Treatment of Acute Hypoxemic Nonhypercapnic Respiratory Insufficiency With Continuous Positive Airway Pressure Delivered by a Face Mask

A Randomized Controlled Trial

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Context Continuous positive airway pressure (CPAP) is widely used in the belief that it may reduce the need for intubation and mechanical ventilation in patients with acute hypoxemic respiratory insufficiency.

Objective To compare the physiologic effects and the clinical efficacy of CPAP vs standard oxygen therapy in patients with acute hypoxemic, nonhypercapnic respiratory insufficiency.

Design, Setting, and Patients Randomized, concealed, and unblinded trial of 123 consecutive adult patients who were admitted to 6 intensive care units between September 1997 and January 1999 with a PaO_2/FIO_2 ratio of 300 mm Hg or less due to bilateral pulmonary edema (n=102 with acute lung injury and n=21 with cardiac disease).

Interventions Patients were randomly assigned to receive oxygen therapy alone (n=61) or oxygen therapy plus CPAP (n=62).

Main Outcome Measures Improvement in PaO_2/FIO_2 ratio, rate of endotracheal intubation at any time during the study, adverse events, length of hospital stay, mortality, and duration of ventilatory assistance, compared between the CPAP and standard treatment groups.

Results Among the CPAP vs standard therapy groups, respectively, causes of respiratory failure (pneumonia, 54% and 55%), presence of cardiac disease (33% and 35%), severity at admission, and hypoxemia (median [5th-95th percentile] PaO_2/FIO_2 ratio, 140 [59-288] mm Hg vs 148 [62-283] mm Hg; $P=.43$) were similarly distributed. After 1 hour of treatment, subjective responses to treatment ($P<.001$) and median (5th-95th percentile) PaO_2/FIO_2 ratios were greater with CPAP (203 [45-431] mm Hg vs 151 [73-482] mm Hg; $P=.02$). No further difference in respiratory indices was observed between the groups. Treatment with CPAP failed to reduce the endotracheal intubation rate (21 [34%] vs 24 [39%] in the standard therapy group; $P=.53$), hospital mortality (19 [31%] vs 18 [30%]; $P=.89$), or median (5th-95th percentile) intensive care unit length of stay (6.5 [1-57] days vs 6.0 [1-36] days; $P=.43$). A higher number of adverse events occurred with CPAP treatment (18 vs 6; $P=.01$).

Conclusion In this study, despite early physiologic improvement, CPAP neither reduced the need for intubation nor improved outcomes in patients with acute hypoxemic, nonhypercapnic respiratory insufficiency primarily due to acute lung injury.

JAMA. 2000;284:2352-2360 www.jama.com

PATIENTS WITH SEVERE HYPOXemic acute respiratory insufficiency often require life-supporting mechanical ventilation (MV). The placement of an endotracheal tube to allow for MV is associated with a significant risk of local airway injury and ventilator-associated pneumonia. Several studies found that noninvasive ventilation (NIV) reduced the need for endotracheal intubation in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD).[1,2]

In addition, reports published over many years have suggested that patients with cardiogenic pulmonary edema (CPE) or non-CPE may benefit from continuous positive airway pressure (CPAP) delivered by a face mask.[3-16] Most of these studies were nonrandomized, and in the few randomized studies, the primary end point was often based on gas exchange criteria after a predetermined duration of

See also pp 2361 and 2376 and Patient Page.

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Caring for the Critically Ill Patient Section Editor: Deborah J. Cook, MD, Consulting Editor, *JAMA*. **Advisory Board:** David Bihari, MD; Christian Brun-Buisson, MD; Timothy Evans, MD; John Heffner, MD; Norman Paradis, MD.

CPAP treatment.[7,13] These studies demonstrated the ability of CPAP to improve hypoxemia but not its ability to reduce the need for intubation and MV. However, one single-center, randomized study found strong evidence that CPAP use reduced the need for endotracheal intubation in patients with severe hypercapnic CPE.[10]

In patients with acute lung injury (ALI), applying positive pressure to the airway opening has been shown to lessen the reduction in functional residual capacity and to improve respiratory mechanics and gas exchange.[17] These data have led intensive care unit (ICU) physicians to widely use CPAP to prevent subsequent clinical deterioration and to reduce the need for endotracheal intubation.[5,6,8,9,11] However, the efficacy of this practice has not been evaluated. In particular, uncertainty continues to surround the potential clinical benefits of CPAP delivered by a face mask to patients with acute hypoxemic, nonhypercapnic, respiratory insufficiency due to bilateral pulmonary edema, with or without underlying cardiac disease.

We conducted a multicenter, prospective, randomized trial to compare the efficacy of CPAP delivered through a full face mask with standard oxygen therapy in ICU patients admitted with ALI with or without underlying cardiac disease.

METHODS

Patients

Between September 28, 1997, and January 19, 1999, 123 consecutive adults admitted with acute respiratory insufficiency secondary to pulmonary edema were recruited prospectively at the medical ICUs of 6 hospitals (Henri Mondor, Créteil, France; La Cavalle Blanche, Brest, France; Croix Rousse, Lyon, France; Sant Pau, Barcelona, Spain; Monastir Hospital, Monastir, Tunisia; and La Sapienza University, Rome, Italy), which previously had participated in NIV studies and had experience with the various NIV techniques.[1,16,19,20] The study protocol was approved by the appropriate institutional review boards. Informed consent was obtained from all the patients.

Inclusion criteria were as follows: (1) acute respiratory insufficiency, defined as the Pa_{O_2}/F_{IO_2} ratio of 300 mm Hg or less after breathing oxygen at 10 L/min or more for 15 minutes, with the inspired fraction of oxygen determined by a portable oxygen analyzer (MiniOX I; Mine Safety Appliances Co, Pittsburgh, Pa); (2) the presence of bilateral lung infiltrates on a posteroanterior chest radiograph; and (3) randomization within 3 hours after the criteria were first fulfilled.

Exclusion criteria were patients younger than 18 years; intubation was refused or contraindicated; history of COPD; acute respiratory acidosis (defined as a pH <7.30 and a Pa_{CO_2} >50 mm Hg); systolic blood pressure less than 90 mm Hg under optimal therapy (fluid repletion); ventricular arrhythmias; coma or seizures; life-threatening hypoxemia (defined as an Sa_{O_2} $<80\%$ with an oxygen mask); use of epinephrine or norepinephrine; and the inability to clear copious airway secretions.

The precipitating cause of acute respiratory insufficiency and the presence of a chronic or acute cardiac disease were recorded at admission. Patients were randomly assigned to standard treatment (oxygen alone) or standard treatment plus CPAP delivered by a face mask. Patients with ALI and no history of chronic lung disease constituted the primary group of interest. Since increased pulmonary permeability may coexist with left atrial or pulmonary capillary hypertension,[18] patients with a history of cardiac disease also were included. The coronary care unit (CCU), independent from the medical ICU, treated patients with ischemic myocardial disease and those with heart failure deemed unlikely to require MV. Patients with obvious cardiac disease were primarily treated in the CCU, however, the only ones who were considered for the study were those patients with cardiac disease who had a possible superimposed noncardiac cause of respiratory failure, patients with extreme severity and no response to treatment, or patients in whom cardiac insufficiency previously was not known.

Because a cardiogenic mechanism contributing to the pulmonary edema might have had a substantial influence on the study results, the randomization was stratified based on whether there was an underlying cardiac disease (chronic cardiac disease with class II, III, or IV of the New York Heart Association functional classification or acute de novo cardiac disease). The stratification was not based on whether it was CPE or non-CPE because in severely ill patients with chronic cardiac disease admitted for acute respiratory insufficiency, it is sometimes difficult to determine on admission whether decompensated heart failure is the only cause of the episode of respiratory insufficiency. Including patients with a history of cardiac disease, it was likely that using clinical examination and simple biological criteria a proportion of these patients would be eventually diagnosed as having cardiac disease. The stratification was to ensure that patients with an underlying cardiac disease were equally distributed between the 2 study groups. Sealed envelopes were used to randomly assign patients to their treatment group.

Standard Treatment

Patients assigned to the standard treatment group (n=61) received oxygen delivered through a face mask. The F_{IO_2} was measured using the same oxygen analyzer in each center: the tip of the oxygen analyzer was introduced via a small hole in the face mask. The goal was to achieve a pulse oximetry Sa_{O_2} greater than 90%. Oxygen was delivered until endotracheal intubation, death, or fulfillment of oxygen delivery cessation criteria (an $Sa_{O_2} \geq 92\%$ without oxygen and a respiratory rate < 30/min).

All patients with suspected cardiac insufficiency received diuretics as required. Infectious causes were treated with antibiotics. Gastrointestinal tract prophylaxis was administered to patients who were intubated with MV or in patients with a history of gastroin-

testinal tract ulcer.[21] Patients did not receive systematic ulcer prophylaxis under CPAP therapy.

CPAP Treatment

Patients assigned to the CPAP plus oxygen group (n=62) received periods of CPAP in addition to the standard treatment. All study centers used a Vital Signs, Inc (Totowa, NJ) device.[22] The device included (1) a Vital Flow 100 CPAP Flow Generator that delivered a flow (rate 0-130 L/min) that could be adjusted to the patient's inspiratory flow requirement, with an adjustable F_{IO_2} within the 34% to 100% range; (2) a spring-loaded, positive end-expiratory pressure (PEEP) valve that provided a fixed end-expiratory pressure (5, 7.5, or 10 cm H_2O) with minimal resistance to airflow; (3) a full face mask composed of a transparent mask and a soft inflatable cushion; and (4) a dedicated headstrap. Airway humidification was achieved by using a heated humidifier (MR640; Fisher & Paykel, Auckland, NZ).

For at least the first 6 to 12 hours, CPAP was given continuously and then discontinuously as indicated based on patient tolerance and on whether the pulse oximetry Sa_{O_2} was greater than 90% under oxygen alone.

For all patients, CPAP was started at 7.5 cm H_2O. The level could be decreased to 5 cm H_2O or increased to 10 cm H_2O as needed based on the clinical response and tolerance. Continuous positive airway pressure was delivered for at least 6 h/d and was continued until endotracheal intubation, death, or fulfillment of the following cessation criteria: Pa_{O_2}/F_{IO_2} ratio greater than 300 mm Hg, or Sa_{O_2} between 95% and 100% and F_{IO_2} of 40% or less without CPAP, or CPAP duration less than 6 h/d. The criteria for oxygen delivery cessation were the same as in the standard therapy group.

Criteria for Intubation

Endotracheal intubation was performed in patients with any of the following: decreased alertness or major agitation requiring sedation, clinical signs of exhaustion (active contraction of the accessory muscles of respiration with paradoxical abdominal or thoracic motion), hemodynamic instability, cardiac arrest, or refractory hypoxemia (Sa_{O_2} <85% with F_{IO_2} of 100%).

Follow-up

Arterial blood gas values, respiratory rate, systolic blood pressure, and pulse rate were collected at baseline, after 1 hour, and between the 6th and 12th hours; the worst value of each of these variables was recorded once a day. The response to treatment was recorded 1 hour after the initiation of CPAP or oxygen treatment by asking patients to grade the effect of treatment on their dyspnea: +2, marked improvement; +1, slight improvement; 0, no change; –1, slight deterioration; and –2, marked deterioration. The Simplified Acute Physiologic Score II[23] (SAPS II) and the Logistic Organ Dysfunction score[24] were calculated 24 hours after ICU admission and 24 hours after study inclusion. Since CPAP use is assigned a specific weight in both scoring systems, the treatment assigned by randomization could in itself modify the scores; consequently, both scores were calculated without including the points for respiratory failure.

The following adverse events were recorded during spontaneous ventilation: facial skin necrosis, conjunctivitis, sinusitis, gastric distension, aspiration, pneumothorax, nosocomial pneumonia (based on clinical criteria), stress gastrointestinal tract ulcer and bleeding, and cardiac arrest; and during MV: cardiac arrest at endotracheal intubation, tracheal injury, pneumothorax, sinusitis, nosocomial pneumonia (based on clinical criteria and quantitative cultures of protected bacteriological sampling of the lungs), and stress gastrointestinal tract ulcer and bleeding. Among these events, only adverse events not present at admission were counted as those that occurred during the ICU stay.

Power and Statistical Analysis

The primary outcome variable was endotracheal intubation and MV at any time during the study. The patient was used as the randomization unit. The randomization protocol, computer-generated by the Department of Biostatistics of Henri Mondor Hospital, was stratified based both on the study center and the presence or absence of an underlying cardiac disease. Based on a preliminary retrospective evaluation of medical charts of patients fulfilling the inclusion criteria, the predicted intubation rate was approximately 40%. Sixty patients per group were required to demonstrate a difference in the rate of endotracheal intubation from 40% to 15% between the 2 groups, with a type I risk of error of 5% and a power of 80%. The 15% rate of intubation was chosen because previous studies had shown that 0% to 6% of patients receiving CPAP to treat CPE were eventually intubated, but that a lower efficacy could be expected in non-CPE.[10,13] Secondary outcome variables were the length of ICU and hospital stays, number of adverse events during spontaneous ventilation or MV (not present at admission; see above), duration of ventilatory assistance, and hospital mortality rate.

Values are reported as medians with the 5th to 95th percentiles. All statistical analyses were performed on an intention-to-treat basis, that is, including all randomized patients. χ^2 Tests or Fisher exact tests were used to compare categorical variables between the 2 treatment groups. Continuous variables were compared using the Wilcoxon rank sum test or Wilcoxon matched pairs signed rank test when appropriate. *P* values for all statistical tests were 2-tailed.

The Kaplan-Meier curve for intubation rates was plotted during the entire follow-up. The log-rank test was used to compare the 2 randomized groups. Independent factors associated with endotracheal intubation were analyzed using a Cox regression model and then used to adjust treatment comparisons considering both a stratified model based on the preexistence of cardiac disease and a nonstratified model. In the nonstratified model, the interaction between the treatment group and the cardiac disease group was formally tested by entering an indicator in-

teraction in the Cox regression model and by using a test for heterogeneity.[25] In the multivariate analysis, in addition to baseline data, the persistence of respiratory failure (defined as a PaO_2/FIO_2 ratio ≤200 mm Hg at 1 hour of treatment) also was evaluated as an index of respiratory severity. This index was determined at admission and at 1 hour, since most patients with fluid overload are already improved at 1 hour, whereas patients with nonhydrostatic lung edema are still hypoxemic. All computations were done using SAS software (SAS Institute, Cary, NC).

The individuals responsible for assessing and recording the outcomes (E.L'H., J.M., F.A., G.C., C.G., F.S., Y.L., and M.A.) only had access to patient medical charts; biostatisticians (C.A. and E.L.) were responsible for the computer database; and patient data were collected by the other investigators (C.D., F.L., and L.B.).

RESULTS

Patient Characteristics

The baseline characteristics of the 123 patients included in this study are shown in TABLE 1. Patients with an underlying cardiac disease were equally distributed between the 2 treatment groups (11 for oxygen alone and 11 for oxygen plus CPAP). The follow-up was complete for all patients (FIGURE 1).

Physiologic Variables

At study entry, all 123 patients had acute respiratory insufficiency (defined as a PaO_2/FIO_2 ratio ≤300 mm Hg and the presence of bilateral infiltrates on chest radiograph). Of these 123 patients, 21 (17%) eventually were classified as having pure cardiac decompensation; 102 patients (83%) had ALI (PaO_2/FIO_2 ratio ≤300 mm Hg due to increased lung permeability), among whom 74 (60%; 59 patients without cardiac disease plus 15 with associated cardiac disease) had a PaO_2/FIO_2 ratio of 200 mm Hg or lower, indicating acute respiratory distress syndrome (ARDS). Precipitating causes of pulmonary edema were equally distributed between the 2 treatment groups (TABLE 2). Infectious causes represented 37 (61%) of the 61 patients treated with oxygen alone and 42 (68%) of the 62 patients treated with oxygen plus CPAP; direct lung injury due to pneumonia was the most frequent cause (55% and 54%, respectively).

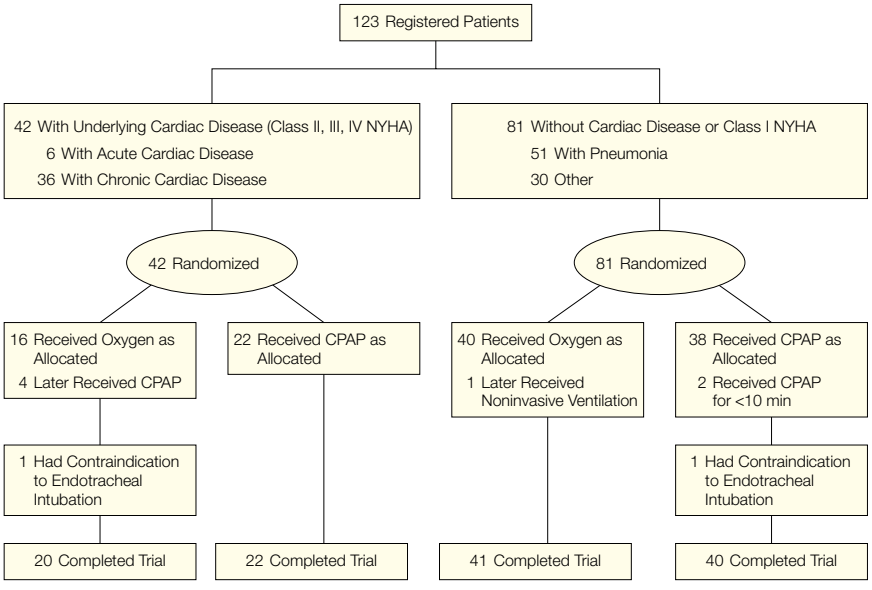
After 1 hour of treatment, patients receiving oxygen plus CPAP had a significantly greater PaO_2/FIO_2 ratio increase ($P = .02$) and a significantly greater subjective response to treatment than patients receiving oxygen

Table 1. Baseline Characteristics of the Patients at Study Entry*

Patient Characteristics	Oxygen Alone Group (n = 61)	Oxygen Plus CPAP Group (n = 62)	*P* Value
Age, median (5th-95th percentiles), y	60 (18-88)	56 (19-85)	.24
Male, No. (%)	40 (66)	38 (61)	.62
PaO_2/FIO_2, median (5th-95th percentiles), mm Hg	148 (62-283)	140 (59-288)	.43
SAPS II, median (5th-95th percentiles)	32 (6-102)	32 (6-87)	.62
Logistic Organ Dysfunction score, median (5th-95th percentiles)	3 (0-15)	3 (0-16)	.39
Preexisting cardiac disease, No. (%)			
Ischemic	11 (18)	11 (18)	.97
Hypertensive	7 (12)	7 (11)	.97
Valvular	5 (8)	6 (10)	.77
Dilated	0	4 (6)	.12
NYHA classification, No. (%)			.58†
I	2 (3)	4 (6)	
II	13 (21)	12 (19)	
III	5 (8)	9 (14)	
IV	0	0	

*CPAP indicates continuous positive airway pressure; SAPS II, Simplified Acute Physiologic Score II[23] (the SAPS II and the Logistic Organ Dysfunction scores[24] were calculated without the respiratory points); and NYHA, New York Heart Association.
†Compares the distribution of NYHA classes between the 2 randomized groups.

Figure 1. Study Design



NYHA indicates New York Heart Association functional classification; CPAP, continuous postitive airway pressure. The contraindications to endotracheal intubation occurred after trial registration.

Table 2. Patients With Precipitating Causes of Pulmonary Edema*

Causes	Oxygen Alone, No. (n = 61)		Oxygen Plus CPAP, No. (n = 62)		*P* Value
	Cardiac Disease (n = 20)	No Cardiac Disease (n = 41)	Cardiac Disease (n = 22)	No Cardiac Disease (n = 40)	
Infectious	7	30	11	31	.41
Noninfectious	13	11	11	9	
Cardiac causes					
Ischemia	9	NA	5	NA	.13
Arrhythmia	2	NA	2	NA	>.99
Fluid overload	4	NA	4	NA	>.99
Hypertension	1	NA	1	NA	>.99
Valvular disease	0	NA	1	NA	>.99
Other	1	NA	2	NA	>.99
Direct lung injury					
Pneumonia	7	26	8	26	.93
Aspiration	0	2	2	1	>.99
Near-drowning	0	5	0	3	.49
Other	0	5	1	6	.56
Indirect lung injury					
SIRS	1	1	3	4	.16
Shock	0	0	1	0	>.99
Other	0	2	3	2	.44

*Some patients had more than 1 precipitating cause. CPAP indicates continuous positive airway pressure; NA, not applicable; and SIRS, systemic inflammatory response syndrome.[24] Precipitating causes were similarly distributed ($P>.05$ for all causes) between the 2 treatment groups. Among the patients with severe cardiac disease (New York Heart Association functional class II or III), 21 had pure cardiogenic pulmonary edema; 8 of these 21 were randomized to oxygen plus CPAP and 13 to oxygen alone ($P = .07$).

alone ($P<.001$) (TABLE 3 and FIGURE 2). Compared with baseline values at entry, CPAP also was associated with a significant reduction in respiratory rate ($P<.001$) and a significant increase in pH levels ($P=.01$) at the end of the first treatment hour. During the remainder of the study, however, these indices showed no significant differences between the 2 treatment groups.

Treatment Compliance

Nine of the 62 patients (14%) were unable to tolerate CPAP treatment: 2 of the 9 tolerated CPAP for less than 10 minutes and 7 for longer than 6 hours. Three of the 9 patients eventually required intubation.

The median percent Sa_{O_2} over time was consistently above 90% in both treatment groups (FIGURE 3). In the oxygen plus CPAP group, the median daily duration of CPAP was significantly longer in patients who eventually required intubation than in those who did not ($P=.03$ at day 2, $P=.048$ at day 3, and $P=.02$ at day 4) (FIGURE 4).

Table 3. Physiologic Variables and Subjective Responses at Study Entry and After 1 Hour in the ICU*

Variables	Oxygen Alone Group (n = 61)			Oxygen Plus CPAP Group (n = 62)			*P* Value Between Treatment Groups‡	
	Entry	1 Hour	*P* Value Within Group†	Entry	1 Hour	*P* Value Within Group†	Entry	1 Hour
Physiologic response, median (5th-95th percentiles)								
Respiratory rate, breaths/min	32 (12-52)	28.5 (16-48)	.11	34 (20-60)	28 (12-51)	<.001	.10	.61
Arterial pH	7.42 (7.22-7.58)	7.44 (7.12-7.54)	.34	7.42 (7.21-7.62)	7.42 (7.30-7.57)	.01	.67	.09
$Paco_2$, mm Hg	35 (22-47)	36 (25-79)	.07	37 (23-61)	36 (26-66)	.17	.06	.52
Pao_2/Fio_2, mm Hg	148 (62-283)	151 (73-482)	.18	140 (59-288)	203 (45-431)	<.001	.31	.02
Heart rate, beats/min	100 (60-144)	98 (65-140)	.03	104 (39-155)	99 (58-155)	.003	.38	.98
Systolic BP, mm Hg	128 (80-261)	120 (90-200)	.23	130 (90-211)	130 (80-181)	.02	.09	.11
Subjective response, No. (%)§								
Worse		21 (44)			8 (13)			<.001
No change		4 (8)			1 (2)			
Slight improvement		15 (31)			31 (51)			
Marked improvement		8 (17)			21 (34)			

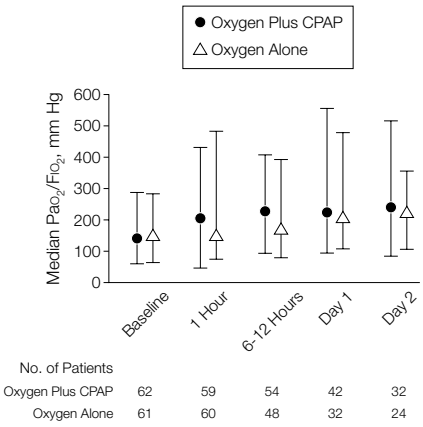
*ICU indicates intensive care unit; CPAP, continuous positive airway pressure; and BP, blood pressure.
†Calculated using the paired Wilcoxon test.
‡Calculated using the χ^2 test or Wilcoxon test as appropriate.
§Subjective response was evaluated by the physician asking patients to grade the effect of treatment on their dyspnea: +2, slight improvement to –2, marked deterioration. There were 13 missing data items in the oxygen alone group and 1 in the oxygen plus CPAP group. Worse means both slight and marked deterioration.
‖Compares the distribution of subjective response classes between the 2 randomization groups.

Clinical Outcome

No significant differences were found between the 2 treatment groups for any of the clinical outcome variables studied, including rate of endotracheal intubation, length of hospital stay, and hospital mortality (TABLE 4 and FIGURE 5). The indications for endotracheal intubation were similar in the 2 treatment groups (TABLE 5). Four patients randomized to the oxygen alone group subsequently were given oxygen plus CPAP treatment, and another patient received NIV pressure support. Two patients (1 in each group) were found a posteriori to meet an exclusion criterion (contraindication to endotracheal intubation); neither patient was intubated and both died in the ICU. Excluding these patients or switching them to the other group had no significant effects on outcomes.

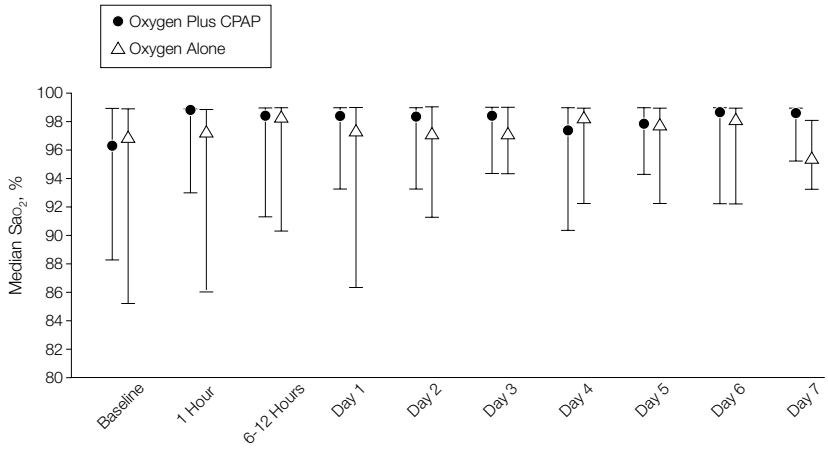
A multivariate analysis demonstrated that the SAPS II score (hazard ratio [HR] per 1 SAPS II point, 1.05; 95% confidence interval, [1.03-1.07]), absence of a cardiac disease (HR, 2.27 [1.08-4.75]), and PaO_2/FIO_2 ratio 200 mm Hg or less at 1 hour of treatment (HR, 2.35 [1.20-4.60]) were independently associated with endotracheal intubation. Treatment group assignment as well as a PaO_2/FIO_2 ratio of 200 mm Hg or less on admission were not associated with endotracheal intubation. The absence of treatment effect remained unchanged

Figure 2. Oxygenation Over Time in the 2 Randomized Groups



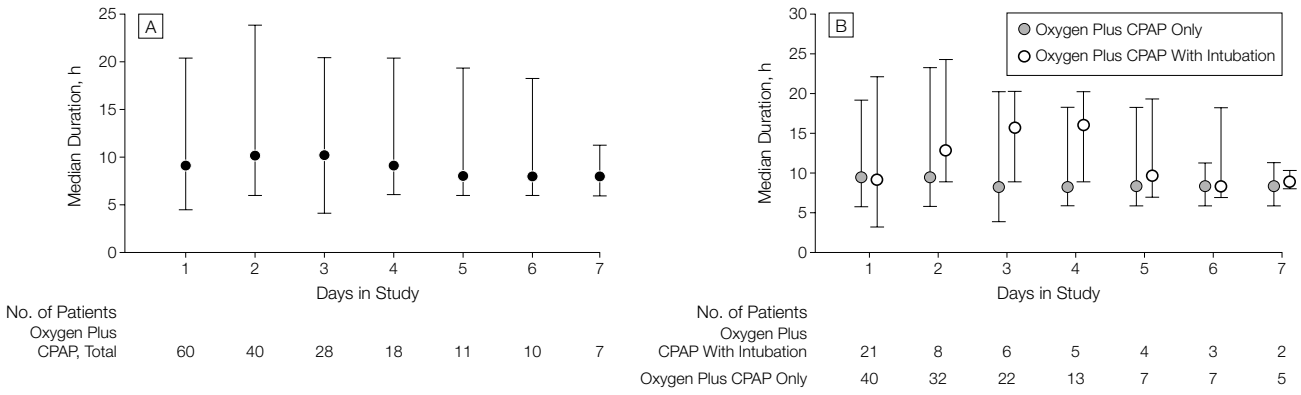
Oxygenation is expressed as the median value (bars, 5th-95th percentiles) of the PaO_2/FIO_2 ratio mm Hg during the first 2 days in the intensive care unit in patients randomized to oxygen alone or oxygen plus continuous positive airway pressure (CPAP). $P = .02$ at 1 hour between groups.

Figure 3. Median Arterial Oxygen Saturation in the 2 Randomized Groups



The median value (bars, 5th-95th percentiles) of the percentage of arterial oxygen saturation (SaO_2 %) during the first 7 days in the intensive care unit is presented in patients randomized to oxygen alone or oxygen plus continuous positive airway pressure (CPAP). Pulse oximetry did not provide reliable measurements in some patients.

Figure 4. Duration of Continuous Positive Airway Pressure (CPAP)



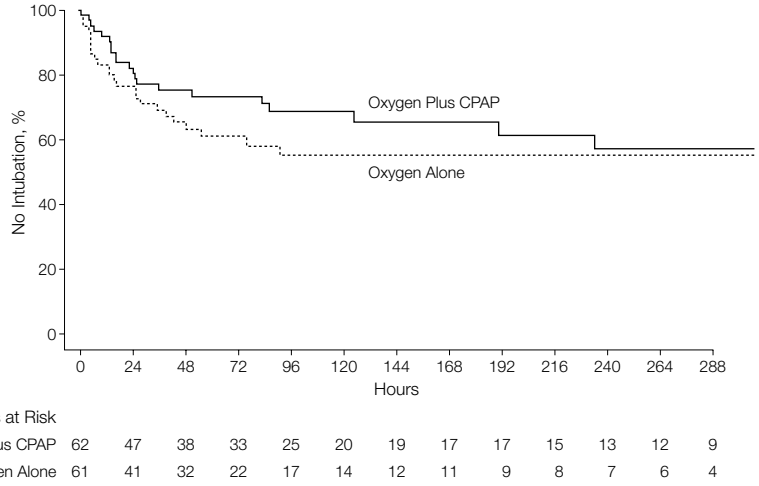
The median duration of CPAP treatment (bars, 5th-95th percentiles) during the first 7 days in the intensive care unit is given for all the patients randomized to the oxygen plus CPAP group (A) and for the patients in the oxygen plus CPAP with intubation group and the oxygen plus CPAP only group (B). *P* values for the oxygen plus CPAP with intubation group vs the oxygen plus CPAP only group were .03 at day 2, .048 at day 3, and .02 at day 4. The median level of positive pressure was 7.5 cm H_2O from day 1 to day 7.

Table 4. Study Outcomes*

Outcome Variable	Oxygen Alone Group (n = 61)		Oxygen Plus CPAP Group (n = 62)		*P* Value Between Treatments	*P* Value Between Groups
	Cardiac Disease (n = 20)	No Cardiac Disease (n = 41)	Cardiac Disease (n = 22)	No Cardiac Disease (n = 40)		
Endotracheal intubation, No. (%)	6 (30)	18 (44)	6 (27)	15 (37.5)	.53	.18
ICU length of stay, median (5th-95th percentiles), d†	3 (1-35)	9 (2-36)	6 (1-31)	9 (2-57)	.43	.01
Hospital length of stay, median (5th-95th percentiles), d	16 (2-35)	16 (2-70)	16.5 (1-121)	14 (2-97)	.77	.83
ICU mortality, No. (%)	6 (30)	9 (22)	4 (18)	9 (22.5)	.63	.29
Hospital mortality, No. (%)	7 (35)	11 (27)	7 (32)	12 (30)	.89	.24

*CPAP indicates continuous positive airway pressure; ICU, intensive care unit. Among the 21 patients with pure cardiogenic pulmonary edema, 2 of 8 patients randomized to oxygen plus CPAP were intubated compared with 4 of 13 patients randomized to oxygen alone.
†$P<.05$ for within-group comparisons of patients with vs without cardiac disease.

Figure 5. Time to Intubation in the 2 Randomization Groups



The percentage of patients who were not intubated is expressed over time in each randomization group (oxygen alone vs oxygen plus continuous positive airway pressure [CPAP]). Oxygen plus CPAP treatment did not significantly influence the need for endotracheal intubation ($P=.30$).

Table 5. Indications for Patients Who Underwent Endotracheal Intubation*

Criteria	Oxygen Alone Group (n = 24)	Oxygen Plus CPAP Group (n = 21)	*P* Value
Agitation	16 (67)	13 (62)	.74
Exhaustion	19 (79)	13 (62)	.20
Hemodynamic instability	6 (25)	5 (24)	.93
Cardiac arrest	0	1 (5)	.28
Refractory hypoxemia	10 (42)	7 (33)	.56
Respiratory acidosis	3 (12)	2 (10)	.97
Other	0	1 (5)	.47

*Values are No. (%). CPAP indicates continuous positive airway pressure. Some patients had more than 1 reason for endotracheal intubation, with the most common combination being agitation plus exhaustion (6 patients in the oxygen alone group and 5 in the oxygen plus CPAP group).

when the stratified analysis on preexistence of cardiac disease was performed. Moreover, there was no interaction between the treatment and the cardiac disease groups.

When patients with and without an underlying cardiac disease were analyzed separately, no significant benefits of oxygen plus CPAP treatment were found for the need for endotracheal intubation, length of hospital stay, or hospital mortality (Table 4).

Adverse Events

Adverse events that occurred during spontaneous and MV were significantly more common in the CPAP group ($P=.01$) (TABLE 6).

COMMENT

This multicenter, randomized, concealed, but unblinded trial of 123 patients showed that, despite early physiologic benefits, treatment with oxygen plus CPAP delivered by a face mask did not reduce the need for intubation in patients with acute, hypoxemic, and nonhypercapnic respiratory insufficiency, among whom a majority had ALI, and it did not impact the length of hospital stay or hospital mortality. A higher number of adverse events occurred with the use of CPAP.

All centers were experienced in the delivery of face-mask ventilation and had previously participated in NIV studies.[1,16,19,20] Analysis of daily CPAP treatment duration data showed that CPAP was used for at least 6 h/d, as required by the study protocol. Use of intubation in patients in the oxygen plus CPAP group was not explained by a low compliance with CPAP treatment. On the contrary, patients who eventually required intubation had significantly longer daily CPAP treatment durations (Figure 3). In addition, Sa_{O_2} goals were achieved in both groups (Figure 2). The fact that a longer duration of CPAP use per day was associated with intubation

could raise the hypothesis that additional respiratory load due to CPAP use may favor intubation. To minimize this problem, we used a continuous flow system with adequate airway humidification and minimal loads imposed by the circuit. Because the CPAP device was an adjustable-flow venturi, when high FIO_2 is used, a slight reduction in total outflow may occur.[22] Thus, it is possible that the CPAP system was less efficient for the most severe patients needing the highest FIO_2 and the highest flow. Nevertheless, the multivariate analysis demonstrated that a PaO_2/FIO_2 ratio at 1 hour of 200 mm Hg or lower was an independent risk factor for intubation whatever the treatment type. This index was taken at 1 hour to more accurately identify patients with ARDS, since most patients with fluid overload are already improved at 1 hour. This parameter was a marker of severity, and this could not be reversed by CPAP treatment despite increasing its use.

Oxygen plus CPAP therapy was associated with a significantly greater improvement of PaO_2/FIO_2 ratio within the first hour than oxygen alone therapy. As a result, oxygenation was improved after 1 hour in the CPAP group and of patient dyspnea. Similar results were obtained with CPAP treatment in patients with cardiac disease or in the short-term studies in patients with ALI.[7,13,17] During the remainder of the study, no differences in oxygenation were demonstrated.

The leading cause of acute respiratory insufficiency in our study was nonhydrostatic edema, that is, ALI (101 [82%] of the patients). The large proportion of these patients with criteria for ARDS is representative of the relative distribution of these 2 degrees of severity found in previous studies (ALI [with no criteria for ARDS]: 1.8% vs ARDS: 6.9%, among all ICU admissions in a recent multicenter prevalence survey).[26] Our population included patients with cardiac dysfunction, a factor that may have influenced the efficacy of CPAP treatment. Results were similar in patients with and without cardiac disease (Table 4). Our study was not powered to determine the efficacy of oxygen plus CPAP treatment in the subgroup of patients with pure CPE nor in specific subsets of patients with non-CPE.

Table 6. Adverse Events Occurring in Patients During Their Intensive Care Unit Stay*

Adverse Event	Oxygen Alone (n = 61)	Oxygen Plus CPAP (n = 62)	*P* Value Between Treatment Groups
During spontaneous ventilation			
Facial skin necrosis	0	2	.50
Gastric distension	0	1	.54
Nosocomial pneumonia	1	0	.97
Cardiac arrest	0	4†	.14
During mechanical ventilation			
Nosocomial pneumonia	4	6	.74
Sinusitis	1	0	.99
Pneumothorax	0	1	.54
Stress ulcer	0	4	.14
Any adverse event, No. (%)	6 (10)	18 (29)	.01
Patients with adverse events, No. (%)	5 (8)	14 (23)	.03

*CPAP indicates continuous positive airway pressure.
†Three patients experienced cardiac arrest at the time of scheduled intubation, in patients previously CPAP-dependent to maintain oxygenation. In another patient, cardiac arrest occurred when CPAP delivered by a face mask was disconnected to allow nursing care, resulting in a rapid worsening of hypoxemia.

Bersten et al[10] reported that oxygen plus CPAP treatment in patients with severe hypercapnic CPE resulted in early physiologic improvement and significantly reduced the need for intubation; the PaO_2/FIO_2 ratio improvement with CPAP use was significant only at 30 minutes, as compared with oxygen alone. The prompt improvement with CPAP use was probably because the patients had rapidly resolving conditions: mean (SD) CPAP duration of use was only 9.3 (4.9) hours and mean (SD) ICU stay length was 1.2 (0.4) days. These results suggest that the patients had extremely acute conditions in which CPAP treatment was beneficial because the rapid improvement it afforded, although transient, lasted long enough to give drug therapy time to act. Similar benefits were suggested by L'Her et al.[16] In these studies, most patients had hypercapnic CPE, indicating frank ventilatory failure (patients with hypercapnia were not included in our study). Hypoxemic nonhypercapnic pulmonary edema in cardiac patients seems to respond to CPAP treatment differently for 2 possible reasons: because the evolution may be spontaneously favorable under medical therapy alone in patients with pure CPE or because the evolution may become similar to ALI when the disease is triggered by a noncardiac event in cardiac patients. The existence of ventilatory failure, with hypercapnia and respiratory acidosis, indicates that the immediate prognosis depends on the ability of the ventilatory function to cope with the loads. This can be obtained by reducing the loads on the system (medications) or by assisting the respiratory muscle function (CPAP or NIV therapy). The absence of frank ventilatory failure may explain why these patients do not clearly benefit from CPAP therapy. Therefore, CPAP may be beneficial in patients with a poorly tolerated but transient hypercapnic episode of CPE but may be less advisable in patients with longer-lasting hypoxemia.

Confalonieri and colleagues[27] recently reported beneficial effects of NIV in patients with severe community-acquired pneumonia, but this result was essentially explained by the subgroup of patients with COPD. In a study by Wysocki et al[28] of NIV in patients without COPD admitted for acute respiratory failure, the need for endotracheal intubation and the time from study entry to endotracheal intubation affected were not decreased by NIV. In addition, the results suggested that benefits occurred only in the subgroup of patients with hypercapnia.

Antonelli et al[20] recently reported the beneficial effects of NIV in selected pa-

tients with hypoxemia and acute respiratory failure deemed to require intubation. They used pressure support ventilation in addition to PEEP (mean [SD], 5.1 [1.4] cm H_2O) and found that this treatment improved gas exchange and was less likely to cause adverse effects compared with conventional MV. Mean (SD) duration of NIV was only 2 (1) days in the patients who did not require intubation. It remains unclear whether the higher level of support provided by the concomitant use of pressure support and PEEP may explain the better results in the study by Antonelli et al[20] as compared with our study. Differences in selection criteria also may have contributed to the differences in results between these 2 studies.

If CPAP therapy does not reduce the need for endotracheal intubation, then it may carry its own risks. Oxygen plus CPAP treatment was accepted by 86% of our patients, initially produced few adverse effects, and improved subjective response compared with oxygen therapy. Nevertheless, of 8 patients treated with CPAP, 4 experienced cardiac arrest and 4 who were treated with CPAP experienced upper gastrointestinal tract bleeding. Continuous positive airway pressure was not associated with a significant increase in adverse events during spontaneous ventilation (7 vs 1, $P = .06$). However, it may be difficult to ensure that the adverse effects occurring during MV may not be explained by the period of spontaneous ventilation, for instance, for gastrointestinal tract bleeding (4 patients in the oxygen plus CPAP group and 0 in the oxygen alone group). In some cases, CPAP may prolong the stressful period of spontaneous breathing, which could have been reduced by MV, allowing to rest the patient. Although this study was not powered enough to detect small benefits of CPAP therapy, it found a significantly higher number of adverse events in centers well trained in the NIV technique.

In conclusion, CPAP provided rapid but transient improvements in oxygenation and dyspnea compared with standard therapy but did not decrease endotracheal intubation in patients with acute, nonhypercapnic respiratory insufficiency. However, we found significantly more adverse events with CPAP.

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Funding/Support: This study was supported by a grant from Vital Signs, Inc (Totowa, NJ), which provided some computer equipment and the equipment for continuous positive airway pressure treatment.
Acknowledgments: Other investigators in this study were Souheil Elatrous, MD, Monastir Hospital, Tunisia; Alvaro Giordano, MD, Créteil, France; Mohamed Boussarsar, MD, Créteil, France; and Eva Ormaechea, MD, Barcelona, Spain.

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