocapnia). Treatment was interrupted and endotracheal intubation performed for patient intolerance or following lack of positive results.

RR and blood gas values were recorded at the following intervals: baseline (T0), 1 h after beginning of treatment (T1), after 3 h (T2), after 12 h (T3), and after 24 h (T4). Throughout the study hemodynamic variables such as mean arterial pressure, heart rate, hourly diuresis, and arterial oxygen saturation (Biox, Ohmeda, France), were continuously monitored in a noninvasive fashion. After some failed attempts to measure physiologic variables we decided to restrict our evaluation to RR analysis to avoid discomfort to the patient.

Values of pH, PaO_2, arterial carbondioxide tension ($PaCO_2$) and the PaO_2/FIO_2 ratio along with RR and heart rate were evaluated by means of the Kruskall–Wallis one-way analysis of variance test. A p value of ≤ 0.01 was regarded as statistically significant.

Results

The results of our study are shown in Table 2. PaO_2 significantly improved ($p < 0.001$) in the first 24 h of treatment along with PaO_2/FIO_2 ($p < 0.001$). Changes in pH and $PaCO_2$ were not statistically significant, nor were changes in RR. A visible improvement in PaO_2 was obtained after 1 h of treatment (Table 2).

Table 1 gives the length of treatment for the 16 patients, which varied from 24 h to 9 days (98 ± 54 h), and the final outcome. The clinical results of the study are summarized in Fig. 1. One patient did not show any improvement in PaO_2/FIO_2 or a reduction in RR, was intubated and died of septic shock. Fifteen responded (i.e., showed an increase at T1 of at least 15 mmHg in PaO_2 breathing the same FIO_2 administered by the Venturi mask); 1 refused after 24 h to continue the noninvasive treatment because of mask intolerance, was intubated, and died 6 days after intubation of septic shock; 3 died during the study because of various complications (massive gastric hemorrhage in 1, cardiogenic shock due to anthracycline myocarditis in 1, and massive bilateral pneumonia with septic shock in 1), while the remaining 11 patients were discharged from hospital in good clinical condition. In these patients the mean ICU stay was 4.3 ± 2.4 days. No patient showed gastric distension, while 5 patients ventilated for longer than 5 days showed nasal abrasions due to the ischemic pressure produced by the Respironics nasal mask. All patients showed hemodynamic stability (Table 2) during treatment and no technical problem was observed during the study. The complications during the study are listed in Table 3.

Discussion

Noninvasive ventilation (NIV) is widely accepted as a valuable alternative to standard mechanical ventilation in respiratory failure of central or peripheral neurologic origin [13–15]. This technique was recently suggested for the treatment of acute episodes in chronic respiratory failure [1, 5, 16]. Moreover, it has been used for patients with acute hypoxemic respiratory failure [7, 12, 17, 18]. The results of these studies suggest that NIV could be successfully used in patients with hematologic malignancies and ARF.

These patients have a peculiar background that bears on their clinical treatment for ARF, even when it is potentially reversible. They exhibit relevant psychological distress due to their primary disease and often refuse to undergo endotracheal intubation and mechanical ventilation. These patients fear spending their final days “attached to a machine”, deprived of autonomy and of comunicating with their relatives. Instead, all patients accept NIV as an alternative to standard mechanical ventilation, which allowed them to keep their autonomy.

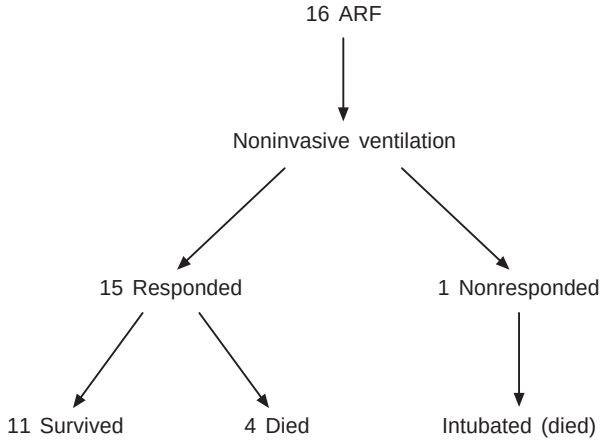

Fig. 1 Clinical results of the study

Many investigators have emphasized a worsened outcome for granulocytopenic patients undergoing tracheal intubation and mechanical ventilation during ARF [19–22], which is a common complication of hematologic malignancies. This results from the combination of the damage caused by opportunistic infections and the direct interstitial pulmonary toxicity of chemotherapy [23–29], and complications related to endotracheal intubation. In immunodeficient and thrombocytopenic patients these complications are greatly increased. Complications can result from the intubation procedure or during mechanical ventilation. In addition to injury to the pharynx and larynx, at the point of contact between tracheal mucosa and the tube or its cuff, edema, ulceration, or hemorrhage with potential stenosis can occur.

The risk of developing nosocomial infections such as sinusitis and ventilator-associated pneumonia is very high. The endotracheal tube is one of the most important predisposing factors to nosocomial pneumonia [35]. It bypasses the mechanical defenses of upper airways and causes local damage. In addition, the portion of the trachea between the cuff and the vocal cords becomes a reservoir of colonized secretions by bacteria originating from the sinuses, the nasal passages, pharynx, oral cavity and the stomach. These infectious secretions can be introduced into the lung with every nursing maneuvre [36].

In this situation, NIV seems to be an interesting alternative because of the low risk of complications [7]. In a recent randomized prospective study on 64 patients with ARF unrelated to COPD, we showed that the incidence of pneumonia was significantly lower in the NIV group than in the conventional mechanical ventilation group [34]. These data support the application of this technique in a group of patients whose hematologic disease was complicated by acute respiratory failure.

We chose PSV-CPAP instead of assisted mechanical ventilation, as it offers the advantage of a good patient-machine interaction with reduced levels of airway pressure, decreasing the risk of air leaks and gastric distension [30–32]. This is a crucial point, as with PSV-CPAP it is possible to maintain an airway pressure below 25 cmH_2O, (i.e., below the upper esophageal opening pressure [31–32]) avoiding the need for a nasogastric tube and the major risk of bleeding related to this maneuvre in thrombocytopenic patients.

In 15 of the 16 patients, NIV produced rapid, effective improvement in arterial oxygenation, a reduction in discomfort due to tachypnea, with a decrease in RR and less use of accessory muscle,throughout the first 24 h. Tognet et al. [7] recently reported the successful use of NIV by face mask in 6 of 11 patients (55%) affected by hematologic malignancies complicated by ARF of various origins. Our results are in agreement, although we used a nasal instead of a full mask, thus confirming the good results obtained in ARF patients with similar equipment by Pennock et al. [18].

The choice of the best fitting mask is a crucial point during NIV, as the mask is the only interface between patient and ventilator. Several authors, including our group [2, 3, 6, 7, 16, 17, 34] have suggested the use of a face mask in patients with ARF, while others [9, 18] obtained good results in the same kind of patients using a nasal mask. Although we currently use a full face mask when treating hypoxemic ARF in our unit, after a careful analysis based not only on clinical but also on psychological and ethical aspects, we chose for this very specific indication (i.e., patients with hematologic malignancies complicated by ARF) to use a nasal mask. The nasal mask offers several advantages over the full face mask: it allows normal sleep rhythms, oral feeding, and talking, all of which are very important in patients in this particular psychological situation due to their primary disease. It is evident that in all patients in whom there are technical problems with the nasal mask, it must be replaced by a fullface mask before endotracheal intubation is considered.

Concerning the problem of nutrition during NIV, we usually suspend enteral nutrition for the first few hours of NIV use; subsequently our patients are allowed to drink or to eat a semisolid diet (according with their clinical status); no patient received continuous enteral nutrition, in order to avoid the risk of bleeding because of the nasogastric tube.

Although in this study the outcome of patients was strongly affected by the severity of the underlying disease, PSV by nasal mask was a useful tool, given the poor prognosis for these patients with conventional treatment [19, 23]: hospital survival was 62% in this prospective nonrandomized study, in the absence of a major complication. It is notable that in a group of 28 patients with acute hematologic malignancies complicated by ARF of various origins, receiving conventional mechanical ventilation in our ICU, during 1987–1991 we report-

ed 82% mortality despite similar Simplified Acute Physiology Scores and PaO_2/FIO_2 ratios [37]. Given the drawbacks of a comparison with historical controls, this major difference in hospital mortality seems to us impressive. Tognet et al. [7] recently reported 100% mortality in hematologic patients invasively ventilated for ARF versus 55% survival among the patients who responded to NIV.

It is of main importance that our results were obtained in an accurately selected group of patients affected by hematologic malignancies who showed a clear cause of decompensation; we excluded all those patients who were considered to be poor responders to the hematologic treatment, had more than two organ failures, were not cooperative, or suffered from chronic disease such as COPD. Other experience suggests that the treatment of ARF with mechanical ventilation must always be carefully evaluated on an individual basis with close collaboration between hematologic specialists and intensivists.

We saw no severe complications throughout or after the study. No gastric distension was observed but no nasogastric tubes were used. Five of the 16 patients presented nasal abrasions after prolonged treatment (> 5 days), but this never interrupted ventilation. Despite 14 of 16 patients showing a platelet count $< 25 \times 10^3$, no patient had a hemorrhagic complication, apart from patient 1 who died of a massive gastric hemorrhage .

It has been reported that the work of physicians and nurses is increased because of the strict control required by the device [32]; however, in our and others' experience [18] this was not confirmed, as the increase in nurses' workload seems to be concentrated only in the first 12–24 h of noninvasive treatment.

Finally, it is important that NIV offers an important ethical advantage for patients with hematologic malignancies, as it allows treatment of patients who refuse endotracheal intubation but not ventilatory support (a case we have often observed), thus permitting the delivery of intensive treatment while respecting the patients' will [33]. Because of good tolerability of NIV, sedative drugs and paralyzing agents were never administered, which are often required during mechanical ventilation for patient anxiety or discomfort and for good adaptation to the ventilator.

In conclusion, we have demonstrated that noninvasive ventilation is feasible and may be a good choice for the treatment of ARF in a selected population of critically ill patients with hematologic malignancies: the results of this pilot study can be the basis for a larger prospective, randomized study comparing noninvasive ventilation with conventional ventilatory support.

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