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NONINVASIVE VENTILATION FOR ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract Background. In patients with acute exacerbations of chronic obstructive pulmonary disease, noninvasive ventilation may be used in an attempt to avoid endotracheal intubation and complications associated with mechanical ventilation.

Methods. We conducted a prospective, randomized study comparing noninvasive pressure-support ventilation delivered through a face mask with standard treatment in patients admitted to five intensive care units over a 15-month period.

Results. A total of 85 patients were recruited from a larger group of 275 patients with chronic obstructive pulmonary disease admitted to the intensive care units in the same period. A total of 42 were randomly assigned to standard therapy and 43 to noninvasive ventilation. The two groups had similar clinical characteristics on admission to the hospital. The use of noninvasive ventilation significantly reduced the need for endotracheal intubation (which was dictated by objective cri-

teria): 11 of 43 patients (26 percent) in the noninvasive-ventilation group were intubated, as compared with 31 of 42 (74 percent) in the standard-treatment group ($P < 0.001$). In addition, the frequency of complications was significantly lower in the noninvasive-ventilation group (16 percent vs. 48 percent, $P = 0.001$), and the mean (\pm SD) hospital stay was significantly shorter for patients receiving noninvasive ventilation (23 ± 17 days vs. 35 ± 33 days, $P = 0.005$). The in-hospital mortality rate was also significantly reduced with noninvasive ventilation (4 of 43 patients, or 9 percent, in the noninvasive-ventilation group died in the hospital, as compared with 12 of 42, or 29 percent, in the standard-treatment group; $P = 0.02$).

Conclusions. In selected patients with acute exacerbations of chronic obstructive pulmonary disease, noninvasive ventilation can reduce the need for endotracheal intubation, the length of the hospital stay, and the in-hospital mortality rate. (N Engl J Med 1995;333:817-22.)

ENDOTRACHEAL intubation and mechanical ventilation can be a life-saving procedure. However, the use of artificial airways may lead to infectious complications and injury to the trachea.¹⁻³ Noninvasive ventilation is an alternative approach that was developed to avoid these complications in patients with acute respiratory failure.⁴⁻⁹ It is often used for acute exacerbations of chronic obstructive pulmonary disease, because such exacerbations may be rapidly reversed and because the hypercapnic ventilatory failure that occurs in patients with this disorder seems to respond well to noninvasive ventilation.^{8,10-16}

Most studies of noninvasive ventilation in patients with acute respiratory failure have not been randomized.^{5,7,8,12-15} The results of our previous case-control study suggest that this approach can reduce the need

for endotracheal intubation and the length of the hospital stay.⁶ One recent prospective, randomized study reported a reduction in mortality with the use of nasal ventilation in patients with chronic obstructive pulmonary disease, when patients who could not tolerate the procedure were excluded from the comparison.¹⁶ However, the potential benefits of noninvasive ventilation in terms of reduced morbidity, mortality, and hospitalization have not been fully delineated.¹⁷ Such data are particularly important in view of the practical and technical difficulties that may be encountered with this new form of therapy.¹⁸

We conducted a multicenter, prospective, randomized trial to compare the efficacy of noninvasive ventilation, delivered through a face mask, with standard medical treatment, in patients admitted because of acute exacerbations of chronic obstructive pulmonary disease.

METHODS

Between September 1990 and November 1991, adult patients hospitalized because of acute exacerbations of chronic obstructive pulmonary disease were prospectively recruited from five hospitals: Henri Mondor Hospital, Antoine Bécélère Hospital, and International

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Hospital of the University of Paris in France, La Sapienza University Hospital in Italy, and Sant Pau Hospital in Spain. The study protocol was approved by the ethics committee of Henri Mondor Hospital, and patients or their relatives gave informed consent.

Patients enrolled in the study had known chronic obstructive pulmonary disease or a high probability of the disease (on the basis of the clinical history, physical examination, and chest film), with respiratory acidosis and an elevated bicarbonate level. Additional criteria for enrollment included an exacerbation of dyspnea lasting less than two weeks and at least two of the following: a respiratory rate above 30 breaths per minute, a partial pressure of arterial oxygen below 45 mm Hg, and an arterial pH below 7.35 after the patient had been breathing room air for at least 10 minutes.

The criteria for exclusion were a respiratory rate below 12 breaths per minute or the need for immediate intubation (as defined below); a tracheotomy or endotracheal intubation performed before admission; the administration of sedative drugs within the previous 12 hours; a central nervous system disorder unrelated to hypercapnic encephalopathy or hypoxemia; cardiac arrest (within the previous five days); cardiogenic pulmonary edema; kyphoscoliosis as the cause of chronic respiratory failure or a neuromuscular disorder; upper airway obstruction or asthma; a clear cause of decompensation requiring specific treatment (e.g., peritonitis, septic shock, acute myocardial infarction, pulmonary thromboembolism, pneumothorax, hemoptysis, severe pneumonia, or recent surgery or trauma); a facial deformity; or enrollment in other investigative protocols. In addition, patients who refused to undergo endotracheal intubation, whatever the initial therapeutic approach, were excluded from the study.

Patients were randomly assigned to receive either standard treatment or standard treatment plus pressure-support ventilation through a face mask. Random assignments were made with sealed envelopes.

Standard Treatment

Patients assigned to the standard-treatment group received oxygen limited to a maximal flow rate of 5 liters per minute, by means of nasal prongs, in order to achieve a level of arterial oxygen saturation above 90 percent. Medications included subcutaneous heparin, antibiotic agents, and bronchodilators (subcutaneous terbutaline, aerosolized and intravenous albuterol, and corticosteroids or intravenous aminophylline or both), with the correction of electrolyte abnormalities.

Noninvasive Ventilation

Patients assigned to the noninvasive-ventilation group received the same medications as the patients in the standard-treatment group, with the addition of periods of noninvasive ventilation. All the par-

ticipating centers used the same apparatus to deliver noninvasive pressure-support ventilation (ARM 25, Taema, Antony, France), which works on the principle of air entrainment.¹⁹ The apparatus is triggered by air flow and maintains a constant pressure during inspiration, with a rapid pressurization rate. It is cycled from inspiration to expiration according to the flow signal and can be adjusted at a rate between 10 and 35 liters per minute to compensate for leaks. Pressure support was initially adjusted at a level of 20 cm of water.^{6,20,21} In the case of leaks, lower levels were used. Expiratory pressure was atmospheric. Oxygen was administered to provide an arterial oxygen saturation above 90 percent. In case of apnea, the machine provided automatic pressure-controlled cycles. A face mask was developed for use in the study (Fig. 1).

Patients underwent noninvasive ventilation for at least six hours each day. The period could be lengthened, depending on the clinical tolerance of the patients. Each day, however, patients were allowed to breathe spontaneously, with oxygen but without assistance, for two hours. The overall duration of noninvasive ventilation was determined on the basis of clinical criteria and arterial-blood gas levels; in each case, the decision was made by the physician in charge.

Criteria for Intubation

To make the decision whether to perform endotracheal intubation as objective as possible, we established criteria based on the clinical experience of the participating physicians and on reported data.^{11,22} The major criteria included respiratory arrest, respiratory pauses with loss of consciousness or gasping for air, psychomotor agitation making nursing care impossible and requiring sedation, a heart rate below 50 beats per minute with loss of alertness, and hemodynamic instability with systolic arterial blood pressure below 70 mm Hg. Minor criteria were a respiratory rate above 35 breaths per minute and above the value on admission; an arterial pH value below 7.30 and below the value on admission; a value for the partial pressure of arterial oxygen below 45 mm Hg, despite oxygen therapy; and an increase in the score for encephalopathy (0, normal; 1, mild asterixis; 2, marked asterixis, mild confusion, or sleepiness during the day; 3, major confusion with daytime sleepiness or agitation; and 4, obtundation or major agitation). In both groups, the presence of one major criterion was considered to indicate the need for intubation and mechanical ventilation, and after the first hour of treatment, the presence of two minor criteria was considered to indicate the need for intubation. In the noninvasive-ventilation group, however, if a criterion was present after the withdrawal of ventilatory support, it could be reintroduced. If the criterion persisted after ventilation had been resumed, intubation was performed. Patients who needed endotracheal intubation were mechanically ventilated in the assist-control mode and were weaned with the pressure-support mode.²³

Follow-up

The respiratory rate, encephalopathy score, and arterial-blood gas levels were determined 1, 3, and 12 hours after the start of treatment. On subsequent days in the intensive care unit, these data were obtained once daily. The simplified acute physiologic score was calculated at 24 hours.²⁴ Pulmonary-function testing was performed before discharge, when possible, or within three months after discharge.

Statistical Analysis

The primary outcome variable was the need for endotracheal intubation and mechanical ventilation at any time during the study. Secondary end points were the length of the hospital stay, complications not present on admission (such as pneumonia, barotrauma, gastrointestinal hemorrhage, renal insufficiency, neurologic events, and pulmonary embolism), the duration of ventilatory assistance, and the mortality rate during hospitalization.

Results are given as means \pm SD. All tests



Figure 1. Photograph of the Face Mask Used to Deliver Noninvasive Ventilation. The white piece of foam was placed inside the mask to reduce the amount of internal dead space.

Table 1. Characteristics of Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease Assigned to Standard Treatment or Noninvasive Ventilation, at Admission and after One Hour of Therapy.*

CHARACTERISTIC	STANDARD TREATMENT			NONINVASIVE VENTILATION			P VALUE†
	ADMISSION (N = 42)	1 HOUR (N = 39)	P VALUE‡	ADMISSION (N = 43)	1 HOUR (N = 42)	P VALUE‡	
	mean ±SD			mean ±SD			
Age (yr)	69±10			71±9			0.28
SAPS	13±5			12±4			0.64
Systolic pressure (mm Hg)	145±25			143±25			0.82
Heart rate (beats/ min)	107±15			105±23			0.61
Encephalopathy score	1.6±1.2	1.9±1.3	0.01	1.8±1.3	1.5±1.1	0.02	0.79
Respiratory rate (breaths/min)	33±7	33±7	0.83	35±7	25±8	<0.001	0.43
PaO ₂ (mm Hg)	39±12	58±24	0.01	41±10	66±17	0.01	0.42
PaCO ₂ (mm Hg)	67±16	72±18	0.003	70±12	68±13	0.17	0.22
pH	7.28±0.11	7.26±0.11	0.01	7.27±0.10	7.31±0.09	<0.001	0.67
Bicarbonate (mmol/ liter)	32±7			33±7			0.49
Hemoglobin (g/dl)	13.8±2.2			14.5±2.0			0.14

*Three patients in the standard-treatment group and one in the noninvasive-ventilation group were intubated at one hour, before new measurements were performed. SAPS denotes simplified acute physiologic score.²⁴ PaO₂, partial pressure of arterial oxygen, and PaCO₂, partial pressure of arterial carbon dioxide. pH, bicarbonate, and hemoglobin were measured in samples of arterial blood.

†P values refer to the comparison between the two groups at the time of admission.

‡P values refer to the comparison between data on admission and data at one hour in each group.

and P values are two-tailed. The group means were compared with the t-test. Multiple comparisons were performed with an analysis of variance for repeated measures, and pairwise comparisons were performed with Fisher's exact test. Qualitative data were compared with the chi-square test. To determine whether endotracheal intubation had a significant influence on mortality, the extended Mantel-Haenszel test was used.²⁵ A P value of less than 0.05 was considered to indicate statistical significance. The BMDP statistical software package was used.

RESULTS

Characteristics of the Patients

Of the 275 patients admitted to the participating hospitals with acute or chronic respiratory failure during the study period, 85 were enrolled in the study; 190 (69 percent) were not included (27 percent were already undergoing mechanical ventilation or required immediate endotracheal intubation, 17 percent had left heart failure, 9 percent had pneumonia or sepsis, 8 percent were in the perioperative period, 6 percent had asthma, and 34 percent were excluded for various other reasons).

Forty-two patients were randomly assigned to standard treatment, and 43 to noninvasive ventilation. The two groups had similar characteristics on admission (Table 1). Ten patients (24 percent) in the standard-treatment group and 12 (28 percent) in the noninvasive-ventilation group had previously been mechanically ventilated for a similar episode. The same medications were administered in the two groups (antibiotic agents were given to 32 patients in the standard-treatment group and 27 in the noninvasive-ventilation group; inhaled or intravenous sympathomimetic agents to 30 and 29 patients in the two groups, respectively; corticosteroids to 24 and 26 patients; diuretic agents to 17

and 24 patients; and aminophylline to 24 and 26 patients).

Clinical Outcomes

Thirty-one of the 42 patients (74 percent) in the standard-treatment group required endotracheal intubation, as compared with only 11 of the 43 patients (26 percent) in the noninvasive-ventilation group (P<0.001). The results were consistent among the five participating centers (Table 2).

The time at which intubation was performed is shown in Figure 2. Twenty-three of 31 patients (74 percent) in the standard-treatment group required intubation within the first 12 hours, as compared with 9 of 11 patients (82 percent) in the noninvasive-ventilation group. Endotracheal intubation was indicated because of the presence of major criteria in 10 of the 31 patients intubated (32 percent) in the standard-treatment group and in 8 of the 11 (73 percent) in the noninvasive-ventilation group. Of the

four patients in whom noninvasive ventilation was withdrawn and then resumed because of the presence of at least two minor criteria, three were intubated because the criteria persisted.

There was a significant improvement in the encephalopathy score, respiratory rate, partial pressure of arterial oxygen, and pH during the first hour of treatment in the noninvasive-ventilation group, whereas there was a significant deterioration in the encephalopathy score, partial pressure of arterial carbon dioxide, and pH in the standard-treatment group (Table 1).

Table 3 shows the characteristics at enrollment, length of hospitalization, and number of deaths, according to whether endotracheal intubation was required. Subgroup differences were noted in the simplified acute physiologic score and the encephalopathy score. In the subgroup successfully treated with noninvasive ventilation, a significant improvement was noted in the respi-

Table 2. Patients Requiring Endotracheal Intubation after Assignment to Standard Treatment or Noninvasive Ventilation, According to the Participating Center.

CENTER No.	STANDARD TREATMENT		NONINVASIVE VENTILATION	
	NO. OF PATIENTS	NO. INTUBATED (%)	NO. OF PATIENTS	NO. INTUBATED (%)
1	9	9 (100)	9	3 (33)
2	6	5 (83)	5	2 (40)
3	9	4 (44)	8	1 (13)
4	4	3 (75)	5	0
5	14	10 (71)	16	5 (31)
Total	42	31 (74)	43	11 (26)

ratory rate (34 ± 7 breaths per minute at base line, 24 ± 8 at 1 hour, 25 ± 7 at 3 hours, and 25 ± 5 at 12 hours), as well as in the partial pressure of arterial oxygen at 1 hour and the partial pressure of arterial carbon dioxide at 12 hours (Fig. 3) ($P < 0.001$ for all comparisons). The encephalopathy score dropped from 1.6 ± 1.3 at base line and 1.3 ± 1.2 at 1 hour to 1.1 ± 1.1 at 3 hours and 0.8 ± 1.0 at 12 hours ($P < 0.001$).

In the standard-treatment group, the 31 patients who required endotracheal intubation were ventilated for a total of 17 ± 21 days. In the noninvasive-ventilation group, the 11 patients who underwent endotracheal intubation were intubated for a total of 25 ± 17 days; the other 32 patients were ventilated with a face mask for a mean of 4 ± 4 days.

Complications and events leading to death are shown in Table 4. The proportion of patients with one or more complications was significantly higher in the standard-treatment group (20 of 42 patients, or 48 percent) than in the noninvasive-ventilation group (7 of 43, or 16 percent; $P = 0.001$). The proportion of patients who died in the hospital was also significantly higher in the standard-treatment group (12 of 42 patients, or 29 percent, vs. 4 of 43, or 9 percent; $P = 0.02$). Ten of the 12 deaths in the standard-treatment group

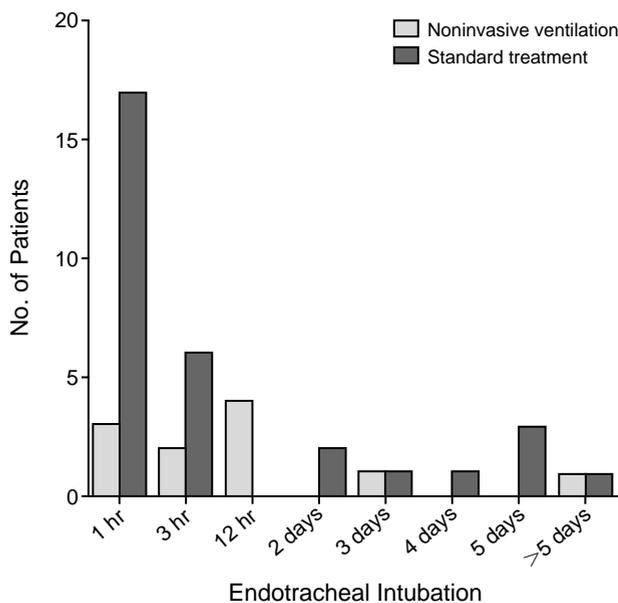


Figure 2. The Time at Which Endotracheal Intubation Was Performed in the Two Treatment Groups.

A total of 17 patients required intubation after the first hour in the standard-treatment group, as compared with only 3 patients in the noninvasive-ventilation group.

Table 3. Characteristics at Admission and Mortality Rate, According to Whether Endotracheal Intubation Was Required after Assignment to Standard Treatment or Noninvasive Ventilation.*

CHARACTERISTIC	STANDARD TREATMENT		NONINVASIVE VENTILATION		P VALUE†
	INTUBATION NOT REQUIRED (N = 11)	INTUBATION REQUIRED (N = 31)	INTUBATION NOT REQUIRED (N = 32)	INTUBATION REQUIRED (N = 11)	
SAPS	10±4	14±5‡	12±3‡	15±4§	0.02
Encephalopathy score	0.7±0.9	1.9±1.2‡	1.6±1.3‡	2.5±1.0	0.007
Respiratory rate — breaths/min	32±8	34±6	34±7	37±7	0.4
PaO ₂ — mm Hg	43±14	37±12	42±11	37±9	0.3
PaCO ₂ — mm Hg	59±15	69±16	70±12	73±11	0.1
pH	7.33±0.09	7.27±0.11	7.28±0.10	7.26±0.10	0.1
Bicarbonate — mmol/liter	31.7±7.7	32.6±6.3	33.7±6.0	32.5±8.4	0.2
Length of hospital stay — days	20±16	41±36‡	17±9	40±22§	<0.001
Deaths — no. of patients (%)	2 (18)	10 (32)	1 (3)	3 (27)	

*Plus-minus values are means ±SD. SAPS denotes simplified acute physiologic score, PaO₂ partial pressure of arterial oxygen, and PaCO₂ partial pressure of arterial carbon dioxide.

†P values, determined by an analysis of variance, are for the comparison among the four subgroups.

‡P<0.05, by Fisher's exact test, for the comparison with the patients assigned to standard treatment who did not require intubation.

§P<0.05, by Fisher's exact test, for the comparison with the patients assigned to noninvasive ventilation who did not require intubation.

and 3 of the 4 in the noninvasive-ventilation group occurred during mechanical ventilation.

Since the numbers of patients requiring intubation were different in the two groups, we compared mortality rates after adjustment for endotracheal intubation, using the Mantel-Haenszel test. After adjustment, we found no significant difference, suggesting that the number of patients requiring intubation was the main factor explaining the difference in mortality.

Reliable pulmonary-function data were obtained within three months after randomization in 23 of the patients in the standard-treatment group and in 24 of those in the noninvasive-ventilation group. The forced expiratory volume in one second (0.68 ± 0.19 liter, or 28 ± 10 percent of the predicted value, in the standard-treatment group, and 0.72 ± 0.21 , or 31 ± 8 percent, in the noninvasive-ventilation group), the vital capacity (1.48 ± 0.58 liters, or 42 ± 13 percent of the predicted value, and 1.28 ± 0.46 liters, or 43 ± 10 percent, respectively), and the ratio of the two measures (51 ± 16 percent and 57 ± 17 percent, respectively) were similar in the two groups.

Hospital Stay

The hospital stay was significantly longer in the group receiving standard treatment (35 ± 33 days) than in the group receiving noninvasive ventilation (23 ± 17 days, $P = 0.02$). Figure 4 shows the length of the hospital stay in the two groups.

DISCUSSION

This study shows that the use of noninvasive ventilation in selected patients admitted for acute respiratory failure due to chronic obstructive pulmonary disease can obviate the need for intubation and thus

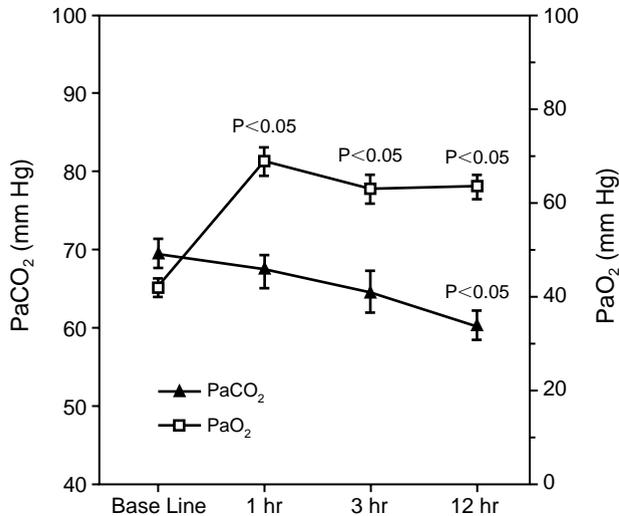


Figure 3. Mean (\pm SE) Values for the Partial Pressure of Arterial Oxygen (PaO₂) and Carbon Dioxide (PaCO₂) during the First 12 Hours in the 32 Patients Successfully Treated with Noninvasive Ventilation.

The P values are for the comparison with the base-line values.

reduce complications and mortality and shorten the hospital stay.

Although noninvasive ventilation has been used in patients with chronic hypoventilatory syndromes, its use in patients with acute respiratory failure has not been firmly established,^{17,26} since most of the studies have been retrospective and uncontrolled. Controlled studies are needed to assess both the efficacy and the safety of this procedure. The results of previous studies, the rapidly reversible nature of most episodes of acute decompensation, and the presence of ventilatory failure rather than hypoxemic lung failure suggest that patients with acute exacerbations of chronic obstructive pulmonary disease should benefit from this approach.

Recently, Bott and coworkers performed a prospective, randomized study of the effects of nasal positive-pressure ventilation in patients with acute exacerbations of chronic obstructive pulmonary disease.¹⁶ Several physiologic measures and the degree of breathlessness were significantly improved in the treated group, as compared with the base-line values and with the data in the control group. This study suggests that benefits can be expected from noninvasive ventilation. In a previous report, we compared the results in a treated group with those in a matched historical control group.⁶ We found that the number of patients requiring intubation and the hospital stay were significantly reduced with the use of pressure support through a face mask. These results are confirmed and extended in the present study.

Our enrollment criteria were designed to select patients who were likely to need endotracheal intubation. Patients who required immediate intubation were not included, although many patients required intubation within the first hour. The criteria for intubation were

not identical in the two groups, since noninvasive ventilation could be resumed in patients assigned to that treatment who had two minor criteria. Noninvasive ventilation was resumed in four patients but failed to prevent subsequent intubation in three of the four, indicating that this difference in the criteria for intubation did not play an important part in the results.

We found that mortality was significantly reduced with the use of noninvasive ventilation. This approach, as compared with standard treatment, was associated with fewer complications, many of which are specifically linked with mechanical ventilation and are believed to have an effect on mortality.¹⁻³ The mortality rate appeared to be high in the control group^{14,27} but was similar to or lower than the rates reported by Bott and coworkers¹⁶ and by other investigators.²⁸⁻³¹ Our patients were probably at a more severe stage of disease than those in the study by Bott et al., as shown by the lower pH values in our patients on admission.²⁷ Also, the complications and causes of death commonly described in patients with chronic obstructive pulmonary disease were recorded in our patients.¹¹ It is noteworthy that the mortality rate and the duration of the hospital stay were similar in the two subgroups of patients in whom endotracheal intubation was required. In addition, the difference in mortality disappeared after adjustment for intubation, suggesting that the benefits observed with noninvasive ventilation resulted from the lower number of patients requiring intubation.

The hospital stay was significantly shortened by noninvasive ventilation, a result in accordance with the findings of previous studies.^{6,14} The absence of sedation, reduced number of complications, and shorter weaning time in the noninvasive-ventilation group probably all

Table 4. Complications and Lethal Events in the Two Treatment Groups.*

COMPLICATION	STANDARD TREATMENT (N = 42)		NONINVASIVE VENTILATION (N = 43)	
	NO. OF COMPLICA- TIONS	NO. LEADING TO DEATH	NO. OF COMPLICA- TIONS	NO. LEADING TO DEATH
Pneumonia	7	2	2	0
Sepsis	3	2†	2	1
Gastrointestinal tract disorders	2	1	1	0
Myocardial infarction	2	1	1	1‡
Multiple pneumothoraxes	1	1	0	0
Difficult or complicated endo- tracheal intubation	4§	1	0	0
Pulmonary embolism	1	1	0	0
Cerebral hemorrhage	0	0	1	1
Cardiac or respiratory problems during weaning	1	1¶	1	1
Cardiac arrest after weaning	2	2‡	0	0
Facial-skin necrosis	0	0	1	0
Total	232	121	9	4

*Each of five patients had two complications.

†One patient was not intubated.

‡The patient was not intubated.

§One patient removed the tube.

¶One patient had a do-not-resuscitate order.

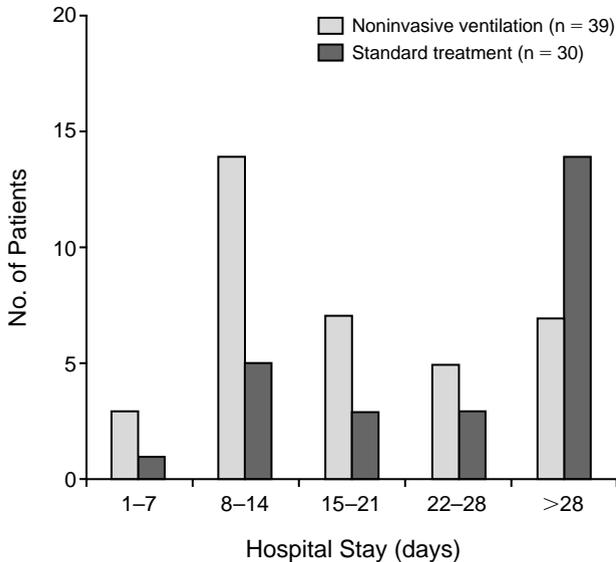


Figure 4. The Length of the Hospital Stay among the Surviving Patients in the Two Treatment Groups.

Seven of the patients (18 percent) in the noninvasive-ventilation group stayed in the hospital for more than four weeks, as compared with 14 (47 percent) in the standard-treatment group ($P=0.004$).

contributed to the shorter hospital stay. This result suggests that noninvasive ventilation may be a cost-saving measure.

Finally, it should be stressed that our study was performed with a carefully selected group of patients. In particular, patients with a clear cause of decompensation requiring a specific therapeutic approach and those in need of immediate intubation were not included in the study. Only 31 percent of all the patients with chronic obstructive pulmonary disease admitted during the study period met the criteria for enrollment. With this limitation in mind, the study demonstrates that noninvasive ventilation can reduce the need for endotracheal intubation in patients with acute exacerbations of chronic obstructive pulmonary disease, thereby reducing associated complications, mortality, and length of hospitalization.

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