European Heart Journal (2002) **23,** 1379–1386
doi:10.1053/euhj.2001.3156, available online at http://www.idealibrary.com on IDEAL®

Randomised controlled trial of continuous positive airway pressure and standard oxygen therapy in acute pulmonary oedema

Effects on plasma brain natriuretic peptide concentrations

C. A. Kelly[1], D. E. Newby[2], T. A. McDonagh[3], T. W. Mackay[1], J. Barr[1], N. A. Boon[2], H. J. Dargie[3] and N. J. Douglas[1]

[1]*Department of Respiratory Medicine, Royal Infirmary, Edinburgh, Scotland, U.K.;* [2]*Department of Cardiology, Royal Infirmary, Edinburgh, Scotland, U.K.;* [3]*Clinical Research Initiative in Heart Failure, Western Infirmary, Glasgow, Scotland, U.K.*

Aims The study aim was to compare the effects of continuous positive airway pressure (CPAP) on clinical outcomes and plasma neurohormonal concentrations in patients with acute pulmonary oedema.

Methods and Results In addition to standard therapy, 58 consecutive patients were randomized to receive 60% inhaled oxygen with or without CPAP at 7·5 cmH_2O pressure. Clinical variables, symptoms and oxygenation were monitored and plasma epinephrine, norepinephrine and brain natriuretic peptide (BNP) concentrations estimated at 0, 1, 6 and 24 h. CPAP was associated with less breathlessness at 1 h ($P<0·001$), no treatment failures and more rapid resolution in respiratory rate ($P<0·001$), heart rate ($P<0·001$) and acidosis ($P<0·005$). Length of hospital stay was similar but there was a trend for a reduction in overall hospital mortality in the CPAP group ($0·10>P>0·05$). Plasma BNP concentrations rose progressively ($P<0·001$) before falling below admission concentrations at 24 h. Plasma neurohumoral concentrations were unaffected by CPAP treatment but were elevated in patients who died or had acute myocardial infarction.

Conclusion CPAP produces a more rapid clinical and symptomatic improvement in patients with acute pulmonary oedema, particularly within the first hour. CPAP is a useful adjunctive treatment in the early management of acute heart failure.
(Eur Heart J, 2002; 23: 1379–1386, doi:10.1053/euhj.2001.3156)

Key Words: Heart failure, ventilation, natriuretic peptides, oedema, oxygen.

See doi: 10.1053/euhj.2002.3247 for the Editorial comment on this article

Introduction

Acute pulmonary oedema is a common medical emergency. Conventional treatment includes the use of oxygen therapy, opiates, diuretics and vasodilators. Patients who fail to respond to such treatment have traditionally required intubation and ventilation with the associated potential complications[1,2].

In recent years non-invasive methods of ventilatory support such as continuous positive airway pressure (CPAP) and bilevel ventilation, have been used to avoid the need for endotracheal intubation. Non-invasive positive pressure ventilation (NIPPV) is achieved using a tightly fitting nasal or face mask, and is able to improve oxygenation, reduce the work of breathing and to improve cardiac output[3–6]. CPAP maintains a positive pressure throughout the respiratory cycle while bilevel ventilation provides a greater pressure to aid inspiration and a lower pressure during expiration. Previous studies have suggested, but not proved, that CPAP may reduce the need for intubation and ventilation but does not affect the length of hospital stay or overall mortality[7–9]. Although bilevel ventilation has been shown to improve

Revision submitted 3 December 2001, and accepted 4 December 2001.

Correspondence: Dr Catherine Kelly, Acute Medicine Directorate, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW, Scotland, U.K.

0195-668X/02/$35.00

haemodynamic variables more rapidly than standard oxygen therapy or CPAP, the data on this form of treatment in acute heart failure are limited[10,11].

Heart failure is characterized by activation of several neurohormonal systems, particularly the sympathetic nervous system and the renin-angiotensin-aldosterone system[12–14]. In addition, counteregulatory mechanisms such as the natriuretic peptide system are activated producing increased plasma concentrations of both atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP)[15,16]. Although BNP is a good indicator of subsequent prognosis and morbidity in chronic heart failure[17,18], there is little information on the significance of BNP in acute heart failure.

The aim of this study was to compare the effects of oxygen therapy and CPAP on clinical outcomes and plasma neurohormonal concentrations in patients presenting with acute pulmonary oedema.

Methods

Study population

Patients requiring hospitalization for acute pulmonary oedema were recruited into the trial. Fifty-eight consecutive patients fulfilling the following entry criteria were recruited: (1) acute onset of breathlessness (within 6 h), (2) respiratory rate >20/min, (3) bilateral basal crackles on chest auscultation, and (4) typical chest X-ray appearance of pulmonary oedema. Patients were excluded if they had chest X-ray features consistent with pneumonia or pneumothorax, or if they had received pre-hospital treatment with interventions other than oxygen, diuretics or opiates. The trial was conducted in accordance with the Declaration of Helsinki (1989) of the World Medical Association and with the approval of the local research ethics committee. All patients gave written informed consent although, in some cases, the clinical condition necessitated initial witnessed verbal consent before subsequent written consent could be obtained.

Study protocol

Patients had baseline measurements of heart rate, blood pressure, respiratory rate, oxygen saturation, creatine kinase and arterial blood gases. Standard therapy for acute pulmonary oedema was administered: 50–100 mg intravenous frusemide, 5 mg buccal nitrate (if systolic blood pressure >90 mmHg) and 2·5–10 mg intravenous morphine sulphate. Patients were randomized, by balanced blocks using sealed envelopes, to receive either 60% oxygen delivered through a Venturi mask or CPAP (Vital Signs, NJ, USA) using a full face mask with a pressure of 7·5 cm water and an inspired oxygen concentration of 60% confirmed by an integral oxygen analyser. Treatment was commenced in the emergency department and continued in the high dependency unit for a minimum period of 6 h, or until no longer clinically indicated. Further drug therapy was given at the discretion of the treating physician.

Measurements

Arterial blood gas analysis was performed on admission and repeated 1 h after commencing treatment. Heart rate, blood pressure, respiratory rate and oxygen saturation were recorded on admission and at 1, 6 and 24 h. Blood samples were taken for the estimation of plasma neurohormone concentrations on study entry. Epinephrine and norepinephrine concentrations were repeated at 1 h and BNP concentrations at 1, 6 and 24 h after starting treatment. Venous blood was withdrawn and 10 ml admixed with each of 1 ml of 1% disodium EDTA and 1 ml of disodium EDTA/2% sodium metabisulphite. Blood samples were placed on ice and immediately centrifuged at 2000 ***g*** for 15 min. Plasma was separated and stored at -70 °C before assay. Plasma BNP was measured using a standard radioimmunoassay (Peninsula, CA, U.S.A.)[19]. Plasma epinephrine and norepinephrine concentrations were determined by an electrochemical method after separation by reverse phase high performance liquid chromatography[20].

Echocardiography

To assess left ventricular function, an echocardiogram was performed within 24 h of admission by the same investigator (D.N.). The left ventricular end systolic and diastolic dimensions were measured from the M-mode recordings at the tips of the mitral valve. The dimensions were measured in both the long and short axis parasternal views and the mean of the two measurements taken. The ejection fraction was estimated by the Teicholz method[21].

Visual analogue scale of dyspnoea

Patients were instructed in the use of a visual analogue scale and were asked to score the severity of their breathlessness at 1 and 6 h after commencing treatment. Since many patients were acutely distressed and severely breathless on admission, it was not feasible to instruct patients in the use of visual analogue scale at this time.

Follow-up

Treatment failure was defined as: (1) the need for intubation and ventilation for any reason, (2) deteriorating hypoxaemia or hypercapnia, or (3) progressive respiratory distress. Patients were followed up until the time of discharge from hospital to determine length of

Table 1 Admission patient characteristics

	Conventional therapy alone	Conventional therapy and CPAP	
Number	31	27	
Age	78 ± 2	77 ± 2	(years)
Male:Female	16:15	10:17	
Shortening fraction	16 ± 2	16 ± 2	(%)
Ejection fraction	40 ± 3	38 ± 3	(%)
Heart rate	113 ± 6	115 ± 3	(/min)
Systolic blood pressure	152 ± 6	155 ± 7	(mmHg)
Diastolic blood pressure	90 ± 4	93 ± 5	(mmHg)
Respiratory rate	27 ± 1	31 ± 1	(/min)
Oxygen saturation	93 ± 2	93 ± 1	(%)
Hydrogen ion	39 ± 2	48 ± 2	(nmol . l^{-1})
Partial pressure of oxygen	10·1 ± 0·8	13·5 ± 1·5	(kPa)
Plasma bicarbonate	23 ± 1	23 ± 1	(mmol . l^{-1})
Partial pressure of carbon dioxide	4·8 ± 0·2	6·1 ± 0·4	(kPa)
Serum urea	15·2 ± 4·5	12·7 ± 2·5	(mmol . l^{-1})
Serum creatinine	134 ± 11	165 ± 29	(μmol . l^{-1})
Serum creatine kinase	169 ± 69	115 ± 29	(IU . ml^{-1})
Frusemide	76 ± 4	77 ± 4	(mg)
Nitrate	3·1 ± 0·4	2·8 ± 0·4	(mg)
Morphine	1·0 ± 0·3	2·5 ± 0·5	(mg)

P=0·37; ANOVA, conventional therapy vs conventional therapy+CPAP.

stay and in-hospital mortality. Myocardial infarction was defined as an elevated creatine kinase more than twice the upper limit of the laboratory reference range with associated accepted ECG changes.

Statistical analysis

Data are expressed as mean ± standard error of the mean and were examined, where appropriate, by analysis of variance (ANOVA) with repeated measures, regression analysis and chi-square test using StatView *v*5.0.1 (SAS Institute Inc., Cary, North Carolina, U.S.A.). Where ANOVA demonstrated significant differences in responses, post-hoc comparisons were made using the Fisher protected least significant difference test (StatView *v*5.0.1). Statistical significance was taken at the 5% level.

Results

Fifty-eight patients were recruited into the trial and their baseline characteristics are shown in Table 1. The study population was elderly with evidence of significant left ventricular systolic dysfunction. On admission, patients were tachypnoeic, tachycardic and hypertensive.

In comparison to conventional therapy alone, patients randomized to CPAP therapy reported less breathlessness at 1 h (Table 2). This was associated with a more rapid reduction in respiratory rate, heart rate and acidosis at 1 h in patients treated with CPAP (Fig. 1). These treatment group differences were not present at 6 h, but patients treated with CPAP continued to feel subjectively less breathless.

There were no treatment failures in the CPAP group. None of the patients reported adverse effects from CPAP other than minor discomfort from the facial mask after 6 h. There were two treatment failures in the non-CPAP group. The first patient was withdrawn from the study after 35 min because of respiratory distress and falling oxygen saturation. Since no intensive care unit beds were immediately available, he was given a trial of CPAP while awaiting review by an intensivist. Following initial rapid improvement in both clinical variables and arterial blood gases, the patient later deteriorated, developed cardiogenic shock and renal failure, and died after 48 h. The second patient was also withdrawn after 45 min because of deteriorating clinical features and increasing respiratory distress. He was given a trial of CPAP with rapid improvement in symptoms and arterial blood gases. He was taken off CPAP at 6 h and was subsequently discharged home with no further problems.

The length of stay in high dependency areas and the total hospitalization times were similar for both treatment groups. However, there was a trend for a reduction in the overall hospital mortality in patients treated with CPAP (2 vs 7; $0{\cdot}10>P>0{\cdot}05$, chi-squared test). All deaths were related to cardiovascular disease with the

Table 2 Clinical outcomes

	Conventional therapy alone	Conventional therapy and CPAP	
Visual analogue score for breathlessness			
1 h	3·8 ± 0·5	1·9 ± 0·2*	(AU)
6 h	1·8 ± 0·3	1·0 ± 0·0*	(AU)
Peak creatine kinase	229 ± 80	222 ± 68	(IU . ml^{-1})
Elevated creatine kinase	9	8	
Length of stay			(days)
Total hospitalization	15·0 ± 2·7	13·7 ± 2·0	
Intensive care unit	0	0	
High dependency unit	0·4 ± 0·2	1·1 ± 0·2	
General medical ward	14·6 ± 2·7	12·6 ± 2·1	
Pre-discharge hospital mortality	7	2	

P=0·02; ANOVA.
*P=0·005; Conventional therapy vs conventional therapy+CPAP.

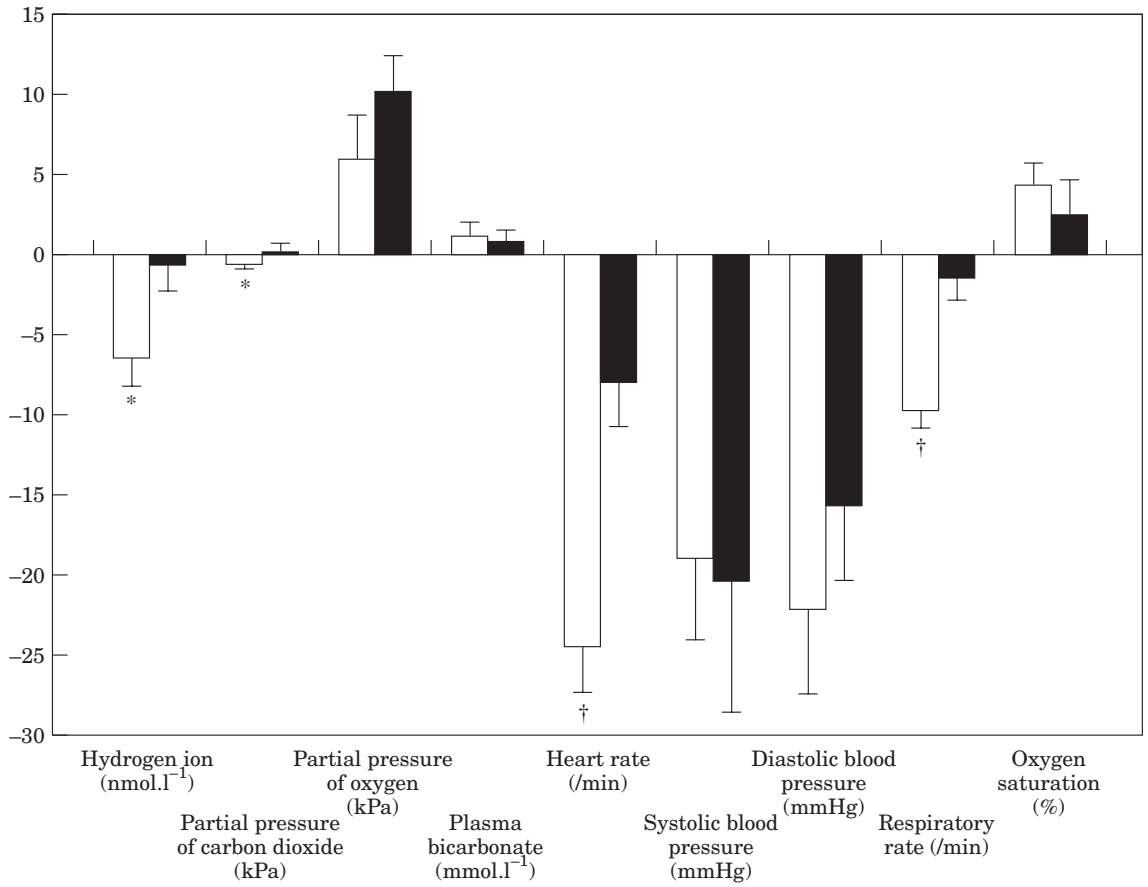

Figure 1 **Absolute change in clinical variables at 1 h with (open bars) and without CPAP (closed bars). ANOVA, P=0·009; unpaired t-test, *P<0·05, †P<0·001.**

exception of one CPAP patient who died of metastatic adenocarcinoma.

Plasma BNP concentrations were markedly elevated on admission and correlated inversely with left ventricular ejection ($r = -0·24$, P<0·001) and shortening ($r = -0·25$, P<0·001) fractions. Plasma BNP concentrations rose at 6 h before falling below admission levels at 24 h in both treatment groups (P<0·001, ANOVA for both groups; Table 3). In contrast, the plasma norepinephrine and epinephrine concentrations showed

Table 3 Plasma neurohormone concentrations during first 24 h

	Conventional therapy alone	Conventional therapy and CPAP	
Plasma norepinephrine concentration†			Normal range $<4{\cdot}0$ nmol . l^{-1}
Baseline	$4{\cdot}9 \pm 0{\cdot}9$	$5{\cdot}7 \pm 1{\cdot}3$	(nmol . l^{-1})
1 h	$3{\cdot}5 \pm 0{\cdot}5$§	$4{\cdot}5 \pm 1{\cdot}2$‡	(nmol . l^{-1})
Plasma epinephrine concentration			Normal range $<0{\cdot}4$ nmol . l^{-1}
Baseline	$0{\cdot}28 \pm 0{\cdot}13$	$0{\cdot}17 \pm 0{\cdot}01$	(nmol . l^{-1})
1 h	$0{\cdot}20 \pm 0{\cdot}06$	$0{\cdot}14 \pm 0{\cdot}01$§	(nmol . l^{-1})
Plasma brain natriuretic peptide concentration*			Normal range <66 pg . ml^{-1}
Baseline	882 ± 114	911 ± 140	(pg . ml^{-1})
1 h	971 ± 123	905 ± 138	(pg . ml^{-1})
6 h	1065 ± 137‡	1061 ± 151‡	(pg . ml^{-1})
24 h	855 ± 121	773 ± 114§	(pg . ml^{-1})

*P70·001, †P70·05; ANOVA with repeated measures vs ‡P70·001, §P70·05; baseline (Fisher's PLSD test).
One outlier was excluded from the catecholamine analysis since the norepinephrine concentration was greater than nine times the standard deviation from the mean.

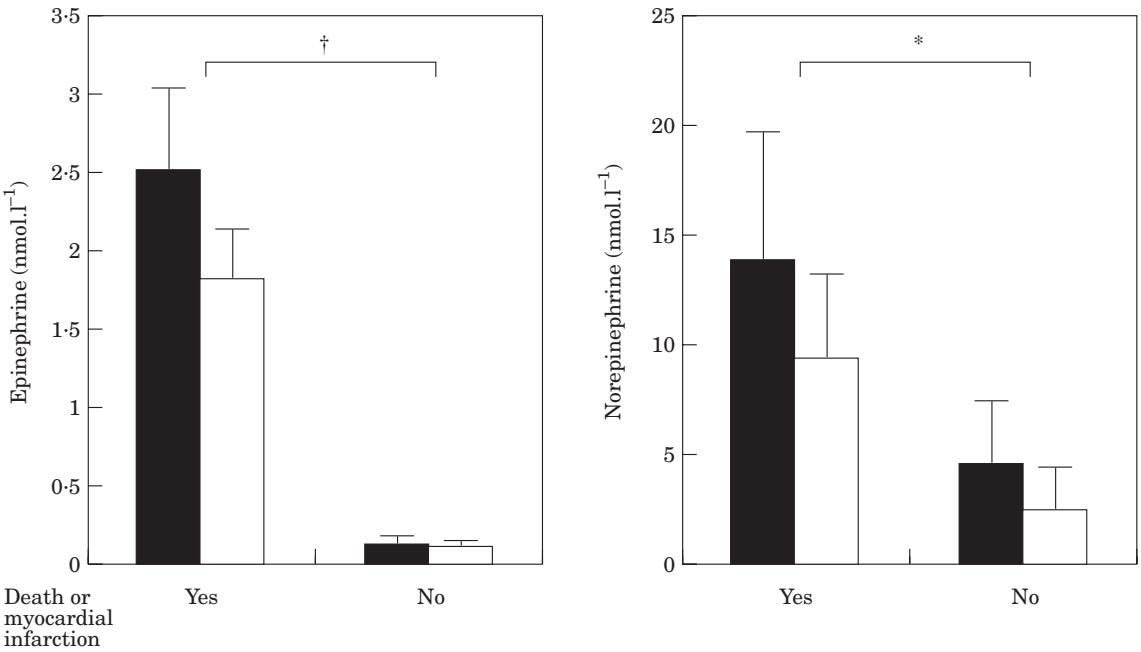

Figure 2 **Plasma epinephrine (left hand panel) and norepinephrine (right hand panel) concentrations at admission (closed bars) and at 1 h (open bars) in patients who subsequently died or survived. Two-way ANOVA, $P<0{\cdot}05$ (admission vs 1 h); *$P=0{\cdot}02$, †$P=0{\cdot}06$ (death or myocardial infarction).**

a more rapid response, falling at 1 h (Table 3). There were no statistically significant differences in the plasma neurohormone concentrations between the two treatment groups (P=ns, 2-way ANOVA). Plasma catecholamine and BNP concentrations were significantly higher in those patients who died or sustained a myocardial infarct (Figs 2 and 3).

Discussion

We have shown that CPAP is an effective treatment for acute pulmonary oedema with a more rapid improvement in symptoms, respiratory rate, heart rate and acidosis as well as a trend for a reduction in overall mortality. These findings are in keeping with previous

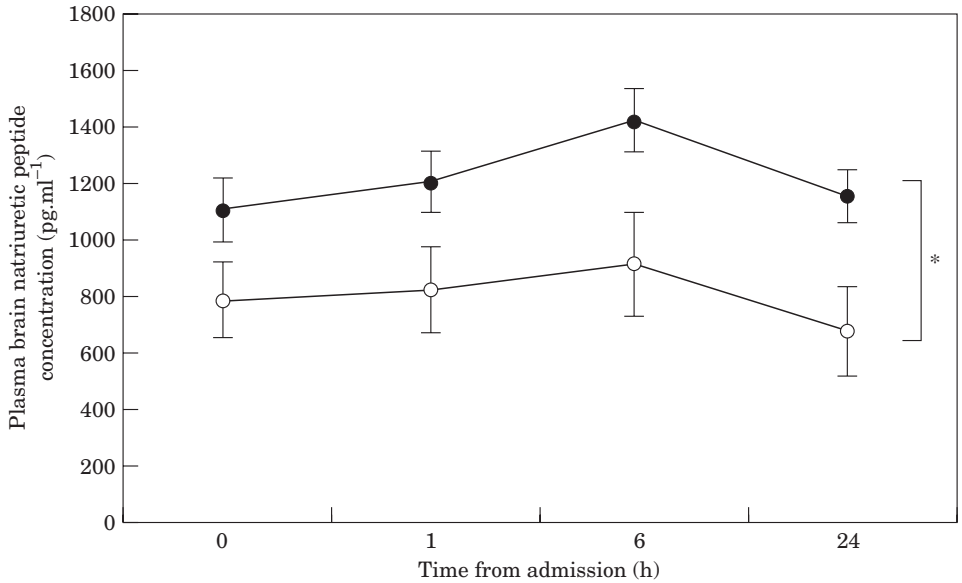

Figure 3 **Plasma brain natriuretic peptide (BNP) concentrations during the first 24 h of admission in patients with (closed circles) or without (open circles) death or myocardial infarction. Two-way ANOVA, $P<0{\cdot}001$ (plasma BNP concentrations over 24 h); $*P=0{\cdot}02$ (death or myocardial infarction).**

similar studies using CPAP and NIPPV[7–9]. Moreover, for the first time, we have described the plasma profile of BNP concentrations during the first 24 h of hospitalization. Although plasma neurohumoral concentrations were unaffected by CPAP treatment, plasma BNP and catecholamine concentrations were elevated in patients who subsequently died or sustained an acute myocardial infarction.

Unlike previous studies, we had a very low treatment failure rate, but this is unlikely to be explained by differences in the study population since our baseline clinical variables, left ventricular ejection fraction and arterial blood gases were similar[7–10]. None of the patients assigned to CPAP required intubation and ventilation or failed to improve with treatment. There were, however, two treatment failures in the non-CPAP group. These patients would have met the criteria for intubation and ventilation in other published studies, but intubation was averted by the introduction of CPAP to which both made a rapid initial response. Unfortunately one patient later died of cardiogenic shock but a decision was made when he subsequently deteriorated, that he would not be ventilated. We had no reports of intolerance to CPAP or any of the associated complications, such as nasal skin necrosis, conjunctivitis, aspiration of gastric contents or barotrauma.

Consistent with previous studies, we failed to demonstrate a significant improvement in the length of hospital stay or on overall mortality. The aim of the study was to assess the effect of CPAP on clinical outcomes and plasma neurohormonal concentrations, and it was not sufficiently powered to show a significant difference in hospital mortality. However, there was a trend for a reduction in mortality and pooling our data with those of previous studies would suggest that CPAP confers an overall survival benefit[22].

The main clinical benefits of CPAP occurred within the first hour, suggesting that treatment should be commenced as soon as possible after admission. In most hospitals treatment should ideally commence within the emergency department or the medical assessment unit. We did not encounter any difficulties commencing CPAP in the emergency department. Previous experience has also shown that non-invasive ventilation has been successfully used in the emergency department for a variety of clinical conditions, including acute pulmonary oedema[23–25].

The role of bilevel ventilation in the management of acute pulmonary oedema is more controversial. Two studies have shown that bilevel ventilation may be associated with an increased frequency of myocardial infarction. The study by Mehta *et al.*[10] which was halted after an interim analysis indicated that, despite a more rapid improvement in ventilation, patients treated with bilevel ventilation had twice the rate of myocardial infarction as those treated with CPAP. However, a recent study comparing NIPPV with conventional oxygen therapy demonstrated that NIPPV was associated with a more rapid improvement in oxygenation and resolution of respiratory symptoms without a significant increase in the rate of myocardial infarction[11]. In a further study comparing NIPPV with high dose intravenous isosorbide dinitrate[26], a higher rate of intubation, death and myocardial infarction and a slower resolution of clinical variables were reported in the NIPPV group. However, data from this latter study is difficult to compare with other published series since

the investigators used much lower mean inspiratory and expiratory pressures, and treatment was delivered pre-hospital by mobile intensive care units rather than on arrival at hospital.

It has been suggested that bilevel ventilation may reduce stroke volume and cardiac output to a greater extent than CPAP, leading to impaired myocardial perfusion that may contribute to the higher rate of myocardial infarction. Takeda and colleagues showed no difference in hospital mortality rates for patients with acute myocardial infarction and pulmonary oedema treated with nasal CPAP[27]. Like Masip *et al.*[11], we demonstrated a poorer outlook for patients with myocardial infarction which was independent of treatment used. Rusterholtz *et al.*[28] also found that 80% of patients who failed to respond to NIPPV and subsequently died had suffered myocardial infarction. This would suggest that patients with myocardial infarction have a poorer prognosis generally but further research is required to determine whether bilevel ventilation, in particular, has detrimental effects on these patients.

Neurohormonal activation has been extensively studied in chronic heart failure, but little is known in the context of acute heart failure. After initiation of treatment, plasma norepinephrine concentrations fell rapidly within the first hour, with a similar trend for epinephrine. In contrast, BNP concentrations continued to rise, peaking at 6 h before falling below baseline values by 24 h. This latter finding is consistent with an animal model of acute heart failure where rapid atrial pacing caused a marked rise in plasma ANP concentrations within 1 h but increases in BNP concentrations took 8 h to develop[29]. This is likely to represent the delay in the up-regulated synthesis and release of BNP since it is rapidly cleared from the plasma through metabolism by neutral endopeptidase 24.11 and via binding to clearance receptors[30].

In patients with chronic heart failure or a recent myocardial infarction, BNP is known to be elevated in proportion to the severity of left ventricular dysfunction and has been shown to be a useful prognostic marker of morbidity and mortality[15–18,31,32]. It is also secreted by infarcted ventricular myocardium[33], peaking at 16 h[34]. All patients in our study, including those with myocardial infarction, had a peak plasma BNP concentration at 6 h. While there did not appear to be a treatment effect of CPAP, plasma epinephrine, norepinephrine and BNP concentrations were higher in those patients who died or sustained an acute myocardial infarction. Although the association of raised catecholamine concentrations and risk of mortality has been demonstrated previously[14,35,36], this is the first description of an association between in-hospital outcome and elevated plasma BNP concentrations in patients with acute heart failure.

Study limitations

Although fully randomized, there appeared to be some differences in baseline variables between the two treatment groups. Patients assigned to CPAP therapy had more severe disease with a slightly greater acidosis and hypercapnia on admission. However, despite this, patients felt subjectively much better on CPAP therapy with a two-fold reduction in the dyspnoea score at 1 and 6 h. The absence of an admission dyspnoea score was predicted and resulted from the inability of many very ill patients to comprehend and complete the required scales when pilot studies were done.

In conclusion, we have shown that CPAP is a safe, well-tolerated treatment for acute heart failure. It causes a more rapid improvement in symptoms and clinical variables without any adverse haemodynamic effects. Plasma neurohormonal concentrations and the frequency of myocardial infarction were unaffected by CPAP treatment. Maximum clinical benefits appear to occur within the first hour of treatment with CPAP, making this a useful adjunctive treatment for the management of patients with acute heart failure in the emergency setting.

This study was supported by a grant from the San Diego Foundation.

References

[1] Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 1993; 94: 281–8.

[2] Stauffer JL, Olsen DE, Petty TL. Complications and consequences of endotracheal intubation and tracheostomy: a prospective study of 150 critically ill patients Am J Med 1980; 70: 65–76.

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

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

[5] Lenique F, Habis M, Lofaso F, Dubois-Rande J-L, Harf A, Brochard L. Ventilatory and haemodynamic effects of CPAP in left heart failure Am J Respir Crit Care Med 1997; 155: 500–5.

[6] Baratz DM, Westbrook PR, Shah PK, Mohsenifar Z. Effect of nasal CPAP on cardiac output and oxygen delivery in patients with congestive heart failure Chest 1992; 103: 1397–1401.

[7] Bernsten 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.

[8] Rasanen J, Heikkila J, Downs J, Nikki P, Vaisanen I, Viitanen A. Continuous positive airway pressure by face mask in acute cardiogenic pulmonary edema Am J Cardiol 1985; 55: 296–300.

[9] Lin M, Yang YF, Chiang HT, Chang M-S, Chiang BN, Cheitlin MD. Reappraisal of continuous positive airway pressure therapy in acute cardiogenic pulmonary edema: short term results and long term follow up. Chest 1995; 107: 1379–86.

[10] Mehta S, Jay GD, Woolard RH *et al.* Randomized, prospective trial of bi-level versus continuous positive airway pressure in acute pulmonary oedema Crit Care Med 1997; 25: 620–8.

[11] Masip J, Betbese AJ, Paez J *et al*. Non-invasive pressure support ventilation versus conventional oxygen therapy in acute cardiogenic pulmonary oedema: a randomised trial Lancet 2001; 356: 2126–32.
[12] Levine TB, Francis GS, Goldsmith SR, Simon AB, Cohn JN. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relation to haemodynamic abnormalities in congestive heart failure Am J Cardiol 1982; 49: 1659–66.
[13] Francis GS, Benedict C, Johnstone DE *et al*. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure Circulation 1990; 82: 1724–9.
[14] Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality Circulation 1990; 82: 1730–6.
[15] Yasue H, Yoshimura M, Sumida H *et al*. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure Circulation 1994; 90: 195–203.
[16] Wei C-M, Heublein DM, Perella MA *et al*. Natriuretic peptide system in human heart failure Circulation 1993; 88: 1004–9.
[17] Yu CM, Sanderson JE. Plasma brain natriuretic peptide — an independent predictor of cardiovascular mortality in acute heart failure Eur J Heart Failure 1999; 1: 59–65.
[18] Tsutamoto T, Wada A, Maeda K *et al*. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction Circulation 1997; 96: 509–16.
[19] Heublin DM, Heser DW, Edwards BS *et al*. N-terminal (1-25) atrial natriuretic factor in human congestive heart failure: a marker for endogenous secretion J Am Coll Cardiol 1989; 13: 9A.
[20] Goldstein DS, Feuerstein G, Kopin IJ, Keiser HR. Validity and reliability of liquid chromatography with electromechanical detection for measuring plasma levels of norepinephrine and epinephrine in man. Life Sci 1981; 28: 467–75.
[21] Bellenger NG, Burgess MI, Ray SG *et al*. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J 2000; 21: 1387–96.
[22] Kelly C, Newby DE, Boon NA, Douglas NJ. Support ventilation versus conventional oxygen Lancet 2001; 357: 1125–7.
[23] Sacchetti AD, Harris RH, Paston C, Hernandez Z. Bi-level positive airway pressure support system use in acute congestive heart failure: preliminary case series Acad Emerg Med 1995; 2: 714–18.
[24] Pollack CV, Torres MT, Alexander L. Feasibility study of the use of bilevel positive airway pressure for respiratory support in the emergency department Ann Emerg Med 1996; 27: 189–92.
[25] Kelly AM, Bau S, Georgakos C, Rosengarten P. Experience with the use of continuous positive airway pressure (CPAP) therapy in the emergency management of acute severe cardiogenic pulmonary oedema Aust NZ J Med 1997; 27: 319–22.
[26] Sharon A, Shpirer I, Kaluski E *et al*. High-dose intravenous isosorbide dinitrate is safer than Bi-PAP ventilation combined with conventional treatment for severe pulmonary edema J Am Coll Cardiol 2000; 36: 832–7.
[27] Takeda S, Takano T, Ogawa R. The effect of nasal continuous positive airway pressure on plasma endothelin-1 concentrations in patients with severe cardiogenic pulmonary edema Anesth Analg 1997; 84: 1091–6.
[28] Rusterholz T, Kempf J, Berton C *et al*. Noninvasive pressure support ventilation (NIPSV) with face mask in patients with acute cardiogenic pulmonary edema Intensive Care Med 1999; 25: 21–8.
[29] Qi W, Kjekshus J, Hall C. Differential responses of plasma atrial and brain natriuretic peptides to acute alteration in atrial pressure in pigs Scand J Clin Lab Invest 2000; 60: 55–63.
[30] Lazzeri C, Franchi F, Porciani C *et al*. Systemic hemodynamics and renal function during brain natriuretic peptide infusion in patients with essential hypertension Am J Hypertens 1995; 8: 799–807.
[31] Motwani JG, McAlpine H, Kennedy N, Struthers AD. Plasma brain natriuretic peptide as an indicator for angiotensin-converting-enzyme inhibition after myocardial infarction. Lancet 1993; 341: 1109–13.
[32] Omland T, Aakvaag A, Bonarjee VVS *et al*. Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long term survival after acute myocardial infarction Circulation 1996; 93: 1963–9.
[33] Sumida H, Yasue H, Yoshimura M *et al*. Comparison of secretion pattern between A-type and B-type natriuretic peptides in patients with old myocardial infarction. J Am Coll Cardiol 1995; 25: 1105–10.
[34] Morita E, Yasue H, Yoshimura M *et al*. Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction Circulation 1993; 88: 82–91.
[35] Cohn JN, Levine TB, Olivari MT *et al*. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure N Engl J Med 1984; 311: 819–23.
[36] Missouris CG, Grouzmann E, Buckley MG, Barron J, MacGregor GA, Singer DR. How does treatment influence endocrine mechanisms in acute severe heart failure? Effects on cardiac natriuretic peptides, the renin system, neuropeptide Y and catecholamines Clin Sci 1998; 94: 591–9.