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Noninvasive mechanical ventilation as a palliative treatment of acute respiratory failure in patients with end-stage solid cancer

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Noninvasive ventilation (NIV) is widely used in the treatment of acute respiratory failure (ARF), but not in patients with end-stage solid cancer in whom any form of mechanical ventilation tends to be avoided. In a prospective study, we investigated the use of NIV in 23 patients with solid malignancies receiving palliative care and who were affected by severe hypoxic or hypercapnic ARF. The most frequent causes of ARF were exacerbations of pre-existing pulmonary diseases and pneumonia. After one hour, NIV significantly improved PaO_2/FiO_2 (from 154 ± 48 to 187 ± 55) and the Borg dyspnoea score (from 5.5 ± 1.2 to 2.3 ± 0.3). NIV also improved pH, but only in the subset of hypercapnic patients. Thirteen of 23 (57%) patients were successfully ventilated and discharged alive, while 10/23 patients (43%) met the criteria for intubation or died after an initial trial of NIV. Only two of these patients accepted invasive ventilation. The mortality rate in this subgroup was 9/10 (90%). A higher Simplified Acute Physiology Score (SAPS II) and a lower PaO_2/FiO_2 on admission were associated with a lower probability of survival. Patients with ARF and end-stage solid malignancies have an overall ICU and 1-year mortality rate of 39% and 87%, respectively, but despite this, a consistent subset of patients may still be successfully treated with NIV, if the cause of ARF is reversible. *Palliative Medicine* 2004; **18:** 602–610

Key words: acute respiratory failure; noninvasive ventilation; palliative care; solid cancer

Introduction

Acute respiratory failure (ARF) is a rather common event in cancer patients.[1–5] Blot *et al*. have shown that episodes of ARF are by far the most common reason for cancer patients being admitted to an Intensive Care Unit (ICU).[6] The ICU mortality rate among cancer patients, especially those requiring mechanical ventilation, is dramatically high and is not related to the type of cancer.[2,6–9] The occurrence of ARF is often seen by oncologists as a terminal phase of the disease, this view being based on studies reporting limited survival at considerable costs in such patients.[2,3,6,8–10] On the other hand, a large proportion of cancer patients with severe respiratory failure are denied admission to an ICU because intensive care specialists are aware that intubation and mechanical ventilation are both strong predictors of mortality in critically ill cancer patients.[2,6,7,9] This holds particularly true in the subset of patients who are not receiving chemotherapy or radiotherapy because of the advanced stage of their disease, and who therefore need palliative care. However, the ARF is not necessarily related to cancer progression (e.g., atelectasis in lung cancer); in some cases it may have a potentially reversible cause such as cardiogenic pulmonary oedema, pulmonary infection or an exacerbation of chronic obstructive pulmonary disease (COPD).

Noninvasive mechanical ventilation (NIV) is now the first line treatment of ARF in selected populations (e.g., those with COPD)[11] and has been used sporadically as a potential treatment of ARF in patients with a 'do-not-intubate' order.[12] The International Consensus Conference on Intensive Care Medicine stated that 'the use of NIV may be justified in selected patients who are "not to be intubated" with a reversible cause of ARF and may provide patient comfort and facilitate physician–patient interaction in the assessment of the reversibility of ARF'.[11] Unfortunately, 'early' NIV has been successfully used so far in cancer patients only to prevent intubation among those with haematological malignancies,[13] while no data are available for patients with advanced solid cancer in whom endotracheal intubation is not recommended or may even be denied.

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In this prospective two-centre pilot study we evaluated the feasibility and efficacy of NIV in patients with ARF complicating a solid tumour being managed palliatively.

Materials and methods

Population

Twenty-three consecutive patients admitted to the Respiratory Intensive Care Unit (RICU) or the Palliative Care Unit of 'S. Maugeri' Foundation (Pavia) or the general ICU of the Catholic University (Rome) were enrolled in this study. All these patients had ARF complicating a solid cancer which was in an advanced stage and which had been judged by the referring oncologist, at some point before enrolment into this study, to be suitable only for palliative care. None of the patients was neutropenic and/or thrombocytopenic. These patients were enrolled from a larger group of 34 patients admitted in the same period of time. Eleven patients were excluded *a priori* for the following reasons: coma ($n=2$), refusal of treatment ($n=4$), failure of more than two organs ($n=2$), inability to protect the airways ($n=1$) and haemodynamic instability ($n=2$).

The main clinical characteristics of the patients are given in Table 1. Thirteen of the 23 patients (56%) had lung cancer (only stage ≥ 3). ARF was precipitated in eight patients by an exacerbation of pre-existing COPD, without pneumonia. In another six patients the cause of the ARF was pneumonia (bacterial $n=4$, unknown $n=2$) diagnosed from the clinical history, chest X-ray, hypothermia or hyperthermia (temperature $<36^{\circ}$C or $>38.2^{\circ}$C), and rapid worsening of gas exchange, and confirmed by cultures of specimens and/or bronchoalveolar lavage, blood cultures and serologic tests. Four patients had cardiogenic pulmonary oedema diagnosed on the basis of congestion on chest X-ray, bilateral rales, dyspnoea and tachypnoea. Three patients had acute lung injury (ALI), defined on the basis of the presence of risk factors for ALI/ARDS,[14] oxygenation fraction (PaO_2/FiO_2), CXR score and acute physiology and chronic health evaluation (APACHE) II score. One patient had clinically and echographically suspected pulmonary embolisms, later confirmed by spiral CT scan, and one patient had generalized sepsis, diagnosed by positive blood cultures and a fever of $>39^{\circ}$C together with positive cultures of biological fluids (urine) from the suspected site of infection.

Major criteria for enrolment into the study were one of the following: 1) PaO_2/FiO_2 ratio <250 [that is, the ratio of arterial oxygen tension (PaO_2 measured in mmHg) to fractional inspired oxygen (FiO_2)] This ratio was recorded at admission, measuring arterial blood gases (ABG) while breathing room air or during O_2 therapy with a Venturi mask; 2) a pH ≤ 7.35 with a partial arterial CO_2 tension ($PaCO_2$) ≥ 50 mmHg.

Minor enrolment criteria were the following: 1) tachypnoea (respiratory rate >30 breaths/minute), 2) in-

Table 1 Individual characteristics of the patients at enrolment

Patient	Age (years)	Causes of ARF	PH admission	PaO_2/FiO_2 admission	$PaCO_2$ admission	SAPS II	Types of cancer
1	65	COPD ex.	7.33	235	67.6	29	Lung
2	78	CPE	7.49	155	33.6	44	Lung
3	81	COPD ex.	7.28	195	75.7	31	Lung
4	75	COPD ex.	7.14	188	94.6	24	Lung
5	66	COPD ex.	7.52	136	42.2	58	Bladder
6	73	CPE	7.3	222	60.5	35	Breast
7	77	Pul. embol.	7.44	154	40.6	42	Lung
8	52	Pneumonia	7.57	98	34.6	20	Stomach
9	60	Pneumonia	7.28	146	77.7	23	Gut
10	64	COPD ex.	7.27	96	71.5	41	Lung
11	47	CPE	7.35	144	54.4	55	Lung
12	66	Pneumonia	7.4	167	43.2	35	Breast
13	80	COPD ex.	7.31	232	57.6	39	Lung
14	73	Pneumonia	7.17	156	40.5	24	Gut
15	55	COPD ex.	7.14	203	101.0	54	Bladder
16	77	ALI	7.38	223	43.4	58	Lung
17	63	ALI	7.39	112	42.5	32	Lung
18	72	Pneumonia	7.39	88	39.4	24	Lung
19	75	CPE	7.15	120	115.0	41	Stomach
20	68	Pneumonia	7.52	80	27.0	46	Testicle
21	82	Sepsis	7.3	121	67.3	44	Lung
22	54	ALI	7.4	115	41.1	62	Lung
23	58	COPD ex.	7.28	156	65.3	57	Stomach
Mean	67.9		7.34	154.0	58.1	39.9	
S.D.	10.0		0.122	47.6	23.2	12.9	

COPD ex = exacerbation of COPD; CPE = cardiogenic pulmonary oedema.
ARF=Acute Respiratory Failure; ALI=Acute Lung Injury.

volvement of accessory muscles of respiration, and 3) paradoxical breathing with patient reporting subjective distress and/or dyspnoea.

One major and one minor criteria had to be present before starting NIV. These are the criteria for intubating ARF patients usually adopted in our units.[15,16] Exclusion criteria were: coma, refusal of treatment, inability to protect the airways, an agitated or unco-operative patient, anatomical abnormalities interfering with mask fit, uncontrolled cardiac ischaemia or arrhythmias, and failure of more than two organs. The study was approved by our institutional Ethics Committee and informed oral consent to participation in the study was obtained from the patients or their next of the kin.

Ventilator settings

All the patients were ventilated with either a ventilator specifically designed for NIV (Helia, Saime, Savigny le Temple, France or BiPAP Vision, Respironics, Pittsburgh, USA) or an ICU ventilator (Puritan Bennet 840, Carlsbad, USA, Evita 4 Draeger, Lübeck, Germany), using a Pressure Support Ventilation (PSV) mode with the addition of continuous positive airway pressure (CPAP).

In patients who had the first major inclusion criterion (hypoxic respiratory failure), the positive end-expiratory pressure was initially set at 5 cm H_2O and could be increased by 1 cm H_2O until a brisk increase in oxygen saturation (SaO_2) was observed, whereas the inspiratory pressure support was initially set at 10 cm H_2O and then increased in increments of 2 cm H_2O up to the maximum tolerated.

For patients with the second major inclusion criterion (hypercapnic respiratory failure), the inspiratory pressure was adjusted according to the patient's tolerance, with the external PEEP not exceeding 6 cm H_2O.

In any case both settings were aimed to achieve a respiratory rate <25 breaths/minute, no evident sign of wasted respiratory efforts on the flow trace, expired VT >6 mL/kg and <10 mL/kg and satisfactory gas exchange (i.e., SaO_2 $>90\%$, with pH >7.35). The inspiratory trigger was set at the minimal level to avoid autotriggering or that delivered by default by the ventilator, while the initial pressurization rate was adjusted according to subjective comfort. The fractional concentration of oxygen was such to achieve an $SaO_2 > 90\%$.

A full face mask was used in all but two patients to start the NIV and was then substituted by a nasal mask after the first few days of ventilation.

NIV was delivered almost continuously in the first 24 hours, interrupted for only short intervals of spontaneous breathing with oxygen supplementation to allow the patients to drink and expectorate (and, in some cases, eat). In the following days the levels of PSV and CPAP were gradually decreased using a modality described in detail elsewhere, if the patient's condition allowed.[15,16] Weaning from NIV was defined as complete freedom from mechanical ventilation for at least 72 hours.

The EKG, SaO_2, blood pressure and respiratory rate were monitored continuously.

Measurements

The following variables were recorded:

- Age, sex, chronic health care status measured using the McCabe index,[17] the number of comorbid conditions and the Simplified Acute Physiology Score (SAPS II index).[18] Neurological status was assessed by the Kelly and Matthay scale,[19] which is specifically designed for respiratory patients.
- Type and cancer status before respiratory failure.
- Arterial blood was withdrawn from a radial artery at baseline and at fixed intervals (see protocol) and analysed immediately (ABL 300 and ABL 625 Radiometer, Copenhagen, Denmark).
- Breathing frequency and haemodynamic variables (i.e., heart rate and blood pressure).
- Dyspnoea score measured with a modified Borg scale.[20]
- Total days on NIV.
- Total days of hospital stay.
- Mortality at hospital discharge, at 6 and 12 months.
- Causes of death.

Protocol

ABG, respiratory rate and haemodynamic variables were recorded at fixed intervals: baseline (T0), 1 hour after beginning the treatment (T1), after 3 hours (T2), after 24 hours (T3), after 48 hours (T4) and at discharge from the hospital (T5).

The Kelly score and McCabe index were recorded only at T0, while the dyspnoea score was measured at T0 and T1 in an attempt to verify the potential effect of NIV on the patient's breathlessness. The SAPS II score was recorded at the end of the first day of admission.

Primary outcomes of the study were: hospital death and NIV failure (i.e., intolerance and no changes or worsening of ABG after 3 hours of ventilation). Secondary outcomes were: 6-month and 12-month mortality, the duration of hospital stay, and changes of some physiological variables over time (i.e., ABG, respiratory rate, dyspnoea).

Statistical analysis

Results are presented as mean $\pm$ standard deviation ($\pm$SD). The patients' characteristics at enrolment and the differences in the subgroups of patients divided according to NIV success and failure were analysed with Fisher's exact test for categorical variables and with the Mann–Whitney test for continuous variables. Re-

peated measures two-way analysis of variance was used to evaluate trends over time for physiological variables, while a Wilcoxon test was employed to analyse the changes in dyspnoea score between T0 and T1. All the tests were two-tailed and a value <0.05 was considered as statistically significant.

Results

Figure 1 is a flow chart showing the clinical outcome of the patients treated with NIV. Thirteen of the 23 patients (56%) responded well to NIV administration and were thereafter discharged from the hospital.

The mean duration of NIV was 6.2 ± 2.3 days. Most of the patients were ventilated in 'protected' environments like the ICU or RICU, but four received the treatment directly in the Palliative Care Unit.

The causes of NIV failure in the remaining 10 patients were intolerance to NIV ($n=4$), a progressive worsening of ABG ($n=3$) (a decrease in the PaO_2/FiO_2 ratio despite a rise in FiO_2 in two patients and a decrease in pH in the other), sudden death ($n=1$), irreversible vomiting ($n=1$) and the need for deep sedation due to severe metastatic pain ($n=1$). Two of the patients (one intolerant of NIV and the other with irreversible vomiting) were intubated upon the decision of the attending physician, three others received NIV *ad libitum*, and four (three of those showing NIV intolerance and one needing deep sedation) were treated only with supportive medical therapy.

All the patients, but one, who failed NIV, died within a short time (mean 3.3 ± 3.1 days). The two patients receiving invasive ventilation died on day 5 and day 9, respectively, the latter after having been extubated.

As shown in Table 2, no statistically significant differences were found at enrolment in the main physiological variables between patients in whom NIV was a success or a failure except for the severity score, as assessed by SAPS II, and McCabe score, which were higher in the failure group, and for the oxygenation ratio

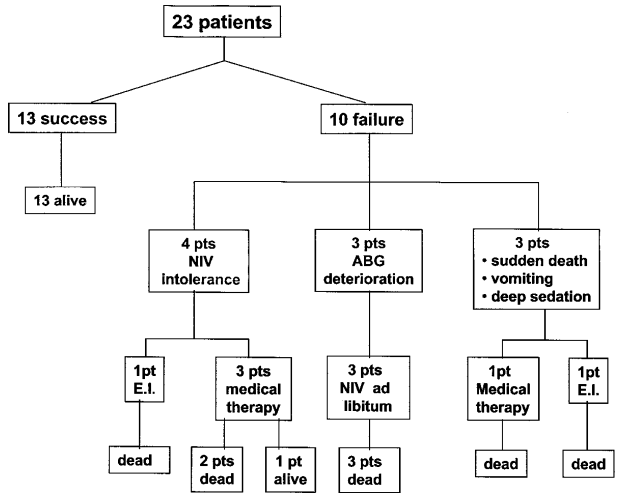

Figure 1 Trial profile and outcomes.

(PaO_2/FiO_2), which was lower. Types of tumours, causes and types (hypoxic and hypercapnic) of ARF were not different between the two subgroups.

As shown in Figure 2, compared to the value at T0, the patients had significantly higher PaO_2/FiO_2 ratios from T1 until discharge (T5). Mean data in the figure relate to the whole patient population, unless a particular patient died before day 2, except for the discharge data that pertain obviously to the survivors. The numbers in brackets represent the patients still alive at a particular time interval.

Figure 3 illustrates the changes in $PaCO_2$ (upper part) and pH (lower part), recorded in the subset of patients affected by hypercapnic respiratory failure. These patients have at admission signs of respiratory 'pump failure' (i.e., $PaCO_2 > 45$ mmHg), and therefore the effects of mechanical ventilation are usually assessed as an improvement in $PaCO_2$ and pH. As a matter of fact, a significant improvement from baseline was observed for both variables from T1 and was maintained throughout the study period. The large majority of these patients

Table 2 Mean values $\pm$ SD in the patients admitted to the trial and divided in success and failure groups[a]

	Success ($n=13$)	Failure ($n=10$)	P value
Age (years)	70.1 ± 9.5	64.9 ± 10.2	NS
SAPS II	32.2 ± 8.2	44.3 ± 14.0	<0.05
McCrabe	2.1 ± 0.3	2.7 ± 0.4	<0.05
pH start	7.35 ± 0.12	7.35 ± 0.11	NS
PaO_2/FiO_2 start	176 ± 44	123 ± 33	<0.01
$PaCO_2$ start	53.2 ± 16.7	54.5 ± 20.1	NS
Hypercapnic ARF $PaCO_2 > 45$ mmHg	7	5	NS
Hypoxic ARF $PaCO_2 < 45$ mmHg	6	5	NS

PaO_2/FiO_2 = the ratio of arterial oxygen tension (PaO_2) to fractional inspired oxygen (FiO_2); $PaCO_2$ = carbon dioxide arterial tension; SAPS II=Simplified Acute Physiology Score; ARF=Acute Respiratory Failure.
[a]Failure of NIV was defined according standardized criteria (see Methods).

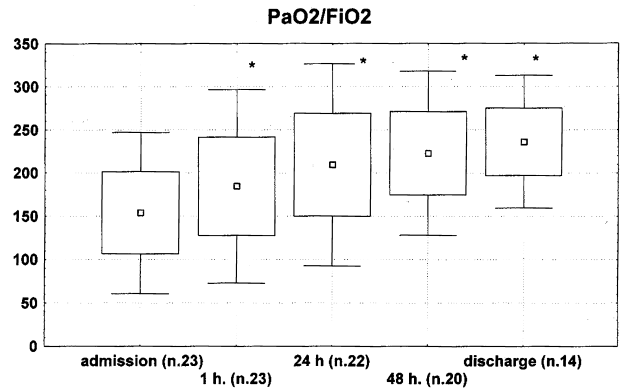

Figure 2 Box-whisker plot of oxygenation ratio (PaO_2/FiO_2) during the time course of the study. Numbers in brackets are the number of survivors at each time intervals. Small square = mean; large square = ±1 standard deviation; vertical line = ±0.96 standard deviation; *P <0.01 versus admission.

(7/12) was affected by COPDs, while in the remaining patients, hypercapnia was due to the ventilatory distress caused either by cardiogenic pulmonary oedema, pneumonia or sepsis (see Table 1). The numbers in brackets represent the patients still alive at a particular time interval.

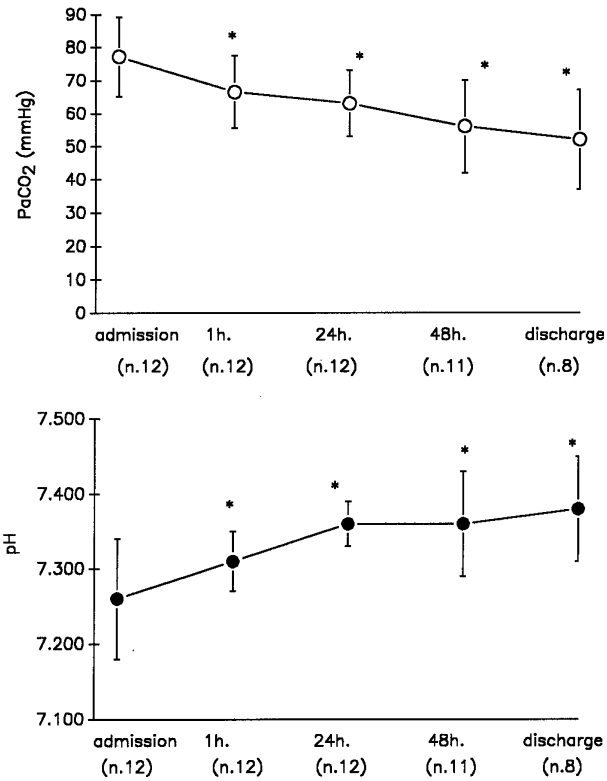

Figure 3 $PaCO_2$ (upper part) and pH (lower part), over time in the subgroup of hypercapnic patients (i.e., $PaCO_2 >$ 45 mmHg at admission). Numbers in brackets are the number of survivors at each time intervals. *P <0.05 versus admission.

In comparison with T0, respiratory rate, dyspnoea score at T1, blood pressure, heart and respiratory rates showed significant improvement, throughout the study period (Table 3).

Table 4 illustrates individual data on the length of hospital stay, long-term mortality, and causes of death, if available. The 6-month and 12-month survival rates were 39% and 13%, respectively.

Discussion

In this pilot study we demonstrated that the use of NIV in patients affected by end-stage solid cancer complicated by ARF is feasible and effective, at least in a consistent portion of patients, in providing rapid improvement in dyspnoea, ABG and other physiological variables. The hospital survival in these critically ill patients is relatively high (about 50%), while the one-year survival is low (13%).

The originality of the study is the first time application of a noninvasive modality of ventilation in a large group of patients with solid cancer in whom endotracheal intubation may be questionable.[2,3,6,8–10]

The large majority of the patients was treated in a protected environment like the RICU or ICU, however a small number ($n = 4$) was directly treated in the Palliative Care Unit. This was mainly due to a shortage of beds in the RICU. It is worthwhile noting that some of the medical and paramedical personnel are skilled with the use of NIV, and they were also helped by the RICU staff, especially in the first few hours of ventilation.

The overall survival of cancer patients admitted to the ICU is very disappointing, especially in the subgroup of patients requiring mechanical ventilation, in whom the mortality rate has been reported to exceed 80%.[2,6,8,9] As a matter of fact, among the various variables recorded at ICU admission, only two have been shown to be independently associated with mortality and quite surprisingly these two variables are not related to the type of cancer (i.e., solid or haematologic malignancy).[6]

The first independent predictor of mortality is obviously the severity of the patient's condition at admission to the ICU, which can be recorded by various scores, such as the SAPS II.[6,9] Our study confirms this, as the SAPS II was the only physiological variable that differed significantly between the survivors and the patients who died. The mean SAPS II in this latter group was rather high (i.e., 44). Kroschinsky *et al*. recently reported that, in patients with haematologic malignancies, a high SAPS II is associated with a high ICU and 18-month mortality.[9] The ratio PaO_2/FiO_2, index of oxygenation was also significantly lower in the failure group, and this confirms that these latter patients were more severely ill.

Table 3 Time course of some physiological variables during the study period

	Admission $n=23$	1 hour $n=23$	24 hours $n=22$	48 hours $n=20$	Discharge $n=14$
Resp Rate	36.6±7.3	30.1±6.5*	22.4±10.1*	18.9±9.3°	18.5±7.7°
Borg scale	5.5±1.2	2.3±0.3*			
Heart rate	128±12	117±12	88±21*	92±21*	87±11*
Mean BP	119±24	100±17*	103±15	100±18	94±13°

*$P<0.05$ versus admission.
°$P<0.01$ versus admission.
Resp Rate = respiratory rate, Mean BP = mean blood pressure.

The second and 'stronger' independent predictive factor of mortality is the need for intubation.[2,6–9] Despite the efforts made to prevent bacterial contamination of the circuit patient/ventilator, ventilator associated pneumonia (VAP) and worsening of pre-existing infections are still the major challenges in intubated patients. Up to 30% of invasively ventilated patients develop VAP at some point, and this percentage is very likely to be higher among oncologic patients.[21–23]

Mortality often exceeds 50% in ventilated patients with lung infections. Torres and coworkers examined correlations between several risk factors and the development of pneumonia;[21] presence of chronic airway obstruction and an endotracheal tube *in situ* for more than three days were significantly associated with an increased risk of VAP. These findings have been confirmed by other investigators, and in particular by Fagon *et al*. who showed how this risk increased by 1% per day of invasive mechanical ventilation.[24]

The endotracheal tube bypasses the mechanical defences 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 secretions colonized by bacteria originating from the sinuses, the nasal passages, pharynx, oral cavity and the stomach.

In this situation, NIV seems to be an interesting alternative because of the low risk of complications.[15,16] For example, in a case-control study, Girou *et al*. demonstrated that the rates of nosocomial infections and nosocomial pneumonia were significantly lower in patients who received NIV than in those treated with invasive mechanical ventilation (18% versus 60% and 8% versus 22%, respectively).[25] Similarly, the daily risk of acquiring an infection, the proportion of patients receiving antibiotics, duration of ventilation, length of ICU stay and crude mortality (4% versus 26%) were all lower among patients who received NIV than among those treated with invasive mechanical ventilation.

Table 4 Individual data for hospital, 6 months and 12 month survivals and hospital length of stay

Patient	NIV success outcome	H survival	H length of stay (days)	6-month survival	12-month survival
1	Success	Yes	12	Yes	Yes
2	Success	Yes	26	Yes	Yes
3	Success	Yes	22	Yes	No
4	Failure	No		No	No
5	Failure	No		No	No
6	Success	Yes	8	No	No
7	Success	Yes	20	No	No
8	Success	Yes	18	Yes	No
9	Success	Yes	22	No	No
10	Failure	No		No	No
11	Failure	Yes	56	Yes	No
12	Success	Yes	14	Yes	n/a
13	Success	Yes	19	Yes	No
14	Success	Yes	5	No	No
15	Success	Yes	23	Yes	Yes
16	Success	Yes	12	No	No
17	Failure	No		No	No
18	Failure	No		No	No
19	Success	Yes	11	Yes	No
20	Failure	No		No	No
21	Failure	No		No	No
22	Failure	No		No	No
23	Failure	No		No	No
Mean	13/23	14/23	16.7±6.5	9/23	3/23
%	(56%)	(61%)		(39%)	(13%)

n/a = not available.

On this basis NIV has been applied not only in COPD patients, in whom it should nowadays be considered the 'first line treatment',[11] but also in patients with other indications, including neutropenic patients with haematologic cancers.[26–28] Several uncontrolled studies reported the efficacy of NIV in this population and the positive results were later confirmed in a randomized, controlled study by Hilbert *et al*. who showed that early initiation of NIV was associated with significant reductions in the rates of endotracheal intubation and serious complications and an improved likelihood of survival to hospital discharge.[13]

NIV has not been applied systematically in patients with solid cancer and ARF except in one case-control study comparing the efficacy of NIV versus invasive mechanical ventilation in patients with different types of malignancies, but the subgroup with solid tumours was made of only six patients.[29]

Patients with end-stage cancer who are receiving only palliative care are potentially ideal candidates for NIV, as most of them are patients with a 'do-not-intubate' code, and even when formal, prospective decisions on this aspect have not been made, many do not receive endotracheal intubation because of the low survival at considerable costs in such patients. Moreover, these disappointing results are obtained at the price of a considerable reduction in the quality of life causes by the act of endotracheal intubation *per se* (i.e., need for sedation, impossibility of speaking, eating and drinking, reduction of personal contacts with relatives and beloved). Indeed, this is a field of great potential interest because a subgroup of these patients may be affected by comorbid conditions and at some point may develop acute failure of a specific organ which is not necessarily related to the site or progression of the cancer. For example, a consistent part of cancer patients are smokers or exsmokers, so they frequently also have chronic pulmonary disease or cardiac disease and the occurrence of an acute exacerbation of COPD or cardiogenic pulmonary oedema, leading to ARF, is relatively common. Despite the fact that most of these episodes may be promptly reversible, if adequately treated, these patients sometimes do not receive any form of ventilatory support, just because they have an underlying tumour. For example most of the studies performed on the use of NIV to treat hypoxic or hypercapnic respiratory failure excluded *a priori* patients with malignancies.[15,25]

The role of NIV in the treatment of ARF due to 'reversible' causes has been clearly documented in the literature. Several randomized, controlled studies support the use of NIV in exacerbations of COPD,[30–33] so that this technique should now be considered the first line treatment in this condition.[11] Concerning the use in episodes of hypoxic respiratory failure, the International Consensus Conference[11] concluded that 'the use of NIV may be also an appropriate treatment in selected patient populations with acute "lung" failure. Single studies have demonstrated NIV to be an adequate alternative to conventional ventilatory support in some pathologies (i.e., Cardiogenic Pulmonary Oedema, ALI)'.[16,34,35]

The success rate of NIV in our study is lower than that observed in most of the previously cited studies,[16,30–35] but it is important to note that our patients were more severely ill. In fact, only 30% of the failures of NIV were due to lack of ABG improvement, while the majority of failures were due to sudden complications or poor compliance to ventilation. Seventeen per cent of our patients did not tolerate NIV, a value that may be related to the particular psychological profile of patients with end-stage cancer, who may be reluctant to try a novel technique knowing that their quod-vitam prognosis is nevertheless poor.

NIV was, however, very efficient in improving the dyspnoea score already one hour after it had been applied. Relief of breathlessness is one of the major goals to achieve in palliative care, as has been clearly stated in a major meta-analysis, consensus conference and state-of-the-art review.[11,36,37] This relief was achieved without using any pharmacological agents.

From an ethical perspective, the use of NIV has been suggested to be the ventilatory mode of first choice for some pathologies, like COPD exacerbation. Elliott has recently concluded an Editorial stating that 'NIV is the golden standard mode (i.e., in this population), with endotracheal intubation regarded as second-line rescue therapy when it fails; as with second-line chemotherapy for cancer this often comes at greater expense and with more risk to the patient'.[38] Does this also apply for end-stage solid cancer patients? Lacking data from randomized controlled trials, we need first of all to identify and propose this ventilatory technique only to those patients with potentially reversible medical problems. The decision to eventually start NIV theoretically requires an individual approach taking account of patients' prior expressed wishes and/or the presence of advance directives. Unfortunately it has been shown that in Europe (especially in the Southern Countries) most of the patients do not give any advance directives while still competent, and that the family members are only rarely involved in the end-of-life decision.[39] Therefore the attitude of the intensivists and respiratory physicians is still rather 'paternalistic' especially in an emergency situation where the physician sees the patients and her/his relatives for the first time. In this scenario intubation is often denied, mainly for the poor outcome associated with this invasive procedure, but on the other hand NIV is not always offered as an alternative option as further life-sustaining procedures, if not oxygen and medical therapy, are considered inappropriate or are often not available. If the cause of ARF is reversible, and the

patient is interested in techniques that could prolong life or alleviate the suffering associated with dyspnoea, without being intubated, NIV should be considered the first line treatment.

This study also has some limitations. First, it was performed on a relatively small population, but our major aim in this pilot trial was just to assess the feasibility and potential efficacy and safety of NIV in this particular group of patients. Secondly, the study design was prospective but uncontrolled. However, as largely discussed before, most of these patients are not likely to receive any form of invasive ventilatory support during an episode of ARF, so that a randomized study versus endotracheal intubation was not easy to perform. On the other hand it has been repeatedly suggested that NIV may be considered the treatment of choice in patients with ARF due to pulmonary exacerbation or cardiogenic pulmonary oedema, so that a study comparing NIV and standard medical therapy was considered unethical by the Ethical Committee.

In conclusion, this prospective pilot study shows, for the first time, that the application of NIV is feasible and useful in quickly improving some physiological variables, such as dyspnoea, in patients with ARF and end-stage solid cancers. The use of NIV, while seeming to improve the immediate outcome in patients who are unlikely to receive any other form of ventilatory support, does not produce any advantage on long-term survival as the majority of patients will die or develop another life-threatening event within one year. Larger, multicentre studies could identify the subgroup of patients who are likely to benefit most from this noninvasive technique.

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