ORIGINAL CONTRIBUTIONS

EFFECTIVENESS OF PREHOSPITAL CONTINUOUS POSITIVE AIRWAY PRESSURE IN THE MANAGEMENT OF ACUTE PULMONARY EDEMA

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ABSTRACT

Objective. To compare the effectiveness of continuous positive airway pressure (CPAP) with standard pharmacologic treatment in the management of prehospital acute pulmonary edema. **Methods.** Using a nonrandomized control group design, all consecutive patients presenting to two participating emergency medical services (EMS) systems with a field impression of acute pulmonary edema between July 1, 2004, and June 30, 2005, were included in the study. The control EMS system patients received standard treatment with oxygen, nitrates, furosemide, morphine, and, if indicated, endotracheal intubation. The intervention EMS system patients received CPAP via face mask at 10 cm H_2O in addition to standard therapy. **Results.** Ninety-five patients received standard therapy, and 120 patients received CPAP and standard therapy. Intubation was required in 8.9% of CPAP-treated patients compared with 25.3% in the control group ($p = 0.003$), and mortality was lower in the CPAP group than in the control group (5.4% vs. 23.2%; $p = 0.000$). When compared with the control group, the CPAP group had more improvement in respiratory rate (-4.55 vs. -1.81; $p = 0.001$), pulse rate (-4.77 vs. 0.82; $p = 0.013$), and dyspnea score (-2.11 vs. -1.36; $p = 0.008$). Using logistic regression to control for potential confounders, patients receiving standard treatment were more likely to be intubated (odds ratio, 4.04; 95% confidence interval, 1.64 to 9.95) and more likely to die (odds ratio, 7.48; 95% confidence interval, 1.96 to 28.54) than those receiving standard therapy and CPAP. **Conclusion.** The prehospital use of CPAP is feasible, may avert the need for endotracheal intubation, and may reduce short-term mortality.

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INTRODUCTION

Respiratory distress is a frequently encountered complaint among patients treated by emergency medical services (EMS) systems. Thirteen percent of EMS responses are for respiratory distress, second only to minor trauma.[1] Of these, a substantial portion will be due to acute pulmonary edema (APE) secondary to congestive heart failure (CHF).

Approximately five million Americans suffer from heart failure, with an estimated 550,000 new cases diagnosed in the United States each year.[2,3] Reports of short-term mortality for APE vary between 20% and 30%.[4–6] With five-year mortality nearing 50%, CHF is the most common cause of hospitalization in patients older than 65 years and is one of the most expensive diagnoses in the U.S. health care system.[7] Mechanical ventilation and intensive care unit admission are among the most significant independent predictors of hospital costs for these patients.[8] Consequently, effective therapies are needed that reduce mortality, shorten hospital stays, and minimize the need for costly ventilator support.

APE is associated with significant morbidity in the prehospital setting.[9] While many patients respond to oxygen, nitrates, morphine, and furosemide, others do not and develop progressive respiratory failure requiring ventilatory support.[5,6,10] Traditionally, this has been provided by endotracheal intubation and mechanical ventilation. Mechanical ventilation has been shown to decrease the work of breathing, decrease cardiac afterload, and enhance alveolar recruitment, thereby decreasing shunt and improving oxygenation.[11–14] However, the traditional treatment of positive pressure

ventilation is associated with traumatic injury to the upper airway and an increased risk of ventilator-associated pneumonia.[14–17]

While no studies have specifically focused on the success rates and outcomes of patients with CHF who have been intubated in the field, there is ongoing debate concerning the safety and efficacy of prehospital endotracheal intubation. Many patients with APE will be awake, leaving nasotracheal and pharmacologically assisted intubation as the most likely prehospital options. Unfortunately, performing nasotracheal intubation in the field is problematic, with reported success rates varying between 52% and 90%, and pharmacologically assisted intubation has also shown variable success and remains controversial.[18–24]

In an effort to reduce the need for endotracheal intubation and avoid the complications associated with mechanical ventilation, noninvasive approaches to treating APE are gaining popularity. Randomized controlled trials of continuous positive airway pressure (CPAP) have demonstrated a significant reduction in the need for endotracheal intubation and a trend toward reduction in mortality of hospitalized patients with APE.[12,14,25,26] Although it is suggested that the prehospital use of CPAP may be beneficial, to date only two studies have investigated this notion. Kallio et al. conducted a retrospective cohort study in Helsinki, Finland.[27] In their series of 121 patients, CPAP was found to improve oxygenation and decrease respiratory rate, heart rate, and systolic blood pressure, with 9.9% of their patients ultimately requiring intubation. In a prospective case-series analysis, Kosowsky et al. described 19 patients who received prehospital CPAP therapy.[28] Oxygen saturations for these patients improved from an average of 83.3% to 95.4% following CPAP. None of the CPAP-treated patients required field intubation; however, two patients (10.5%) did not tolerate the CPAP mask and required intubation upon arriving in the emergency department. Although both of these studies report encouraging results with prehospital CPAP, the absence of a comparison group makes the interpretation of these findings difficult. Therefore, we sought to determine the impact of CPAP using a nonrandomized control group design.

METHODS

Study Design

We conducted a prospective study of the effectiveness of CPAP using a nonrandomized control group design. Data were obtained prospectively from EMS transport reports, emergency department charts, and hospital discharge records. Patients were enrolled concurrently based on the treating paramedic's field impression of APE. Accuracy of the field impression was evaluated by reviewing the discharge diagnosis in the hospital record.

Pretreatment physiologic variables (oxygen saturation, heart and respiratory rate, dyspnea rating, and systolic and diastolic blood pressure) were obtained from the first set of vital signs recorded on-scene. Posttreatment physiologic variables were obtained from the final set of vital signs measured before patient transfer in the emergency department. The dyspnea rating was self-reported by the patient using an ordinal scale ranging from 0 (no dyspnea) to 10 (extreme dyspnea). Improvement in dyspnea level was also self-reported using a nominal scale (yes or no) just prior to patient transfer in the emergency department. Patients rated their improvement in reference to their perceived degree of dyspnea at the time of EMS arrival on-scene.

This study included all eight clinically important outcome measures for the evaluation of prehospital treatment of APE as identified by Welsford and Morrison,[29] and all of the outcome and risk adjustment measures recommended by Keim et al., with the exception of peak expiratory flow rate and the substitution of the verbal dyspnea scale for the visual analog dyspnea scale.[30]

Endotracheal intubation was the primary end point and was measured as any field intubation attempt or the need for intubation at any point during the hospital stay. Secondary outcome measures included mortality, hospital length of stay, and changes in physiologic variables. All patients were followed through hospital discharge or death.

Population and Setting

All consecutive adult patients (18 years or older) transported by two participating EMS systems between July 1, 2004, and June 30, 2005, with a field diagnosis of acute cardiogenic pulmonary edema were enrolled. Study subjects for the CPAP group were patients transported by a county government–based EMS system with an annual call volume of approximately 30,000 calls and an average emergency response time of eight minutes. CPAP had been used in this system for one year before this study. Patients were transported to one of two participating hospitals within the county. One hospital is a Level 1 trauma center with 801 inpatient beds and 38 emergency department beds with an annual volume of 64,000 emergency department visits. The second hospital has 906 inpatient beds and a 45-bed emergency department with an annual volume of 80,000 emergency department visits.

Control subjects were patients transported by a second EMS system with demographics similar to the first. This system is also a county government–based EMS system with a tiered response that shares a common border with the intervention EMS system. The annual call volume is approximately 36,000 with an average emergency response time of 7.5 minutes. Patients were

TABLE 1. Power Calculations for Differences in Outcomes Between CPAP and Standard Therapy

Variable	CPAP	Standard Therapy	Difference	Power* (N = 100)
Oxygen saturation (mean change)	6.2	3.7	2.5	0.940
Respiratory rate (mean change)	−12	−8	−4	0.940
Heart rate (mean change)	−16	−12	−4	0.940
Systolic blood pressure (mean change)	−38	−41	3	0.940
Intubation rate	0.08	0.39	−0.31	0.999
Mortality rate	0.101	0.177	−0.076	0.350
Hospital length of stay	9.0	9.5	−0.5	0.093

CPAP = continous positive airway pressure.
*$\alpha = 0.05$.

transported to one of two participating hospitals in the county. The first hospital is a Level 2 trauma center with 529 inpatient beds and an annual volume of 60,000 emergency department visits. The second hospital has 220 inpatients beds and an annual volume of 44,000 emergency department visits.

Human Subject Review

Institutional review board approval for this study was obtained from Western Carolina University and from each of the receiving hospitals. A waiver of informed consent was granted by the institutional review board.

Experimental Protocol

Patients in the control group were treated according to preexisting patient treatment algorithms, including the use of oxygen, intravenous access, electrocardiography, nitroglycerin, morphine, and furosemide. Under preexisting protocols, patients in the CPAP group received treatment similar to the control group but with the addition of CPAP. CPAP was administered using the Caradyne Whisperflow System (Caradyne Limited, Galway, Ireland). The system has an oxygen-powered flow generator with a variable flow rate of 0 to 140 L/min and a variable fraction of inspired oxygen (F_iO_2) of 35%–95%. Flow is delivered via a disposable ventilator circuit to a soft-seal mask, with a resistor valve set to maintain CPAP at 10 cm H_2O. The operator adjusts flow and F_iO_2 depending on tolerance, pulse oximetry, and dyspnea. In accordance with preexisting protocols, face mask intolerance or any deterioration in mental status, vital signs, or degree of dyspnea were reported to medical control and managed appropriately, including discontinuation of CPAP and/or endotracheal intubation.

Sample Size and Power

The primary end point was the difference in endotracheal intubation rates. Because no suitable reports of intubation rates exist for prehospital patients receiving CPAP, power calculations for intubation were based on hospitalized patients. Using pooled data among hospitalized patients from Bersten et al.,[6] Lin et al.,[10] and Takeda et al.,[31] power calculations for intubation rates were based on an 8% intubation rate for patients treated with CPAP and a 39% rate for non–CPAP-treated patients. Secondary end points included differences in mortality, differences in hospital length of stay, and changes in physiologic variables. Power calculations for hospital length of stay were based on the findings of Lin et al.,[10] and mortality power calculations were based on the pooled data of Pang et al.[14] Power calculations for differences in the mean change in oxygen saturation, respiratory rate, systolic blood pressure, and heart rate were based on the findings of Crane et al. (Table 1).[32] When standard deviations from these studies were not adequately reported by their authors for the purpose of calculating power, the standard deviation was set equal to twice the mean observed difference.

A sample of 100 subjects in the CPAP and control groups provided adequate power for the primary outcome variables of interest.

Analytical Methods

All data were entered into a Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA) and later imported into SPSS 11.0 (SPSS Inc., Chicago, IL) and SAS 9.1 (SAS Institute, Inc., Cary, NC) for analysis. All statistical analyses were two-tailed with statistical significance established at $p \leq 0.05$.

All demographic variables, baseline characteristics, and treatment variables measured on an interval scale were tested for equivalency between the CPAP and control groups using the t-test or, when variables were not normally distributed, the Mann–Whitney rank sum test. Variables measured on an ordinal scale were analyzed using the Mann–Whitney rank sum test.

A univariate comparison of outcome variables (intubation rate, mortality rate, hospital length of stay, patient-reported improvement in dyspnea, and mean changes in physiologic variables) between the CPAP and control groups was performed using a t-test, Mann–Whitney rank sum test, chi-square test with Yate's correction, or Fisher's exact test as appropriate.

Frequencies were calculated for the CPAP complication variables of gastric distention, vomiting, hypotension, and mask intolerance.

Binary logistic regression was used to explore the impact of CPAP on mortality and the need for intubation, while controlling for other potentially confounding predictor variables. All potential predictor variables were entered into the regression model using a forward stepwise procedure based on the likelihood ratio, with all statistically significant variables retained in the final model. A second logistic regression model was developed using a data set limited to the subset of patients with a confirmed discharge diagnosis of APE.

Hospital length of stay was modeled using Kaplan–Meier survival analysis methods with patients stratified by treatment groups of CPAP versus no CPAP. Differences between groups were assessed using the Wilcoxon statistic. Additional survival analysis modeling of hospital length of stay was performed using a Cox proportional hazards model to control for potentially confounding predictor variables.

RESULTS

Between July 1, 2004, and June 30, 2005, 215 patients received a field diagnosis of APE and were enrolled in the study. Of these, 52 (24%) ultimately received a hospital discharge diagnosis other than APE (Table 2). Because of the potential confounding effects of misdiagnosis, data were analyzed for all patients on an intention-to-treat basis and then repeated on the subset of patients with confirmed APE.

Of the 215 patients enrolled, 120 (55.8%) received CPAP. For patients with confirmed APE, the study groups were not significantly different in baseline characteristics with the exception of age and pretreatment dyspnea score. The CPAP group was younger (70.9 vs. 75.3 years; $p = 0.05$) and reported a higher dyspnea score (8.68 vs. 7.67; $p = 0.01$) than the control group. When all patients are included, there was a greater degree of dissimilarity between the control and CPAP groups. Patients in the CPAP group tended to be younger (70.1 vs. 73.9 years; $p = 0.03$) but reported a greater degree of dyspnea as measured by the dyspnea score (8.84 vs. 7.47; $p = 0.00$). In addition, the baseline respiratory rate (33.47 vs. 28.01 breaths/min; $p = 0.00$) and systolic (180.6 vs. 163.8 mm Hg; $p = 0.00$) and diastolic (100.4 vs. 92.0 mm Hg; $p = 0.03$) blood pressures were elevated in comparison with the control group. Table 3 summarizes the baseline characteristics of the study population.

TABLE 2. Final Diagnoses of Patients Misdiagnosed by Emergency Medical Services

	CPAP		Control	
Diagnosis	n	%	n	%
Acute respiratory failure	2	9.5	2	6.5
Anemia	0	0.0	1	3.2
Atrial fibrillation	1	4.8	0	0.0
Bronchitis	1	4.8	1	3.2
Cancer	1	4.8	2	6.5
Chronic obstructive pulmonary disease	11	52.3	10	32.3
Hypothermia	0	0.0	1	3.2
Lupus	0	0.0	1	3.2
Myocardial infarction	2	9.5	0	0.0
Pneumonia	3	14.3	9	29.1
Pneumothorax	0	0.0	1	3.2
Pulmonary embolus	0	0.0	1	3.2
Sepsis	0	0.0	1	3.2
Other	0	0.0	1	3.2
Total	21	100	31	100

CPAP = continous positive airway pressure.

The mean prehospital time, measured as the interval between arrival of EMS at the scene and arrival at the emergency department, was similar between the CPAP and control groups. During this time, patients received the standard treatments of oxygen administration, electrocardiography, intravenous access, sublingual nitroglycerin, and intravenous furosemide and morphine sulfate. While the percentage of patients receiving morphine was similar between the two groups, a larger proportion of patients in the control group received at least one dose of furosemide and nitroglycerin than in the CPAP group. Furthermore, the mean dose of furosemide and morphine was higher in the control group, whereas the mean dose of nitroglycerin was higher in the CPAP group. Treatment characteristics are summarized in Table 3.

The mean duration of prehospital CPAP was 16.31 (±9.12) minutes. Of the 120 patients receiving CPAP, 23 patients (19%) presented with mask intolerance. However, discontinuation of CPAP was required in only one patient (0.8%). Hypotension (systolic blood pressure <90 mm Hg) developed in 4 patients (3.3%), and two patients (1.6%) developed gastric distention.

Among patients in the control group, 19 (20.0%) received CPAP in the emergency department, and an additional three patients (3.15%) were placed on CPAP during their hospital stay for a total of 22 patients (23.15%) ultimately receiving hospital CPAP. Of these, three patients eventually required hospital intubation. An additional 21 patients in the control group who did not receive CPAP during their hospital stay required intubation. Overall, 45.2% of patients in the control group ultimately received CPAP and/or intubation during their hospital stay.

When considering all patients, 24 (25.26%) of the patients in the control group required intubation compared with 10 patients (8.92%) in the treatment group ($p = 0.003$). Of these, seven (7.36%) of the patients in the control group required field intubation compared with five (4.20%) in the CPAP group ($p = 0.483$). Of the subset of patients with confirmed APE, none of the CPAP-treated patients required field intubation

TABLE 3. Univariate Analysis of Baseline Characteristics and Treatment

	All Patients			Patients With Confirmed Pulmonary Edema		
	CPAP	Control	p-value	CPAP	Control	p-value
Baseline characteristics						
No.	120	95		90	64	
Age (yr)	70.12	73.92	0.034	70.90	75.30	0.048
Gender (% male)*	42.50	37.9	0.587	45.55	34.37	0.221
Pretreatment respiratory rate (breaths/min)*	33.47	28.01	0.000	33.69	28.83	0.694
Pretreatment pulse rate (beats/min)	108.57	105.87	0.403	107.10	105.44	0.664
Pretreatment systolic blood pressure (mm Hg)	180.63	163.76	0.003	182.72	170.71	0.054
Pretreatment diastolic blood pressure (mm Hg)	100.49	92.08	0.033	101.07	96.17	0.285
Pretreatment oxygen saturation (%)*	85.78	86.18	0.586	85.44	87.13	0.392
Pretreatment Glasgow Coma Scale score*	14.55	13.93	0.739	14.64	13.88	0.821
Pretreatment dyspnea score*	8.84	7.47	0.000	8.68	7.67	0.011
Treatment characteristics						
Mean prehospital time (min)	31.54	29.62	0.077	31.56	29.06	0.082
Prehospital furosemide*						
Patients receiving (%)*	47.50	91.57	0.000	54.44	90.62	0.000
Mean dose (mg)*	45.79	62.84	0.005	45.31	63.74	0.008
Prehospital morphine						
Patients receiving (%)*	19.16	16.84	0.794	22.22	20.31	0.932
Mean dose (mg)	1.22	5.00	0.000	1.30	5.38	0.000
Prehospital nitroglycerin						
Patients receiving (%)*	52.50	74.73	0.001	55.55	76.56	0.012
Mean dose (mg)*	0.62	0.44	0.000	0.62	0.44	0.000
Mean CPAP time (min)	16.31			16.40		

CPAP = continous positive airway pressure.
*Analyzed using nonparametric tests.

compared with six patients (9.37%) in the control group (p = 0.011), and 18 (28.12%) of the patients in the control group required intubation at some point during their treatment compared with six (6.66%) of the patients in the CPAP group (p = 0.001). Intubation rates are summarized in Table 4.

Logistic regression coefficients for intubation are shown in Table 5. All relevant baseline variables as well as drug administration totals from Table 3 were submitted based on a forward stepwise procedure for maximizing the likelihood ratio. The baseline and treatment variables retained in the final model included pretreatment oxygen saturation (odds ratio, [OR], 0.953; 95% confidence interval, [CI], 0.920 to 0.987), pretreatment pulse rate (OR, 1.042; 95% CI, 1.020 to 1.064), and no CPAP (OR, 4.045; 95% CI, 1.644 to 9.951) on an intention-to-treat basis. For the subset with confirmed APE, patients who did not receive CPAP had an OR for intubation of 4.21 (95% CI, 1.088 to 16.282). Pretreatment oxygen saturation (OR, 0.926; 95% CI, 0.877 to 0.977) and pretreatment respiratory rate (OR, 0.910; 95% CI, 0.835 to 0.991) were also significant predictors of intubation.

The overall mortality rate was 5.35% in the CPAP group, which was significantly lower than the 23.15% rate observed in the control group (p = 0.000). The mortality rate among patients with a confirmed diagnosis of APE was 5.55% in the CPAP group and 25.00% in the control group (p = 0.001). Mortality rates are summarized in Table 4.

TABLE 4. Univariate Analysis of Outcomes by Mode of Treatment

	All Patients			Patients With Confirmed Pulmonary Edema		
	CPAP	Control	p-value	CPAP	Control	p-value
Intubation, field only (%)*	4.20	7.36	0.483	0.00	9.37	0.011
Intubation, anytime (%)*	8.92	25.26	0.003	6.66	28.12	0.001
Mortality (%)*	5.35	23.15	0.000	5.55	25.00	0.001
Mean hospital length of stay (days)*	5.58	7.66	0.755	5.36	7.19	0.989
Mean change in oxygen saturation (%)*	5.66	8.17	0.273	6.05	6.98	0.714
Mean change in respiratory rate (beats/min)*	−4.55	−1.81	0.001	−4.63	−2.34	0.015
Mean change in pulse rate (beats/min)*	−4.77	0.82	0.013	−5.57	−0.619	0.019
Mean change in systolic blood pressure (mm Hg)*	−15.11	−14.00	0.321	−14.85	−15.85	0.514
Mean change in dyspnea score*	−2.11	−1.36	0.008	−2.25	−1.28	0.011
Patient reported improvement (%)*	70.00	67.36	0.791	74.44	65.62	0.314

CPAP = continous positive airway pressure.
*Analyzed using nonparametric tests.

TABLE 5. Logistic Regression Model Results for Intubation

Parameter	Estimate (B)	OR	p-value	95% Confidence Interval
All patients*				
Pretreatment O_2 saturation	−0.048	0.953	0.006	0.920, 0.987
CPAP†	1.398	4.045	0.002	1.644, 9.951
Pretreatment pulse rate	0.041	1.042	0.000	1.020, 1.064
Constant	−3.016	0.049	0.100	
Patients with confirmed pulmonary edema‡				
Pretreatment O_2 saturation	−0.077	0.926	0.005	0.877, 0.977
CPAP†	1.437	4.210	0.037	1.088, 16.282
Pretreatment respiratory rate	−0.095	0.910	0.030	0.835, 0.991
Constant	6.700	812.559	0.015	

OR, odds ratio; CPAP, continuous positive airway pressure.
*Accuracy of the prediction of the model is 83.9%. −2 Log likelihood = 141.82; model chi-square = 31.18; p = 0.000.
†OR represents intubation risk associated with nonuse of CPAP.
‡Accuracy of the prediction of the model is 88.9%. −2 Log likelihood = 71.29; model chi-square = 22.07, p = 0.000.

Using logistic regression to control for differences in baseline physiologic and treatment variables, the overall OR of death was 7.48 (95% CI, 1.963 to 28.547) for all non–CPAP-treated patients on an intention-to-treat basis and 7.69 (95% CI, 1.591 to 37.208) for patients with confirmed APE who did not receive CPAP. Age was a significant predictor of mortality for all patients (OR, 1.081; 95% CI, 1.025 to 1.141) and for the subset with confirmed APE (OR, 1.071; 95% CI, 1.009 to 1.138). Total prehospital nitroglycerin dose was also a predictor of mortality for all patients (OR, 0.019; 95% CI, 0.001 to 0.464) as well as the subset with confirmed APE (OR, 0.019; 95% CI, 0.000 to 0.709). Pretreatment oxygen saturation was a significant marker for mortality overall (OR, 0.944; 95% CI, 0.902 to 0.989) but was not significant when limited to the subset of patients with confirmed APE. Coefficients of the regression model for mortality are provided in Table 6.

Of all the patients who survived, the average hospital length of stay was 5.58 days in the CPAP group compared with 7.66 days in the control group (p = 0.755). Of the survivors with a discharge diagnosis of APE, the mean length of stay was 5.36 days in the CPAP group and 7.19 days in the control group (p = 0.989) (Table 4). A Kaplan–Meier curve of length of stay of the survivors stratified by treatment group showed no difference between groups (p = 0.75). The Kaplan–Meier curve is provided in Figure 1. After controlling for differences in baseline physiologic and treatment variables using a Cox proportional hazards model, no statistically significant difference in length of stay was apparent.

DISCUSSION

We found substantial differences in outcomes in this prospective comparison of CPAP and conventional therapy in the management of prehospital APE. When controlling for differences in baseline physiologic variables and prehospital medication administration, the use of CPAP was associated with a substantially lower rate of intubation. Intubation was performed in 25.26% of control patients compared with 8.92% of CPAP-treated patients for an absolute risk reduction of 16.34%.

If CPAP alone was the cause of this difference, then six patients with presumed APE would need to be treated with CPAP to prevent one intubation. Similarly, mortality was 23.15% in the control group compared with 5.35% in the CPAP group, yielding an absolute risk

TABLE 6. Logistic Regression Model Results for Mortality

Parameter	Estimate (B)	OR	p-value	95% Confidence Interval
All patients*				
Pretreatment O_2 saturation	−0.057	0.944	0.016	0.902, 0.989
CPAP†	2.013	7.487	0.003	1.963, 28.547
Age	0.078	1.081	0.004	1.025, 1.141
Total nitroglycerin dose	−3.959	0.019	0.015	0.001, 0.464
Constant	−3.480	0.031	0.144	
Patients with confirmed pulmonary edema‡				
CPAP†	2.040	7.693	0.011	1.591, 37.208
Age	0.069	1.071	0.025	1.009, 1.138
Total nitroglycerin dose	−3.974	0.019	0.032	0.000, 0.709
Constant	−7.539	0.001	0.002	

OR, odds ratio; CPAP, continuous positive airway pressure.
*Accuracy of the prediction of the model is 90.2%. −2 Log likelihood = 77.87; model chi-square = 31.14; p = 0.000.
†OR represents mortality risk associated with nonuse of CPAP.
‡Accuracy of the prediction of the model is 88.9%. −2 Log likelihood = 59.45; model chi-square = 22.17; p = 0.000.

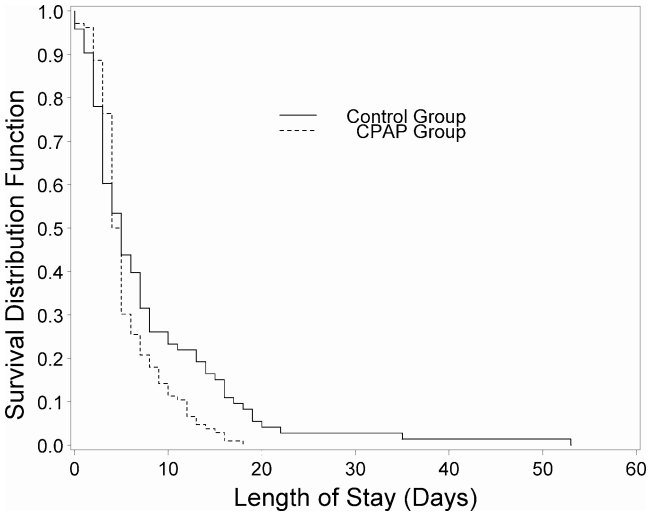

FIGURE 1. Kaplan–Meier curve of length of stay for survivors stratified by treatment group.

reduction of 17.8% and a number needed to treat of 6 to prevent one death. While there are no prehospital studies with control groups with which to compare our findings, reports of hospitalized patients have shown CPAP to decrease the need for intubation by 26% and reduce mortality by 6.6%.[14] However, dissimilarities in the patient populations between hospitalized and prehospital patients make a direct comparison problematic. Although our study design does not allow us to definitively attribute these findings solely to CPAP use, we are nonetheless encouraged by these results. We believe that any decrease in the need for intubation is in itself a positive finding given the recent concern for success rates and complications when performing this procedure in the field.[33–40] Even for patients who ultimately require intubation, CPAP may serve as a temporizing measure for patients until they arrive in the emergency department, where their airway can be managed in a more controlled environment.

Notwithstanding the differences in mortality and intubation rates, CPAP improved most of the physiologic variables, including dyspnea scores, to a greater extent than did conventional therapy. The exception was oxygen saturation. Similar to the findings of Crane et al. and Moritz et al., our data did not demonstrate a statistically significant improvement in oxygenation in comparison with standard therapy.[32,41] We offer two possible explanations for this finding. The first explanation concerns the timing of reassessment. In the study by Moritz et al., oxygen saturation was measured at 30 minutes, and even though there was significant improvement in other physiologic parameters, there was no significant improvement in oxygen saturation.[41] Similarly, Crane et al. found that oxygen saturation was significantly lower in the CPAP group compared with controls at 10, 20, and 30 minutes following randomization, but this disparity disappeared at 60 minutes.[32] It is possible that improvements in oxygen saturation lag behind those of other physiologic variables. Given the mean CPAP time of 16 minutes in our patients, it is possible that oxygen saturations may not have had time to plateau in the CPAP group.

The second plausible explanation for the lower gain in oxygen saturation is a lower delivered F_iO_2 with CPAP. Eighty percent of control patients received oxygen via a non-rebreather mask compared with 62% of CPAP-treated patients. For patients in the CPAP group, the non-rebreather mask was eventually removed and replaced with CPAP. The CPAP unit used in this study has an ungraduated control that varies F_iO_2 from 35% to 95% and was adjusted in response to the patient's oxygen saturation. Only those patients provided the maximum F_iO_2 allowed by the device received oxygen concentrations similar to the patients in the control group. Consequently, delivered oxygen concentrations may have been lower in the CPAP group.

Hospital length of stay was nearly two days shorter in the CPAP group compared with the control group, although this difference did not reach statistical significance. Most previous comparisons have also yielded a trend toward a decrease in length of stay but were underpowered to detect a statistically significant effect. We believe our results suffer from a similar lack of power.

Very few complications were encountered with the use of CPAP. The soft-seal mask used to deliver CPAP was particularly well tolerated in our patients. Mask intolerance was encountered in 23 (19%) of our patients, with only one (0.83%) significant enough to warrant discontinuing treatment. This is consistent with the findings of Kallio et al., who reported only one instance of mask intolerance requiring suspension of treatment in their series of 110 patients.[27] Consistent with previous investigations that report a low incidence of hypotension, systolic blood pressure decreased to 90 mm Hg in only 4 (3.3%) of our patients.[4,27,28,41]

In addition to the potential benefits of CPAP on short-term survival, our data also revealed a negative association between nitrate treatment and mortality. Nitrate use was independently significant in our logistic regression model of mortality (OR, 0.019). In contrast, we found no apparent benefit of morphine and furosemide. Although the number of patients receiving these drugs in our sample was small, these results are similar to previous investigations of prehospital APE. Bertini et al. reported an OR for death of 0.29 (95% CI, 0.09 to 0.97) for patients treated with nitroglycerin in a series of 640 patients but failed to identify any benefit of furosemide or morphine.[42] Similarly, Hoffman and Reynolds compared various prehospital drug regimens and concluded that nitroglycerin was beneficial, whereas furosemide and morphine had no additive effect when combined with nitroglycerin and were occasionally detrimental.[43] In emergency department patients, Sacchetti et al. found that higher-dose

nitroglycerin reduced the need for intubation but found that morphine administration resulted in higher intubation rates and higher intensive care unit admission rates. Similar to the other studies, they found no positive effect of furosemide.[44] Although our study design does not permit us to reach clear conclusions on the effectiveness of morphine and furosemide, taking into consideration the results of previous investigations, the benefits of morphine and furosemide remain suspect.

LIMITATIONS

It is difficult to relate a brief period of CPAP in the prehospital setting to mortality several days or weeks later. Our findings are limited by our lack of randomization and the difficulties of accurately quantifying disease severity using only the clinical data available in the prehospital setting. Consequently, our ability to control for severity of disease is imperfect and some variation did arise in our data set. The patients in the control group tended to be older, whereas the CPAP group showed a greater degree of distress as evidenced by higher baseline respiratory rates, blood pressures measurements, and pretreatment dyspnea scores. Furthermore, blood pressure measurements and respiratory rates were assessed manually and with unknown reliability. Inaccuracies in blood pressure measurements due to ambulance noise have been previously reported.[45] It is unclear how these limitations in physical assessments and variations in baseline characteristics may have affected our findings.

While our sample size was adequate for evaluating the primary outcome measures, we lacked statistical power to detect differences in hospital length of stay. Although our study as designed would have been underpowered to detect a 7.6% absolute difference in mortality rate, our actual difference in mortality was substantially larger and did achieve statistical significance.

Patient selection in our study was dependent on the accuracy of paramedics to correctly identify patients with pulmonary edema. Paramedic diagnosis of APE agreed with the final discharge diagnosis in 76% of our cases, with chronic obstructive pulmonary disease and pneumonia representing the most frequently misdiagnosed conditions. This is consistent with previous reports of paramedic false-positive rates of 11%–32%, which also reported chronic obstructive pulmonary disease and pneumonia-associated dyspnea as the conditions most often mistaken for APE.[9,27,28,43,46–48] Underscoring the difficulty of diagnosing prehospital APE based on clinical presentation alone is the 31% false-positive rate reported by Kallio et al., in which the diagnoses were made in the field by physicians who routinely staff the ambulances in Helsinki, Finland.[27] Arguably, the diagnostic accuracy of paramedics should not be expected to exceed that of physicians working in the field under similar circumstances. Consequently, given the well-known inaccuracies of clinical signs for diagnosing CHF and the difficulty in differentiating CHF from chronic obstructive pulmonary disease, some degree of prehospital misdiagnosis is probably unavoidable.[46,49,50]

Sampling bias may also have been introduced into our study because we included only those patients diagnosed with APE by paramedics in the field. No effort was made to identify any patients with an ultimate diagnosis of APE who were not diagnosed by paramedics and therefore were not enrolled in the study. This limitation results in the true utility of CPAP being understated, because some of the patients with unrecognized APE may have benefited from CPAP. However, the introduction of CPAP in any EMS system will likely include some degree of misdiagnosis by paramedics. Our 24% false-positive rate is consistent with previously reported misdiagnosis rates and, although we did not assess our rate of false-negative diagnosis, we have no reason to believe it to be substantially different from other urban EMS systems. We therefore believe our findings to be consistent with the expected benefit of CPAP when implemented in other clinical settings.

With the exception of the addition of CPAP, the pulmonary edema treatment protocols of the participating EMS systems were virtually identical. However, some variation in treatment between the CPAP and control groups was apparent. A larger proportion of patients in the control group received furosemide and nitroglycerin than in the CPAP group. Although the average total dosage of nitroglycerin was greater in the CPAP group, the CPAP group received substantially less furosemide and morphine than did the control group. In addition, the CPAP unit used in our study provided a continuously variable liter flow and F_iO_2. It was not possible to identify the precise flow rate or delivered oxygen concentration, and it is possible that some patients received greater flow rates and oxygen concentrations than others.

Our patients were transported to four different hospitals, where continued treatment may not have been uniform. It has been demonstrated that care of patients with CHF can vary considerably between institutions and among practitioners, with subsequent variability in outcomes.[51] Although our hospitals were similar, there was no attempt to control for any potential variations in hospital treatment. It is possible that the benefits of CPAP realized in our study are not entirely independent of variations in hospital treatment.

CONCLUSIONS

Despite the methodological limitations of our study design, we are encouraged by our results. For prehospital patients with presumed APE, patients in the CPAP treatment group had reduced mortality and a lower rate

of endotracheal intubation. Furthermore, when compared with the control group, the CPAP group demonstrated a greater degree of improvement in most physiologic variables, including dyspnea score. We were also able to confirm the positive association between prehospital administration of nitroglycerin and mortality reported in previous studies. However, these are preliminary results, and additional randomized trials are needed to fully assess the impact of CPAP in the management of prehospital APE. Such studies should control for differences in hospital treatment, evaluate the role of nitrates and other medications when used in combination with CPAP, and should be sufficiently powered to detect any significant differences in hospital length of stay.

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