

## Treatment and outcome of acute cardiogenic pulmonary oedema presenting to an emergency department in Hong Kong: retrospective cohort study

香港一所急症室之急性心原性肺水腫治療及結果的回顧性組列研究

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**Objectives:** To explore the epidemiology, treatment and outcome of acute cardiogenic pulmonary oedema (ACPO) in a Hong Kong emergency department (ED). **Methods:** This was a retrospective cohort study in a university hospital ED. Cases were identified from ED records and resuscitation room logbooks. The study extended from 1 September 2004 to 30 April 2005. Parametric tests and logistic regression were used to identify predictors of survival. **Results:** A total of 140 patients were identified, with a mean age of 75 years and male:female ratio of 1:1.4. Mean values (range) on presentation were as follows: pulse rate 103 beats/minute (36-108); blood pressure (BP) 169/88 mmHg (77-274/20-162) and respiratory rate 31 breaths/minute (12-88). Past medical history included previous ACPO (12.1%), diabetes (45.7%), chronic obstructive pulmonary disease (9.3%), ischaemic heart disease (45.0%), hypertension (72.1%) and congestive heart failure (40.7%). On admission, 47.1% had pH<7.35 and 40.7% had PaCO<sub>2</sub>>5.5kPa. ED treatments included: sublingual nitrates (n=2), intravenous (IV) nitrates (n=89, median 10 mg/hr), IV frusemide (n=85, median 40 mg), IV morphine (n=25, median 3 mg). There were 21 patients on non-invasive ventilation; 27 intubations and 41 patients were admitted to the intensive care unit. Survival to discharge was 95.7%; and median length of hospital stay was 8 days. The 90-day all-cause hospital readmission rate was 30.0%. The 30-day mortality was 12.9% (n=18) and 90-day mortality was 29.3% (n=41). Logistic regression showed that past history of hypertension (p=0.0061), higher systolic BP on ED discharge (p=0.0102) and lower creatinine following treatment (p=0.035) were predictors of improved survival at 90 days. **Conclusion:** ACPO commonly presents to the ED in Hong Kong and has a high 90-day mortality. Previous hypertension, higher systolic blood pressure on leaving the ED and lower creatinine following treatment predict improved survival at 90 days. (*Hong Kong j.emerg.med.* 2006;13:148-154)

**目的：**探索香港一所急症室急性心原性肺水腫之流行病學、治療及結果。**方法：**這是一所大學醫院急症室內的回顧性組列研究。從急症室的記錄及急救房的登記簿識別出案例。這研究由 2004 年 9 月 1 日延續至 2005 年 4 月 30 日。使用參數測試及邏輯回歸法去識別出預示存活的因子。**結果：**共有 140 名病者，平均年齡為 75 歲，男女比例為 1:1.4。到診時的平均值(範圍)如下：脈搏率每分鐘 103 (36-108)；血壓 169/88 mmHg (77-274 / 20-162) 及呼吸率每分鐘 31 (12-88)。過往病歷包括曾有急性心原性肺

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水腫 (12.1%)，糖尿病 (45.7%)，慢性阻塞性肺病 (9.3%)，缺血性心臟病 (45.0%)，高血壓 (72.1%) 及充血性心臟衰竭 (40.7%)。入院時 47.1% 的  $\text{pH} < 7.35$  及 40.7% 的  $\text{PaCO}_2 > 5.5 \text{ kPa}$ 。急症室的治理包括：舌下硝酸鹽 (n=2)，靜脈注射硝酸鹽 (n=89，中位數 10 mg/hr)，靜脈注射呋塞米 (n=85，中位數 40 mg)，靜脈注射嗎啡 (n=25，中位數 3 mg)。21 位病者接受非侵入性輔助換氣，有 27 名接受氣道插管及 41 名入住深切治療部。95.7% 存活至出院。留院期的中位數為 8 天。90 天內所有原因而再度入院率為 30.0%，30 天死亡率為 12.9% (n=18) 及 90 天死亡率為 29.3% (n=14)。邏輯回歸法顯示高血壓的病歷 (p=0.0061)，急症室出院時高收縮壓 (p=0.0102) 及治療後低的肌酸酐 (p=0.035) 為 90 天存活率改善的預示因子。**總結：**急性心原性肺水腫在香港急症室很常見，其 90 天死亡率很高。高血壓的病歷、急症室出院時高的收縮血壓及治療後低的肌酸酐可以預示 90 天的存活率會改善。

**Keywords:** Drug therapy, epidemiology, heart diseases, hospital emergency service, mortality

**關鍵詞：**藥物治療、流行病學、心臟病、醫院緊急服務、死亡率

## Introduction

Acute cardiogenic pulmonary oedema (ACPO) is a common medical problem presenting to the emergency department (ED).<sup>1</sup> The condition has a poor prognosis with a reported in-hospital mortality of up to 20%.<sup>2</sup> The high mortality rate is multifactorial in nature, but could perhaps be related to patients not receiving optimal treatment.<sup>2,3</sup> The range of reported mortality rates suggests that there could be therapeutic differences worldwide in the emergency treatment of ACPO.

The main pharmacological treatments for ACPO comprise oxygen, frusemide, morphine, nitrates (both intravenous [IV] and sublingual [SL]) and occasionally oral angiotensin converting enzyme inhibitors (ACEI). Newer potential treatments including those involving atrial natriuretic peptide and other agents are currently being evaluated.<sup>1</sup> Several studies have compared the efficacy of nitrates and frusemide with results favouring the former. A high dose of nitrates either as an initial IV bolus or infusion and low dose frusemide has been shown to be a superior combination for these patients.<sup>4</sup>

The respiratory components of ACPO can be managed with non-invasive ventilation (NIV), non-invasive positive pressure ventilation (NIPPV), continuous positive airways pressure (CPAP) and bilevel positive airways pressure (BiPAP). Invasive techniques include endotracheal intubation and mechanical ventilation.<sup>5</sup> NIPPV, a more recent form of ventilation which does not require intubation, has been used in the

management of ACPO.<sup>6</sup> Several studies have compared NIPPV with other forms of respiratory support in terms of outcome, including the need for intubation and mortality rates.

ACPO is associated with a poor prognosis. Studies have suggested that certain clinical and physiological characteristics and initial treatment are important prognostic factors. In particular, a low systolic pressure and ACPO associated with myocardial infarction were poor prognostic factors. Le Conte identified poor prognostic factors in terms of mortality rates, which included: observed mottling on presentation, low diuresis, high respiratory rate and lack of response to the initial treatment (six hours post treatment).<sup>3</sup> Myocardial infarction, respiratory infection and unknown precipitant of ACPO were related to more deaths.<sup>3</sup>

The aim of this study was to explore the epidemiology, treatment patterns and outcome of ACPO in a single Hong Kong ED.

## Methods

The setting for this retrospective case note review was Prince of Wales Hospital (PWH), an acute general hospital with 1,200 beds within the New Territories East Cluster (NTEC) and it also functions as the primary teaching hospital of the Chinese University of Hong Kong (CUHK).

Patients who presented to the ED with shortness of breath and a clinical diagnosis of ACPO as coded on the ED computer system or entered into the resuscitation room logbook were included. Patients who had shortness of breath predominantly due to other diagnoses (chronic obstructive pulmonary disease, pneumonia, etc.) were excluded. The study period extended from 1 September 2004 to 30 April 2005 – a total of eight months.

At the time of the study, there was no formal written protocol within the ED for the management of ACPO, but treatment was at the discretion of the attending doctor (trainee and/or specialist). Management typically involved standard pharmacological (nitrates, frusemide, oxygen, opiates) and non-pharmacological treatments (non-invasive ventilation, intubation, ventilation via tracheal tube, etc.).

Information was collected on: patient demographic details (age, sex); outcome predictors (past medical history, including past history of ACPO, diabetes, hypertension, chronic obstructive pulmonary disease, and smoking); risk factors on admission (systolic and diastolic blood pressures [BP], mean arterial pressure, respiratory rate, oxygen saturation, pH, partial pressures of oxygen and carbon dioxide); and clinical data after initial pharmacological treatment (pulse rate, blood pressure, respiratory rate).

Data relating to the pharmacological treatments used was collected (sublingual nitrates, IV nitrates, IV frusemide, IV morphine) along with details of any ventilatory support. For outcome measures, the following information was collected: length of hospital stay; 30-day and 90-day mortality rates; need for non-invasive ventilation in the ED (NIV – defined as any form of positive pressure support not requiring endotracheal intubation, e.g. CPAP and BiPAP); intubation and invasive ventilation in the ED (defined as ventilation via an endotracheal tube); and readmissions to Hong Kong hospitals within 90 days of discharge from the index admission.

Data was entered on to SPSS version 13 for statistical analysis. Descriptive statistics and univariate analyses

were performed to identify which factors were associated with survival or mortality. Paired t-tests were used to compare paired physiological parameters before and following ED treatment and unpaired t-tests were used to compare characteristics of patients who survived 90 days with those who did not. Chi square tests were used to compare categorical data.

Following univariate analysis, stepwise logistic regression was used to identify those factors which predicted survival at 90 days following the index episode of ACPO. All potential candidate variables were initially included in the regression analysis. Statistical significance was defined as  $p < 0.05$ , and 95% confidence intervals (CI) were given where appropriate.

Ethical approval for this study was obtained from the CUHK-NTEC Clinical Research Ethics Committee.

## Results

### *Demographic data*

Approximately 64,000 non-trauma patients presented to the ED between 1 September 2004 and 30 April 2005. Of these, 140 (0.22%) patients with a diagnosis of ACPO required medical admission. Based on these figures, the estimated annual incidence of ACPO requiring admission is 3 per 10,000 populations, using an average figure of 450 daily admissions to the ED in PWH in Hong Kong drawn from a local population of around 800,000 persons.

The mean age was 75 years (range 34-92) with 58 males and 82 females. Among the 140 patients, 56 patients (40.0%) were triage category 1, with 41 patients (29.3%) each in triage categories 2 and 3. The remaining two patients were in triage category 4. Table 1 shows details of the past medical history.

### *Physiological parameter changes following ED treatment*

Mean values of presenting physiological parameters included: pulse rate 103 beats per minute (range 36-108); BP 169/88 mmHg (range 77-274/20-162) and respiratory rate 31 breaths per minute (range 12-88).

**Table 1.** Past medical history of emergency department ACPO patients

Variable	Number	%
Previous episode of ACPO	17	12.1
Diabetes mellitus	64	45.7
Chronic obstructive pulmonary disease	13	9.3
Coronary artery disease	63	45.0
Hypertension	101	72.1
Congestive heart failure	57	40.7

Table 2 shows the statistically significant differences in patients' physiology and arterial blood gases following ED treatment.

At ED presentation, 66 (47.1%) patients were acidotic ( $\text{pH} < 7.35$ ) and 57 (40.7%) patients had arterial hypercarbia ( $\text{PaCO}_2 > 5.5$  kPa), and 44 (31.4%) patients were hypoxaemic ( $\text{PaO}_2 < 10.0$  kPa).

Treatment in the ED included sublingual nitrates ( $n=2$ ), IV nitrates ( $n=89$ , 63.6%, median initial dose 10 mg/hr; range 2-40mg/hr), IV frusemide ( $n=85$ , 60.7%, median dose 40 mg, range 20-120 mg), and IV morphine ( $n=25$ , 17.9%, median dose 3 mg, range 1-5 mg). NIV was administered to 21 patients (15 CPAP, 6 BiPAP) in the ED.

Subgroup analysis of those given IV morphine showed a trend towards increased admissions to ICU ( $\chi^2=3.182$ ,  $\text{df}=1$ ,  $p=0.074$ ) and increased intubations ( $\chi^2=3.161$ ,  $\text{df}=1$ ,  $p=0.075$ ) but these did not reach statistical significance. There were no significant differences between the doses of IV morphine given to those who were intubated (2.50 mg) versus those who were not intubated, (2.65 mg,  $p=0.68$ , independent samples t-test) or between those who were admitted to the intensive care unit (2.82 mg) versus

those who were not (2.43 mg,  $p=0.25$ , independent samples t-test).

### Outcome measures

Table 3 shows the outcomes for the patients in this study. Twenty-one patients received NIV (15 CPAP, 6 BiPAP) in the ED, 27 patients were intubated and 41 patients were admitted to ICU. Initially, 134 (95.7%) patients survived to hospital discharge and the median length of stay was 8 days. However, 18 (12.9%) patients died within 30 days and the 90-day mortality was 29.3% (41/140).

Forty-two patients (30.0%) were readmitted to Hong Kong hospitals within 90 days of discharge, and 33 (78.6%) readmissions were due to recurrent pulmonary oedema.

Table 4 shows a comparison of variables (including pre-treatment and post-treatment parameters) for those who were alive at 90 days compared with those who had died.

Stepwise multiple logistic regression showed that only a past history of hypertension (adjusted odds ratio 3.4, 95%CI 1.42 to 8.23,  $p=0.0061$ ), higher systolic blood pressure on ED discharge (adjusted odds ratio 1.02, 95%CI 1.005 to 1.036,  $p=0.0102$ ) and a lower creatinine following ED treatment (adjusted odds ratio 0.998, 95%CI 0.996 to 1.000,  $p=0.035$ ) were predictors of improved 90-day survival.

### Discussion

ACPO is a common presenting complaint to the ED in Hong Kong and is associated with high mortality at 90 days, confirming its 'malignant' nature in the local

**Table 2.** Mean physiological parameter changes before and after treatment in ED

Variable	N*	Pre-treatment	Post-treatment	95% CI for difference	p-value (paired t-test)
Pulse (beats per minute)	123	102	97	2 to 9	0.002
Systolic blood pressure (mmHg)	125	171	154	10 to 24	<0.001
Diastolic blood pressure (mmHg)	125	90	79	6 to 15	<0.001
Mean arterial pressure (mmHg)	125	117	104	7 to 18	<0.001
$\text{PaCO}_2$ (kPa)	125	6.79	5.89	0.6 to 1.2	<0.001
Arterial pH	125	7.26	7.32	-0.08 to -0.04	<0.001

\* N = number of pairs available for testing for each parameter (140 patients in total). Some patients did not have parameters available for comparison due to missing case notes, and this is reflected in the reduced number of pairs available for comparison in relation to the total number.

population. Only previous hypertension, higher systolic blood pressure on leaving the ED and lower creatinine following initial treatment were shown to be predictors of survival.

The mean age of our cohort was 75 years which is consistent with those described in other studies with a range of 69-80 years, implying that the elderly are commonly affected.<sup>7-9</sup>

**Table 3.** Outcome

Outcome	Number	%
Intensive care unit admission	41	29.3
In-hospital mortality	6	4.3
Mortality: 30 days	18	12.9
Readmission within 90 days	42	30.0
Recurrent pulmonary oedema	33	78.6
Acute coronary syndromes	3	7.1
Mortality: 90 days (all causes)	41	29.3

**Table 4.** Differences between parameters for survivors and non-survivors at 90 days

Variable	Survived	Died	95% CI for difference	p-value*
Age (years)	75.2	75.4	-3.9 to 4.4	0.91
<b>Past medical history (n)</b>				
Previous episode of ACPO	14	3		0.26
Diabetes mellitus	44	20		0.64
Chronic obstructive pulmonary disease	8	5		0.45
Coronary artery disease	44	19		0.84
Hypertension	77	24		0.02
Congestive heart failure	39	18		0.62
<b>Pre-treatment (means)</b>				
Systolic blood pressure (mmHg)	173	159	-29 to 1	0.069
Mean arterial pressure (mmHg)	119	107	-22 to -2	0.022
Diastolic blood pressure (mmHg)	92	80	-20 to -2	0.021
Respiratory rate (breaths per minute)	32	31	-5 to 3	0.73
Pulse rate (beats per minute)	105	98	-17 to 3	0.17
Arterial pH	7.256	7.272	-0.04 to 0.07	0.59
PaCO <sub>2</sub> (kPa)	6.97	6.29	-1.75 to 0.40	0.21
PaO <sub>2</sub> (kPa)	17.0	14.1	-7.4 to 1.5	0.19
Bicarbonate level (mmol/L)	22.0	20.5	-3.7 to 0.7	0.17
Arterial oxygen saturation (%)	92	89	-8 to 2	0.23
Sodium level (mmol/L)	136.8	136.5	-2.3 to 1.6	0.73
Potassium level (mmol/L)	4.1	4.2	-0.2 to 0.4	0.36
Urea (mmol/L)	13.1	16.1	-0.3 to 6.3	0.077
Creatinine (μmol/L)	227	315	-5.9 to 181.9	0.066
<b>Post-treatment (means)</b>				
Systolic blood pressure (mmHg)	159	144	-27 to -3	0.017
Mean arterial pressure (mmHg)	108	97	-21 to -2	0.022
Diastolic blood pressure (mmHg)	82	73	-15 to -1	0.020
Respiratory rate (breaths per minute)	31	31	-10 to 11	0.94
Pulse rate (beats per minute)	97	95	-11 to 8	0.74
Arterial pH	7.321	7.312	-0.06 to 0.04	0.72
PaCO <sub>2</sub> (kPa)	5.94	5.75	-1.14 to 0.77	0.70
PaO <sub>2</sub> (kPa)	16.9	16.5	-5.2 to 4.5	0.88
Bicarbonate level (mmol/L)	22.0	20.6	-3.6 to 0.7	0.20
Arterial oxygen saturation (%)	93	90	-8 to 3	0.35
Sodium level (mmol/L)	137.6	136.8	-2.7 to 1.1	0.42
Potassium level (mmol/L)	4.1	4.1	-0.3 to 0.2	0.76
Urea (mmol/L)	13.5	15.9	-1.0 to 5.7	0.16
Creatinine (μmol/L)	222	314	0.3 to 183.9	0.049

\* chi-squared test for past medical history (categorical); unpaired t-test for parameters (means)

Nitrates are widely used in the treatment of ACPO in this ED. The rationale behind the use of nitrates is based on the evidence that pulmonary oedema is related to severe vasoconstriction related to the maximally stimulated adrenergic system. Thus, agents such as nitrates which result in a controlled vasodilatation should be effective in patients with ACPO.<sup>1</sup>

Nitrates are not suitable for all those who present with ACPO; those with fixed cardiac output states have increased sensitivity to the effects of parenteral nitrates. Nitrates have been shown to improve the patient's clinical state, as well as being safe and effective in the out-of-hospital setting.<sup>10</sup>

In this study, 65.0% received either sublingual or IV nitrates. Despite this, the study was unable to determine whether nitrates were associated with survival. This is probably due to the high proportion of patients receiving nitrates which makes the analysis less sensitive to their potential effects. There is strong clinical evidence to support the use of high dose nitrates in ACPO, and this should be encouraged.<sup>4,7,8</sup>

Furosemide was used in 60.7% of the patients in this study. Furosemide has been suggested to work in two ways in ACPO.<sup>1</sup> The first effect is to induce a diuresis which leads to a reduction in intravascular volume; this in turn promotes the return of extravascular lung water to the circulation for excretion by the kidneys. Its other effect is to induce a reduction in vascular resistance, which is independent of the diuretic effect. Patients who are acutely vasoconstricted and hypotensive may not benefit from furosemide, as the drug will not reach the kidney in therapeutic concentrations under these circumstances. When comparing nitrates and furosemide, nitrates reduce the left ventricular end diastolic pressure more than furosemide<sup>11</sup> and therefore nitrates have a greater role in managing ACPO in the ED.

Previous studies have suggested a strong relationship between opiate use and intensive care unit (ICU) admission and endotracheal intubation.<sup>1,12</sup> The low rate of prescription of IV opiates in this study (17.9% of patients) appears to be consistent with appropriate

practice based on this evidence. Our data suggest a trend towards increased ICU admission or increased intubations with IV morphine use. However, it is also possible that those who were more unwell on presentation were given IV morphine as part of their treatment.

This study examined the use of non-invasive ventilation in the management of patients who present to the ED with ACPO. As expected, the frequency of use of NIV was low, with CPAP given to 10.7% and BiPAP given to 4.3%. NIV was not shown to improve outcome in terms of survival in this study, but previous studies suggested a temporary physiological benefit.<sup>13-15</sup> The use of NIV in ACPO is perhaps suboptimal due to fears of infection, and also due to the lack of evidence of the role NIV plays in survival. However, NIV improves the patient's physiology, which could be related to improved outcomes.

Intubation rates were 19.3% in this cohort which is double the rate in similar studies;<sup>7</sup> and 29.3% of patients were admitted to ICU, reflecting the severe nature of ACPO. The in-hospital mortality rate in this population was 4.3%, which is significantly lower than previous reports of 10-30%.<sup>4,7,10</sup> This study did not look at one-year mortality rates, however, previous work suggests that patients who present with ACPO have increased one-year mortality rates.<sup>7</sup> The 90-day mortality rate in this study was 29.3% which is high, consistent with previous work.<sup>3</sup>

The observed 90-day all-cause readmission rate of 30.0% is high. Readmission is associated with increased mortality rates, and the majority of readmissions are related to recurrent pulmonary oedema. Recurrent pulmonary oedema may reflect the severity of the underlying heart disease, suboptimal treatment or non-compliance with treatment, all of which warrant further study.

This study identified that previous hypertension, higher systolic blood pressure on leaving the ED and lower creatinine following initial treatment were significantly associated with improved 90-day survival. This is consistent with previous studies which have

identified poor prognostic factors such as low systolic blood pressure and associated myocardial infarction which were related to a poor prognosis.<sup>3</sup>

## Limitations

This was a retrospective study (with all the associated drawbacks thereof) with a relatively small sample size covering a short period of eight months. It would have been ideal to look at 12 months' data, as this may reduce any seasonal bias.

## Conclusion

This retrospective study suggests that ACPO is a common presenting complaint to the ED in Hong Kong and is associated with high 90-day mortality. Previous hypertension, higher systolic blood pressure on leaving the ED and lower creatinine following initial treatment were shown to predict improved outcomes in terms of survival. Nitrates, frusemide and NIV remain the mainstay of ED treatment in Hong Kong despite the lack of good quality efficacy evidence for frusemide and NIV.

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