ORIGINAL ARTICLE

Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema

Alasdair Gray, M.D., Steve Goodacre, Ph.D., David E. Newby, M.D., Moyra Masson, M.Sc., Fiona Sampson, M.Sc., and Jon Nicholl, M.Sc., for the 3CPO Trialists*

From the Royal Infirmary of Edinburgh, Edinburgh (A.G., M.M.), the University of Sheffield, Sheffield (S.G., F.S., J.N.), and the University of Edinburgh, Edinburgh (D.E.N.) — all in the United Kingdom. Address reprint requests to Dr. Gray at the Department of Emergency Medicine, Royal Infirmary of Edinburgh, Little France, Edinburgh EH16 4SA, United Kingdom, or at alasdair.gray@luht.scot.nhs.uk.

*The participants in the Three Interventions in Cardiogenic Pulmonary Oedema (3CPO) trial are listed in the Appendix.

N Engl J Med 2008;359:142-51.
Copyright © 2008 Massachusetts Medical Society.

ABSTRACT

BACKGROUND

Noninvasive ventilation (continuous positive airway pressure [CPAP] or noninvasive intermittent positive-pressure ventilation [NIPPV]) appears to be of benefit in the immediate treatment of patients with acute cardiogenic pulmonary edema and may reduce mortality. We conducted a study to determine whether noninvasive ventilation reduces mortality and whether there are important differences in outcome associated with the method of treatment (CPAP or NIPPV).

METHODS

In a multicenter, open, prospective, randomized, controlled trial, patients were assigned to standard oxygen therapy, CPAP (5 to 15 cm of water), or NIPPV (inspiratory pressure, 8 to 20 cm of water; expiratory pressure, 4 to 10 cm of water). The primary end point for the comparison between noninvasive ventilation and standard oxygen therapy was death within 7 days after the initiation of treatment, and the primary end point for the comparison between NIPPV and CPAP was death or intubation within 7 days.

RESULTS

A total of 1069 patients (mean [±SD] age, 77.7±9.7 years; female sex, 56.9%) were assigned to standard oxygen therapy (367 patients), CPAP (346 patients), or NIPPV (356 patients). There was no significant difference in 7-day mortality between patients receiving standard oxygen therapy (9.8%) and those undergoing noninvasive ventilation (9.5%, P=0.87). There was no significant difference in the combined end point of death or intubation within 7 days between the two groups of patients undergoing noninvasive ventilation (11.7% for CPAP and 11.1% for NIPPV, P=0.81). As compared with standard oxygen therapy, noninvasive ventilation was associated with greater mean improvements at 1 hour after the beginning of treatment in patient-reported dyspnea (treatment difference, 0.7 on a visual-analogue scale ranging from 1 to 10; 95% confidence interval [CI], 0.2 to 1.3; P=0.008), heart rate (treatment difference, 4 beats per minute; 95% CI, 1 to 6; P=0.004), acidosis (treatment difference, pH 0.03; 95% CI, 0.02 to 0.04; P<0.001), and hypercapnia (treatment difference, 0.7 kPa [5.2 mm Hg]; 95% CI, 0.4 to 0.9; P<0.001). There were no treatment-related adverse events.

CONCLUSIONS

In patients with acute cardiogenic pulmonary edema, noninvasive ventilation induces a more rapid improvement in respiratory distress and metabolic disturbance than does standard oxygen therapy but has no effect on short-term mortality. (Current Controlled Trials number, ISRCTN07448447.)

The New England Journal of Medicine
Downloaded from nejm.org on May 2, 2011. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

Acute cardiogenic pulmonary edema is a common medical emergency that accounts for up to 1 million hospital admissions for acute conditions per year in the United States.[1] It is a leading cause of hospitalization, accounting for 6.5 million hospital days each year.[2] In-hospital mortality from acute cardiogenic pulmonary edema is high (10 to 20%),[3] especially when it is associated with acute myocardial infarction.[4]

Patients who do not have a response to initial therapy often require tracheal intubation and ventilation, with the associated potential for complications.[5] Noninvasive methods of ventilation can avert tracheal intubation by improving oxygenation, reducing the work of breathing, and increasing cardiac output.[6-9] Two common noninvasive methods involve continuous positive airway pressure (CPAP) or noninvasive intermittent positive-pressure ventilation (NIPPV) delivered with the use of a face mask. CPAP maintains the same positive-pressure support throughout the respiratory cycle, whereas NIPPV increases airway pressure more during inspiration than during expiration. As compared with CPAP, NIPPV produces greater improvements in oxygenation and carbon dioxide clearance and a greater reduction in the work of breathing in patients with pulmonary edema.[10]

Clinical studies of noninvasive ventilation in patients with acute cardiogenic pulmonary edema include case series and small, randomized, controlled trials. Most compare CPAP or NIPPV with standard therapy and suggest that noninvasive ventilation improves symptoms, physiological variables, and rates of invasive ventilation.[11-14] Recently published systematic reviews have suggested reduced mortality in patients treated with CPAP.[15-18] Comparison of CPAP with NIPPV reveals no significant difference between the two interventions, despite the postulated physiological advantages of NIPPV. One meta-analysis suggested an increase in the rate of acute myocardial infarction in patients treated with NIPPV.[16]

To date, all randomized, controlled trials known to us have been small, and most have been conducted at single centers.[15-18] There has been considerable variation in study populations, the type of ventilation intervention, concomitant therapies, and trial end points.[16] Therefore, it is uncertain whether these results are either generalizable or robust. In light of this uncertainty, we conducted a large, randomized, controlled trial involving patients with acute cardiogenic pulmonary edema to determine whether noninvasive ventilation improves survival and whether NIPPV is superior to CPAP.

METHODS

PATIENTS

Patients were recruited from 26 emergency departments in district and regional hospitals in the United Kingdom between July 2003 and April 2007. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the United Kingdom Medical Research Council, complied with the United Kingdom Data Protection Act 1998, and was approved by the Scotland A Research Ethics Committee (02/0/074, U.K.).

The inclusion criteria were an age of more than 16 years, a clinical diagnosis of acute cardiogenic pulmonary edema, pulmonary edema shown by a chest radiograph, a respiratory rate of more than 20 breaths per minute, and an arterial hydrogen-ion concentration of greater than 45 nmol per liter (pH <7.35). The exclusion criteria were a requirement for a lifesaving or emergency intervention, such as primary percutaneous coronary intervention; inability to give consent; or previous recruitment into the trial. All patients received standard concomitant therapy for acute pulmonary edema.

Depending on the severity of the illness, informed written or witnessed oral consent from the patient or witnessed consent from a relative was obtained at entry into the study. Whenever possible, written consent for continued participation in the trial was obtained from the patient in the subsequent 7 days.

STUDY DESIGN

The study was an open, randomized, controlled, parallel-group trial with three treatment groups: standard oxygen therapy, CPAP, and NIPPV. Patients were randomly assigned to one of the three treatments at a 1:1:1 ratio with the use of a 24-hour telephone randomization service. The randomization sequence was stratified according to center, with variable block length.

TRIAL INTERVENTION

CPAP and NIPPV were delivered through a full-face mask by a Respironics Synchrony ventilator. Supplemental oxygen was supplied at a rate of up to 15 liters per minute with a maximum fraction of

The New England Journal of Medicine
Downloaded from nejm.org on May 2, 2011. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

inspired oxygen of 0.6 in order to maintain peripheral oxygen saturation above 92%. CPAP was commenced at 5 cm of water and increased to a maximum of 15 cm of water. NIPPV was started at an inspiratory positive airway pressure of 8 cm of water and an expiratory positive airway pressure of 4 cm of water and was increased to a maximum inspiratory pressure of 20 cm of water and a maximum expiratory pressure of 10 cm of water. Patients assigned to standard medical therapy received supplemental oxygen to maintain saturations above 92% through a variable-delivery oxygen mask with a reservoir. All patients received their assigned treatment for a minimum of 2 hours. Further use of CPAP, NIPPV, or intubation (invasive ventilation) was at the discretion of the treating clinician. The trial protocol allowed early intubation if the patient did not have a sustained response with CPAP or NIPPV.

The trial was coordinated from Edinburgh and supported by a regional network of research nurses and clinicians. To ensure core competency in the use of noninvasive ventilators, training was delivered at multiple levels, including regional research nurses, site leaders, and the manufacturer of the ventilator.

RESPONSE TO THERAPY

Repeat analyses of arterial blood gases were performed 1 hour after recruitment. Pulse rate, respiratory rate, oxygen saturation, and noninvasively measured blood pressure were recorded at 1 hour and 2 hours. The patients reported their degree of dyspnea on a visual-analogue scale ranging from 0 (no breathlessness) to 10 (maximal breathlessness) at recruitment and at 1 hour.

OUTCOME MEASURES

The primary end point for the comparison between noninvasive ventilation (NIPPV or CPAP) and standard oxygen therapy was death within 7 days after the initiation of treatment. The primary end point for the comparison between NIPPV and CPAP was a composite of death within 7 days or tracheal intubation within 7 days. The a priori secondary end points were dyspnea, physiological variables, intubation within 7 days, length of hospital stay, admission to the critical care unit, and death within 30 days.

Myocardial infarction was defined according to the 1971 criteria of the World Health Organization and the criteria of the universal definition of myocardial infarction.[19] Two cardiologists who were unaware of the treatment assignments classified the patients as having definite myocardial infarction, probable myocardial infarction, possible myocardial infarction, or no myocardial infarction. Newly diagnosed cases of myocardial infarction were defined as cases of definite or probable myocardial infarction.

STATISTICAL ANALYSIS

The data and safety monitoring committee ensured that the criteria for early termination due to either efficacy (according to the Peto–Haybittle guidelines, with a criterion of $P<0.001$) or harm ($P<0.05$) of the treatment were not met.

To have an 80% chance of detecting an absolute difference of 6% in mortality (9% vs. 15%) with the use of a two-sided test with a significance level of 0.05, we needed 400 patients assigned to standard facial oxygen therapy and 800 patients assigned to either CPAP or NIPPV. With 400 patients each in the CPAP and NIPPV groups, the trial had 80% power, with the use of a two-sided test with a significance level of 0.05, to detect an absolute difference of approximately 7% in the composite end point (18% vs. 11%) and of approximately 6% in mortality (12% vs. 6%).

The data were analyzed according to the intention-to-treat principle. The primary analysis compared the rates of 7-day mortality in each group with the use of a logistic-regression model with the degrees of freedom for differences among the three treatments decomposed into the two orthogonal contrasts of standard therapy versus noninvasive therapy (CPAP or NIPPV) and CPAP versus NIPPV. Kaplan–Meier survival curves were plotted for the same comparisons, and survival was compared among the groups with the use of the log-rank test. The rates of 30-day mortality, myocardial infarction, intubation within 7 days, admission to the critical care unit (intensive or coronary care), and the composite end point of death or intubation were compared with the use of logistic regression. At 1 hour after initiation of treatment, changes in dyspnea score, physiological variables, and arterial blood gas values were compared with the use of Student's t-test. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

Logistic regression was used to explore interactions between treatment effect (noninvasive ventilatory support vs. standard therapy) and severity

The New England Journal of Medicine
Downloaded from nejm.org on May 2, 2011. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

Table 1. Baseline Characteristics of the Patients.*

Characterisic	Standard Oxygen Treatment (N=367)	CPAP (N=346)	NIPPV (N=356)
Age (yr)	79±9	78±10	77±10
Male sex (%)	42	45	43
Symptoms of myocardial infarction at presentation (%)	22	22	22
Ischemic heart disease (%)	64	64	60
Congestive heart failure (%)	45	42	47
Valvular heart disease (%)	12	11	9
Chronic obstructive pulmonary disease (%)	19	15	21
Hypertension (%)	56	55	57
Diabetes mellitus (%)	30	30	33
Hypercholesterolemia (%)	30	33	31
Current smoking (%)	16	19	19
Peripheral vascular disease (%)	10	11	10
Cerebrovascular disease (%)	18	17	16
Pulse rate (beats/min)	114±24	113±21	112±22
Blood pressure (mm Hg)			
Systolic	161±38	162±35	161±36
Diastolic	87±25	89±23	87±24
Respiratory rate (breaths/min)	33±7	32±7	32±7
Peripheral oxygen saturation (%)	91±8	90±8	90±8
Arterial pH	7.22±0.08	7.21±0.09	7.22±0.09
PaO_2 (kPa)	13.1±7.6	13.5±7.7	13.4±8.6
$PaCO_2$ (kPa)	7.6±2.5	7.5±1.9	7.7±2.3
Serum bicarbonate level (mmol/liter)	21±4	21±4	21±5
Dyspnea score†	8.9±1.5	8.9±1.8	8.8±1.6

* Plus–minus values are means ±SD. CPAP denotes continuous positive airway pressure, NIPPV noninvasive intermittent positive-pressure ventilation, $PaCO_2$ partial pressure of arterial carbon dioxide, and PaO_2 partial pressure of arterial oxygen. To convert values for PaO_2 and $PaCO_2$ to mm Hg, multiply by 7.50062.

† The patients reported their degree of dyspnea on a visual-analogue scale ranging from 0 (no breathlessness) to 10 (maximal breathlessness).

of illness, which was defined a priori according to baseline arterial pH and post hoc according to systolic blood pressure.[20,21] Further exploratory analyses examined the interaction between treatment effect and age, sex, presence or absence of previous heart failure, and presence or absence of acute myocardial infarction.

RESULTS

Of 1842 potentially eligible patients, 1511 were screened and 1156 underwent randomization. Eighty-seven patients were excluded after randomization because of ineligibility or previous recruitment into the trial (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). There were no significant differences in baseline characteristics among the three groups (Table 1). The patients were elderly (mean [±SD] age, 77.7±9.7 years) and had marked tachycardia, tachypnea, hypertension, acidosis, and hypercapnia. Most of the patients (56.9%) were women.

TRIAL INTERVENTION

Patients and concomitant therapies were evenly assigned across the intervention groups (Table 2; also see the Supplementary Appendix). Although

The New England Journal of Medicine
Downloaded from nejm.org on May 2, 2011. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

Table 2. Treatment of Patients.*

Variable	Standard Oxygen Treatment (N=367)	CPAP (N=346)	NIPPV (N=356)	All Patients (N=1069)	P Value†
Initial treatment — % of patients					
Nitrates	93	88	91	90	0.11
Diuretics	90	89	89	89	0.89
Opioids	55	50	49	51	0.31
Inspired oxygen — liters/min	12±4	12±4	12±4	12±4	0.44
Ventilation pressure — cm of water	—	10±4	Inspiratory 14±5, expiratory 7±3	—	
Started assigned treatment — no./total no. (%)‡	365/366 (99.7)	337/343 (98.3)	344/354 (97.2)	1046/1063 (98.4)	0.02
Completed assigned treatment — no./total no. (%)§	298/363 (82.1)	285/340 (83.8)	267/352 (75.9)	850/1055 (80.6)	0.02
Changed to new treatment — no.					
Intubation	3	1	4		
CPAP	43	—	12		
NIPPV	13	5	—		
Standard treatment	—	31	49		
New treatment not stated	6	18	20		
Reason for not completing assigned treatment — no. (%)¶					
Patient discomfort	1 (0.3)	18 (5.2)	30 (8.4)		<0.001
Worsening arterial blood gas values	26 (7.1)	10 (2.9)	15 (4.2)		0.03
Respiratory distress	31 (8.4)	5 (1.4)	12 (3.4)		<0.001
Other	18 (4.9)	24 (6.9)	29 (8.1)		0.21

* Plus–minus values are means ±SD. CPAP denotes continuous positive airway pressure, and NIPPV noninvasive intermittent positive-pressure ventilation.
† P values are for the comparison among the three groups.
‡ Data were missing for six patients.
§ Data were missing for 14 patients.
¶ A patient may have had more than one reason for not completing the assigned treatment.

the overall completion rates were similar, standard oxygen therapy was associated with a greater failure rate due to respiratory distress, whereas noninvasive ventilation, especially NIPPV, was associated with a higher rate of noncompletion due to patient discomfort (Table 2). The mean duration of therapy was 2.2±1.5 hours for CPAP and 2.0±1.3 hours for NIPPV.

PRIMARY OUTCOMES

There was no significant difference in the primary end point of 7-day mortality between patients receiving noninvasive ventilation (CPAP or NIPPV) (9.5%) and those receiving standard oxygen therapy (9.8%; odds ratio, 0.97; 95% confidence interval [CI], 0.63 to 1.48; P=0.87) (Fig. 1 and Table 3). The 7-day mortality rate in nonrecruited patients was 9.9%. The rate of the primary composite end point of death or intubation within 7 days (Fig. 1 and Table 4) was similar for the CPAP and the NIPPV groups (11.7% and 11.1%, respectively; odds ratio, 0.94; 95% CI, 0.59 to 1.51; P=0.81).

There were no interactions between treatment effect and severity of illness, as defined by either baseline arterial pH (P=0.94) or systolic blood pressure (P=0.17). Further exploratory subgroup analysis found no interactions between treatment effect and age (P=0.52), sex (P=0.33), presence or absence of a history of heart failure (P=0.28),

The New England Journal of Medicine
Downloaded from nejm.org on May 2, 2011. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

and presence or absence of myocardial infarction at presentation (P=0.93).

SECONDARY OUTCOMES

There was no significant difference in the 30-day mortality rate between patients receiving standard oxygen therapy and those receiving noninvasive ventilation (16.4% and 15.2%, respectively; odds ratio, 0.92; 95% CI, 0.64 to 1.31; P=0.64) (Table 3). Mortality rates were similar in the CPAP and the NIPPV groups at 7 days (9.6% and 9.4%, respectively; odds ratio, 0.97; P=0.91) and at 30 days (15.4% and 15.1%, respectively; odds ratio, 0.98; P=0.92) (Table 4).

Noninvasive ventilation (CPAP or NIPPV) was associated with greater reductions in dyspnea, heart rate, acidosis, and hypercapnia than was standard oxygen therapy (Table 3). Patients receiving standard oxygen therapy and those receiving noninvasive ventilation had similar rates of tracheal intubation, admission to the critical care unit, and myocardial infarction. Patients receiving CPAP and those receiving NIPPV also had similar rates of these outcomes (Table 4).

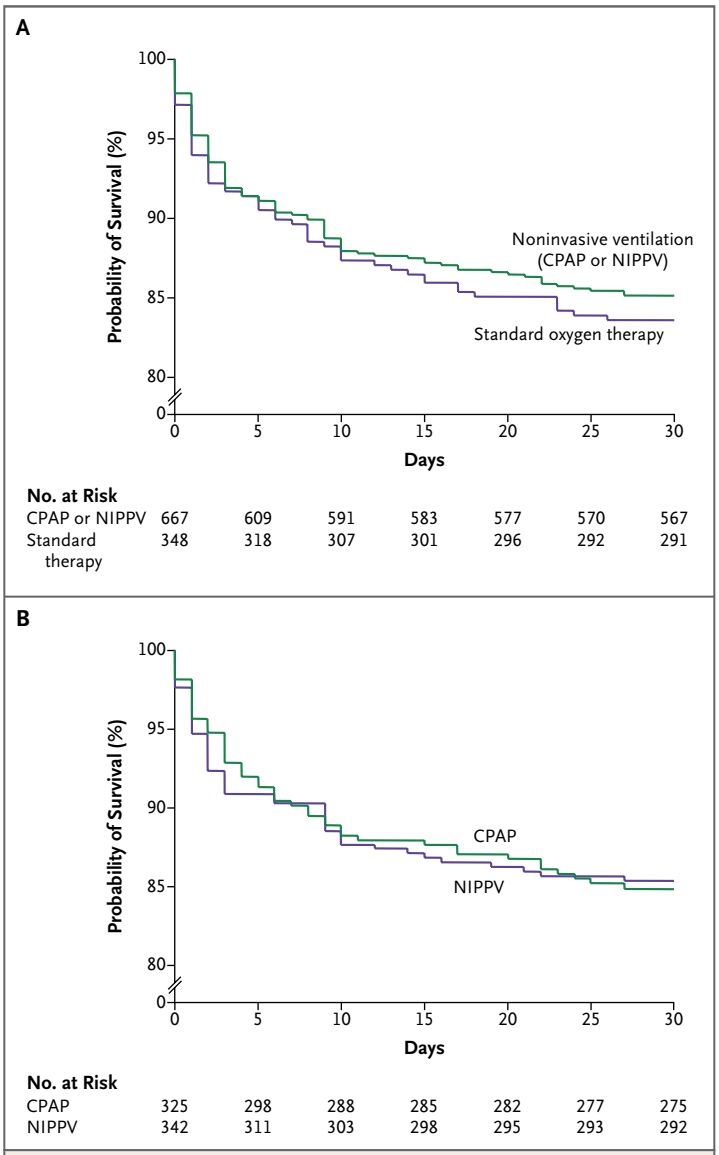

Figure 1. Kaplan–Meier Survival Curves.

Panel A shows the comparison between noninvasive and standard oxygen therapy, and Panel B the comparison between continuous positive airway pressure (CPAP) and noninvasive intermittent positive-pressure ventilation (NIPPV). The values for 7-day survival are marginally different from those reported as a primary outcome (Tables 3 and 4), because data from patients who did not consent to follow-up or withdrew after 7 days are not included. Data were missing for two patients in the NIPPV group.

DISCUSSION

Despite early improvements in symptoms and in surrogate measures of disease severity, we found no difference in the effect on short-term mortality between standard oxygen therapy and noninvasive ventilation. Furthermore, there were no major differences in treatment efficacy or safety between the two noninvasive ventilation treatments, CPAP and NIPPV.

Meta-analyses and systematic reviews of immediate treatment with noninvasive ventilation in patients with acute cardiogenic pulmonary edema have reported a 47% reduction in mortality.[15] The Three Interventions in Cardiogenic Pulmonary Oedema (3CPO) trial was adequately powered to assess an effect of this magnitude and recruited more patients than the total number of patients included in these analyses and reviews. Although the 95% confidence intervals overlap with results from meta-analyses, the 3CPO trial showed no effect of treatment with noninvasive ventilation on mortality.

Was the study population inappropriate? On the basis of the results of previous studies, we applied strict inclusion and exclusion criteria and completed this large trial. The baseline characteristics and event rates were similar to those in previous studies and indicate that we recruited patients with severe disease. There was no evidence of patient-selection bias, since the 7-day mortality rates among nonrecruited patients (9.9%) were virtually the same as those among patients who were recruited to the trial (9.6%). In keeping

The New England Journal of Medicine
Downloaded from nejm.org on May 2, 2011. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

Table 3. Primary and Secondary End Points for Patients Receiving Standard Oxygen Treatment and Those Receiving Noninvasive Ventilation (CPAP or NIPPV).*

Variable	Standard Oxygen Treatment (N=367)	CPAP or NIPPV (N=702)	Odds Ratio (95% CI)	P Value
Death within 7 days (% of patients)	9.8	9.5	0.97 (0.63 to 1.48)	0.87
Death within 30 days (% of patients)	16.4	15.2	0.92 (0.64 to 1.31)	0.64
Intubation within 7 days (% of patients)	2.8	2.9	1.05 (0.49 to 2.27)	0.90
Admission to critical care unit (% of patients)	40.5	45.2	1.21 (0.93 to 1.57)	0.15
Myocardial infarction (% of patients)				
WHO criteria	24.9	27.0	1.12 (0.84 to 1.49)	0.46
Universal criteria	50.5	51.9	1.06 (0.82 to 1.36)	0.66
			Difference between Means (95% CI)†	
Mean length of hospital stay (days)	10.5	11.4	0.9 (–0.2 to 2.0)	0.10
Mean change at 1 hr after start of treatment‡				
Dyspnea score§	3.9	4.6	0.7 (0.2 to 1.3)	0.008
Pulse rate (beats/min)	13	16	4 (1 to 6)	0.004
Blood pressure (mm Hg)				
Systolic	34	38	3 (–1 to 8)	0.17
Diastolic	22	22	0 (–3 to 3)	0.95
Respiratory rate (breaths/min)	7.1	7.2	0.2 (–0.8 to 1.1)	0.74
Peripheral oxygen saturation (%)	3.5	3.0	–0.4 (–1.4 to 0.6)	0.41
Arterial pH	0.08	0.11	0.03 (0.02 to 0.04)	<0.001
Arterial PaO_2 (kPa)	0.7	–0.6	–1.2 (–2.6 to 0.1)	0.07
Arterial $PaCO_2$ (kPa)	0.8	1.5	0.7 (0.4 to 0.9)	<0.001
Serum bicarbonate level (mmol/liter)	1.7	1.8	0.1 (–0.7 to 1.0)	0.77

* CI denotes confidence interval, CPAP continuous positive airway pressure, NIPPV noninvasive intermittent positive-pressure ventilation, $PaCO_2$ partial pressure of arterial carbon dioxide, PaO_2 partial pressure of arterial oxygen, and WHO World Health Organization. To convert values for PaO_2 and $PaCO_2$ to mm Hg, multiply by 7.50062.

† The difference between means may not equal the difference between the two means for each category of change because of rounding.

‡ Positive values in the Standard Oxygen Treatment and CPAP or NIPPV columns represent improvement in the variable.

§ The patients reported their degree of dyspnea on a visual-analogue scale ranging from 0 (no breathlessness) to 10 (maximal breathlessness).

with previous analyses,[16] there was no interaction between treatment effect and the severity of disease, a result suggesting that the inclusion of those with milder disease did not obscure potential benefits in the sickest patients. We therefore believe that we targeted and assessed the correct patient population.

Was the intervention correctly delivered? More than 80% of the centers had experience with the use of noninvasive ventilation before the start of the trial. There was a comprehensive training program for all centers to ensure the competence and consistency of the operators of the ventilation devices throughout the trial. We used a readily applied portable ventilator that allows both CPAP and NIPPV to be used and is not affected by leaks around the face mask of up to 50 liters per minute. Although we did not measure the concentration of inspired oxygen, the circuit delivers oxygen in concentrations of up to 60%. There was an apparent drop in the partial pressure of arterial oxygen after treatment with noninvasive ventilation at 1 hour, but the size of the decrease was moderate and of questionable clinical relevance. Indeed, in contrast to standard oxygen therapy, there were no treatment failures due to worsening hypoxia in the noninvasive-ventilation groups. The mean pressures in both the CPAP group (10 cm of

The New England Journal of Medicine
Downloaded from nejm.org on May 2, 2011. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

Table 4. Primary and Secondary End Points for Patients Receiving CPAP and Those Receiving NIPPV.*

Variable	CPAP (N=346)	NIPPV (N=356)	Odds Ratio (95% CI)	P Value
Death or intubation within 7 days (% of patients)	11.7	11.1	0.94 (0.59 to 1.51)	0.81
Death within 7 days (% of patients)	9.6	9.4	0.97 (0.58 to 1.61)	0.91
Death within 30 days (% of patients)	15.4	15.1	0.98 (0.64 to 1.49)	0.92
Intubation within 7 days (% of patients)	2.4	3.5	1.48 (0.60 to 3.67)	0.40
Admission to critical care unit (% of patients)	44.5	45.8	1.06 (0.78 to 1.43)	0.73
Myocardial infarction (% of patients)				
WHO criteria	27.2	26.8	0.98 (0.70 to 1.37)	0.90
Universal criteria	49.1	54.7	1.25 (0.93 to 1.69)	0.14
			Difference between Means (95% CI)†	
Mean length of hospital stay (days)	11.3	11.5	0.2 (–1.1 to 1.5)	0.81
Mean change at 1 hr after start of treatment‡				
Dyspnea score§	4.7	4.5	–0.2 (–0.8 to 0.4)	0.52
Pulse rate (beats/min)	17	15	–2 (–5 to 1)	0.26
Blood pressure (mm Hg)				
Systolic	38	37	–1 (–6 to 5)	0.77
Diastolic	23	21	–2 (–6 to 2)	0.31
Respiratory rate (breaths/min)	7.3	7.1	–0.1 (–1.2 to 1.0)	0.82
Peripheral oxygen saturation (%)	3.5	2.6	–0.9 (–2.2 to 0.3)	0.14
Arterial pH	0.12	0.10	–0.01 (–0.02 to 0.00)	0.05
Arterial PaO_2 (kPa)	–1.1	0.0	1.2 (–0.5 to 2.8)	0.16
Arterial $PaCO_2$ (kPa)	1.5	1.4	–0.1 (–0.3 to 0.2)	0.67
Serum bicarbonate level (mmol/liter)	2.3	1.3	–0.9 (–1.8 to 0.0)	0.04

* CI denotes confidence interval, CPAP continuous positive airway pressure, NIPPV noninvasive intermittent positive-pressure ventilation, $PaCO_2$ partial pressure of arterial carbon dioxide, PaO_2 partial pressure of arterial oxygen, and WHO World Health Organization. To convert values for PaO_2 and $PaCO_2$ to mm Hg, multiply by 7.50062.

† The difference between means may not equal the difference between the two means for each category of change because of rounding.

‡ Positive values in the CPAP and NIPPV columns represent improvement in the variable.

§ The patients reported their degree of dyspnea on a visual-analogue scale ranging from 0 (no breathlessness) to 10 (maximal breathlessness).

water) and the NIPPV group (inspiratory and expiratory pressures of 14 cm of water and 7 cm of water, respectively) were similar to those in previous studies.[15,16]

Was the trial intervention ineffective? Irrespective of the method of treatment, noninvasive ventilation produced a greater reduction in respiratory distress and metabolic abnormalities. These findings are consistent with the majority of previous studies investigating the benefits of CPAP and NIPPV[11-14,22,23] and confirm that the therapeutic intervention in our trial was delivered successfully and appropriately. We acknowledge that the improvement in dyspnea (0.7 on a 10-point scale) was moderate,[24] but the visual-analogue scale used is a crude measure of dyspnea, and noninvasive ventilation, when not associated with patient discomfort, was associated with fewer treatment failures due to respiratory distress than was the standard treatment. Finally, despite the theoretical additional benefits of NIPPV as compared with CPAP,[10] we observed no differences in therapeutic efficacy between the two noninvasive-treatment methods.

The New England Journal of Medicine
Downloaded from nejm.org on May 2, 2011. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

Were the meta-analyses wrong? Recent meta-analyses and systemic reviews have included numerous randomized clinical trials. However, the individual trials had small treatment groups that ranged from 9 to 65 patients, with recruitment rates of only 10 to 30% (as compared with the 62% of patients assigned to treatment in the 3CPO trial). In the meta-analyses, the total number of outcome events was below the recommended threshold of 200,[25] which limits the generalizability of their findings. There is concern about reporting, publication, and recruitment bias in individual published studies that will be compounded by pooled analyses. The discrepancy between the results of our large, randomized, controlled trial and previous pooled data is not unique, and the limitations of meta-analyses have been well documented.[26]

The mortality rate in our trial was higher than the rates reported in registry data for patients with acute heart failure (6.7% in the EuroHeart Failure Survey II[27] and 4% in the Acute Decompensated Heart Failure National Registry [ADHERE][28]), and our participants were older than the patients in those registries and were predominantly female. These discrepancies in mortality and in patient characteristics are likely to be related to differences in the study populations. Acute heart failure registries include all patients with decompensated heart failure rather than only those with severe pulmonary edema. Indeed, in the EuroHeart Failure registry, only 16% of the patients had a qualifying diagnosis of acute pulmonary edema.

Mehta and colleagues prematurely terminated their trial comparing CPAP with NIPPV because of concerns about an increased rate of myocardial infarction in the NIPPV group.[29] A subsequent study by Bellone et al. did not replicate this finding and showed no effect of NIPPV on the rate of myocardial infarction.[30] The systematic review by Peter et al. reported a weak relationship between NIPPV and an increase in the rate of myocardial infarction.[16] This finding was largely the result of the weight given to the study by Mehta et al. in the pooled data.[26] The 3CPO trial showed no relationship between the rate of myocardial infarction and treatment with either CPAP or NIPPV.

Previous trials have indicated that the physiological improvement seen with noninvasive ventilation results in a reduction in the rate of tracheal intubation.[11,12] Pooled data from the meta-analysis by Peter et al. suggest that six patients need to be treated with CPAP and seven with NIPPV to avert intubation and mechanical ventilation in one patient.[16] In contrast, the 3CPO trial found no benefit of noninvasive ventilation in reducing the rate of intubation, a result that may reflect the relatively low intubation rates we observed. The reasons for these low rates in our study are unclear but may be related to differences between our study and others in patient populations, concomitant therapies, and thresholds for intubation and mechanical ventilation. Given that the present and previous trials were by necessity open, there is concern about treatment bias as a result of various thresholds for intervention according to treatment allocation. For example, patients receiving standard oxygen therapy may be more likely to undergo intubation than those already gaining the apparent benefit of noninvasive ventilation.

In conclusion, noninvasive ventilatory support delivered by either CPAP or NIPPV safely provides earlier improvement and resolution of dyspnea, respiratory distress, and metabolic abnormalities than does standard oxygen therapy. However, these effects do not result in improved rates of survival. We recommend that noninvasive ventilation (CPAP or NIPPV) be considered as adjunctive therapy in patients with acute cardiogenic pulmonary edema who have severe respiratory distress or whose condition does not improve with pharmacologic therapy.

Supported by a grant (01/43/01) from the Health Technology Assessment Programme of the National Institute for Health Research.

No potential conflict of interest relevant to this article was reported.

The views expressed are those of the authors and do not necessarily reflect those of the United Kingdom National Health Service or the Department of Health.

We thank all emergency department staff who supported this trial by recruiting patients and Dr. Nicholas Boon for his assistance with end-point adjudication.

APPENDIX

The participants in the 3CPO Trial were as follows (all in the United Kingdom): **Trial management group** — A. Gray (chief investigator), D. Newby, C. Kelly, N. Douglas, M. Masson, Royal Infirmary of Edinburgh; S. Goodacre, Northern General Hospital, Sheffield, and University of Sheffield; J. Nicholl, F. Sampson, K. Paulucy, Y. Oluboyede, K. Stevens, University of Sheffield; S. Crane, York Hospital; M. Elliott, P. Plant, St. James University Hospital, Leeds; T. Hassan, Leeds General Infirmary. **Regional research coordinators** — Y. Meades, Leeds General Infirmary; A. Saunderson, E. Mowat, Royal Infirmary of Edinburgh; V. Lawler, E. Gendall, H. Purvis, Frenchay Hospital, Bristol; E. Norwood, Crosshouse Hospital, Kilmarnock; T. Woodrow, Z. Gall, Hope Hospital, Salford; C. Roberts, Royal Devon and Exeter Hospital, Exeter; D. Mill, Torbay Hospital, Torquay; J. Groves, J. Gilks, G. Symmons, Birmingham Heartlands Hospital; Y. Whattam, James Cook University Hospital, Middlesbrough. **Trial steering group** — T. Coats (chair), Leicester Royal Infirmary; R. Davies, Oxford University; M. Elliott, St. James University Hospital, Leeds; S. Goodacre, Northern General Hospital, Sheffield, and

The New England Journal of Medicine
Downloaded from nejm.org on May 2, 2011. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.

University of Sheffield; A. Gray (chief investigator), D. Newby, M. Masson, Royal Infirmary of Edinburgh; T. McDonagh, Royal Brompton Hospital, London; P. Hall, Edinburgh. **Data and safety monitoring committee** — R. Prescott (chair), University of Edinburgh; A. Hargreaves, Falkirk and District Royal Infirmary, Falkirk; C. Selby, Queen Margaret Hospital, Dunfermline; U. MacIntosh, Stirling Royal Infirmary. **Recruiting sites and clinical leaders** (numbers of recruited patients in parentheses) — Royal Infirmary of Edinburgh, A. Gray (161); Southern General Hospital, Glasgow, P. Munro (23); Ninewells Hospital, Dundee, N. Nichol (21); Crosshouse Hospital, Kilmarnock, C. McGuffie (50); Hairmyres Hospital, Kilmarnock, J. Keaney (28); Northern General Hospital, Sheffield, S. Goodacre (136); York Hospital, S. Crane (63); St. James University Hospital, Leeds, S. Bush (56); Leeds General Infirmary, T. Hassan (37); Barnsley Hospital, J. Brenchley (54); Harrogate Hospital, H. Law (19); Pinderfields Hospital, Wakefield, M. Shepherd (8); Frenchay Hospital, Bristol, J. Kendall (68); Royal United Hospital, Bath, D. Williamson (60); Bristol Royal Infirmary, J. Benger (32); Royal Devon and Exeter Hospital, Exeter, G. Lloyd (39); Torbay Hospital, Torquay, S. Cope (31); Hope Hospital, Salford, C. Gavin (29); Manchester Royal Infirmary, J. Butler (28); Whiston Hospital, Prescot, F. Andrews (29); Wythenshawe Hospital, Manchester, D. Walter (21); Warrington Hospital, M. Higgins (11); Birmingham Heartlands Hospital, A. Bleetman (19); Selly Oak Hospital, Birmingham, P. Doyle (30); James Cook University Hospital, Middlesbrough, P. Dissmann (11); Princess Royal University Hospital, Farnborough, I. Stell (5).

REFERENCES

1. Heart disease and stroke statistics — 2005 update. Dallas: American Heart Association, 2005.

2. Felker GM, Adams KF Jr, Konstam MA, O'Connor CM, Gheorghiade M. The problem of decompensated heart failure: nomenclature, classification, and risk stratification. Am Heart J 2003;145: Suppl:S18-S25.

3. Girou E, Brun-Buisson C, Taillé S, Lemaire F, Brochard L. Secular trends in nosocomial infections and mortality associated with noninvasive ventilation in patients with exacerbation of COPD and pulmonary edema. JAMA 2003;290:2985-91.

4. Stevenson R, Ranjadayalan K, Wilkinson P, Roberts R, Timmis AD. Short and long term prognosis of acute myocardial infarction since introduction of thrombolysis. BMJ 1993;307:349-53. [Erratum, BMJ 1993;307:909.]

5. British Thoracic Society Standards of Care Committee. Non-invasive ventilation in acute respiratory failure. Thorax 2002; 57:192-211.

6. Katz JA, Marks JD. Inspiratory work with and without continuous positive airway pressure in patients with acute respiratory failure. Anesthesiology 1985;63: 598-607.

7. Baratz DM, Westbrook PR, Shah PK, Mohsenifar Z. Effect of nasal continuous positive airway pressure on cardiac output and oxygen delivery in patients with congestive heart failure. Chest 1992;102: 1397-401.

8. Lenique F, Habis M, Lofaso F, Dubois-Randé JL, Harf A, Brochard L. Ventilatory and hemodynamic effects of continuous positive airway pressure in left heart failure. Am J Respir Crit Care Med 1997; 155:500-5.

9. Naughton MT, Rahman MA, Hara K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure. Circulation 1995;91:1725-31.

10. Chadda K, Annane D, Hart N, Gajdos P, Raphaël JC, Lofaso F. Cardiac and respiratory effects of continuous positive airway pressure and noninvasive ventilation in acute cardiac pulmonary edema. Crit Care Med 2002;30:2457-61.

11. Bersten AD, Holt AW, Vedig AE, Skowronski GA, Baggoley CJ. Treatment of severe cardiogenic pulmonary edema with continuous positive airway pressure delivered by face mask. N Engl J Med 1991; 325:1825-30.

12. Masip J, Betbesé AJ, Páez J, et al. Noninvasive pressure support ventilation versus conventional oxygen therapy in acute cardiogenic pulmonary oedema: a randomised trial. Lancet 2000;356:2126-32.

13. Kelly CA, Newby DE, McDonagh TA, et al. Randomised controlled trial of continuous positive airway pressure and standard oxygen therapy in acute pulmonary oedema: effects on plasma brain natriuretic peptide concentrations. Eur Heart J 2002;23:1379-86.

14. Nava S, Carbone G, DiBattista N, et al. Noninvasive ventilation in cardiogenic pulmonary edema: a multicenter randomized trial. Am J Respir Crit Care Med 2003;168:1432-7.

15. Masip J, Roque M, Sánchez B, Fernández R, Subirana M, Expósito JA. Noninvasive ventilation in acute cardiogenic pulmonary oedema: systematic review and meta-analysis. JAMA 2005;294:3124-30.

16. Peter JV, Moran JL, Phillips-Hughes JK, Graham P, Bersten AD. Effect of noninvasive positive pressure ventilation (NIPPV) on mortality in patients with acute cardiogenic pulmonary oedema: a meta-analysis. Lancet 2006;367:1155-63.

17. Agarwal R, Aggarwal AN, Gupta D, Jindal SK. Non-invasive ventilation in acute cardiogenic pulmonary oedema. Postgrad Med J 2005;81:637-43.

18. Collins SP, Mielniczuk LM, Whittingham HA, Boseley ME, Schramm DR, Storrow AB. The use of noninvasive ventilation in emergency department patients with acute cardiogenic pulmonary edema: a systematic review. Ann Emerg Med 2006;48:260-9.

19. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. Eur Heart J 2007;28:2525-38.

20. Tavazzi L, Maggioni AP, Lucci D, et al. Nationwide survey on acute heart failure in cardiology ward services in Italy. Eur Heart J 2006;27:1207-15.

21. Gheorghiade M, Abraham WT, Albert NM, et al. Systolic blood pressure at admission, clinical characteristics, and outcome in patients hospitalized with acute heart failure. JAMA 2006;296:2217-26.

22. L'Her E, Duquesne F, Girou E, et al. Noninvasive continuous positive airway pressure in elderly cardiogenic pulmonary edema patients. Intensive Care Med 2004;30:882-8.

23. Crane SD, Elliott MW, Gilligan P, Richards K, Gray AJ. Randomised controlled comparison of continuous positive airways pressure, bilevel non-invasive ventilation, and standard treatment in emergency department patients with acute cardiogenic pulmonary oedema. Emerg Med J 2004; 21:155-61.

24. Karras DJ, Sammon ME, Terregino CA, Lopez BL, Griswold SK, Arnold GK. Clinically meaningful changes in quantitative measures of asthma severity. Acad Emerg Med 2000;7:327-34.

25. Flather MD, Farkouh ME, Pogue JM, Yusuf S. Strengths and limitations of meta-analysis: larger studies may be more reliable. Control Clin Trials 1997;18:568-79.

26. LeLorier J, Grégoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomised, controlled trials. N Engl J Med 1997;337:536-42.

27. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;27:2725-36.

28. Adams KF Jr, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005;149:209-16.

29. Mehta S, Jay GD, Woolard RH, et al. Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. Crit Care Med 1997;25:620-8.

30. Bellone A, Monari A, Cortellaro F, Vettorello M, Arlati S, Coen D. Myocardial infarction rate in acute pulmonary edema: noninvasive pressure support ventilation versus continuous positive airway pressure. Crit Care Med 2004;32:1860-5.

Copyright © 2008 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org on May 2, 2011. For personal use only. No other uses without permission.
Copyright © 2008 Massachusetts Medical Society. All rights reserved.