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Acute heart failure: focusing on acute cardiogenic pulmonary oedema

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Heart failure is one of the most common medical discharge diagnoses in the UK and other countries at a similar stage of social development.[1] However, heart failure, acute or chronic, is an imprecise clinical diagnosis for which there is no universally agreed definition or test.[2] In order to discuss heart failure in a sensible fashion it is necessary first to consider existing and new definitions and the clinical presentations of the patients.

Definitions of acute heart failure

In daily UK clinical practice the term 'acute heart failure' (AHF) is most often used to mean worsening breathlessness leading to breathlessness at rest when sitting upright, often considered synonymous with the term acute cardiogenic pulmonary oedema (ACPOE). However, in guidelines and clinical trials it often means something else.[2] Recent European Society of Cardiology (ESC) guidelines suggest that the term AHF might be abandoned or should refer to new-onset heart failure regardless of its severity.[3]

The ESC recognises six subgroups of patients with AHF but it is not clear whether this classification is practically useful.[3] These include:

- cardiogenic shock
- hypertensive heart failure
- heart failure with acute coronary syndrome
- isolated right heart failure
- worsening chronic heart failure and, finally,
- ACPOE.

Many clinical trials and epidemiological studies treat admission for heart failure as synonymous with AHF, despite many of these patients having worsening exertional dyspnoea and peripheral oedema and being comfortable at rest.[4]

Very few randomised treatment trials have studied ACPOE exclusively.[5,6] Most trials of AHF have included a mixed population of patients with ACPOE and 'subacute' heart failure. This article concentrates on ACPOE.

Pathophysiology of ACPOE

ACPOE reflects pulmonary venous (left atrial) hypertension. The precise left atrial pressure (LAP) at which ACPOE will develop varies depending on alveolar-capillary membrane permeability, plasma oncotic pressure and the efficiency of pulmonary lymphatic drainage. Patients with chronic heart failure may be less likely to develop ACPOE at a given LAP because of hypertrophy and constriction of precapillary arterioles, increased lymphatic drainage or reduced alveolar-capillary membrane permeability. Increases in LAP may be due to fluid retention or fluid translocation. The former, but not the latter, is associated with weight gain and peripheral oedema. Sudden severe mitral regurgitation (Fig 1), severe myocardial ischaemia, atrial fibrillation (AF) with a rapid ventricular response (Fig 2), or severe systemic hypertension associated with a stiff and hypertrophied left ventricle (LV) may all lead to pulmonary

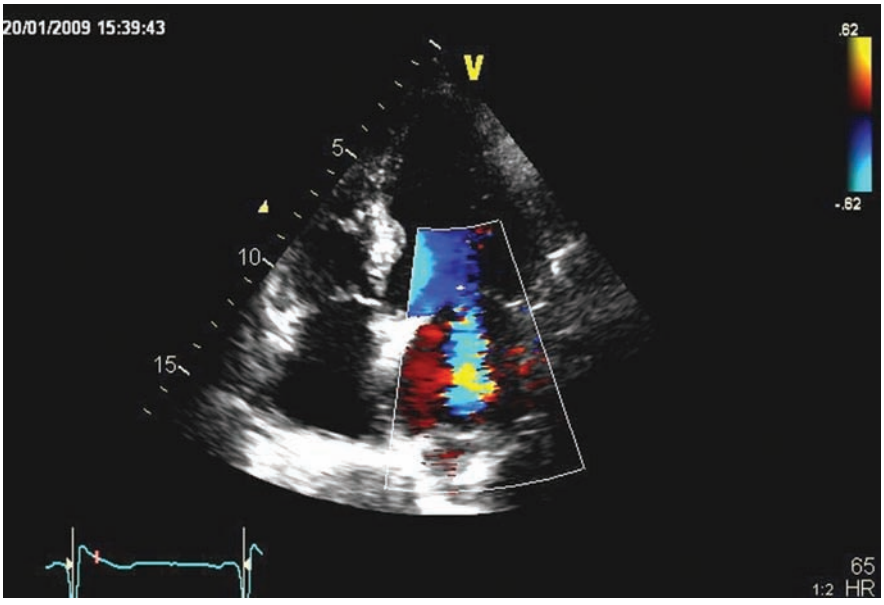

Fig 1. Severe mitral regurgitation. The coloured area represents mitral regurgitation (backward flow from the left ventricle through the mitral value into the left atrium).

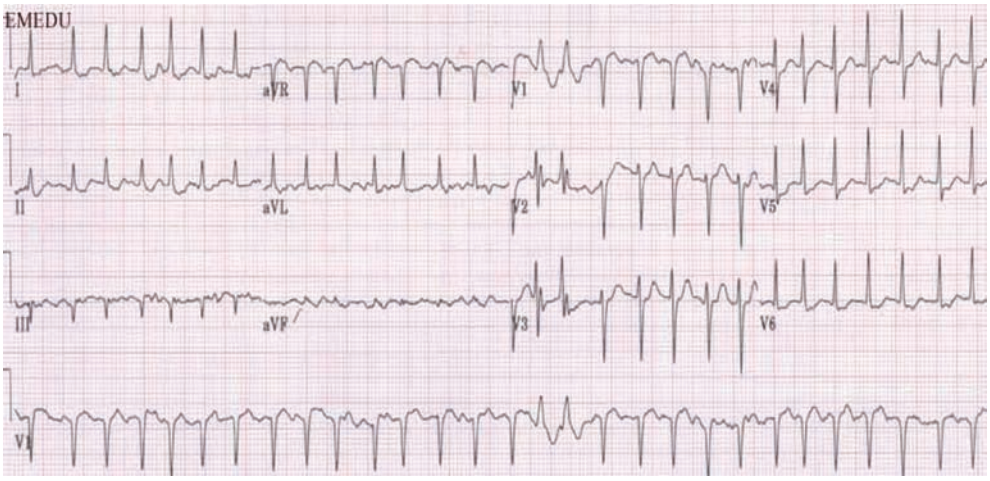

Fig 2. Atrial fibrillation with rapid ventricular response and a few ventricular ectopic beats.

oedema without weight gain or obvious fluid retention. Logically, diuretics should be reserved for acute treatment of fluid retention but are often used to treat other causes of ACPOE.

Epidemiology of acute heart failure

Accurate description of the epidemiology is confounded by the lack of attention to the precise meaning of the term AHF. In England and Wales in 2007 there were 107,297 deaths or discharges with heart failure coded in the first-discharge-coding-position and a further 286,049 episodes coded in other positions. This translates into about 200 primary death or discharge diagnoses per 100,000 population per year and about 750 per 100,000 per year coded in any position. However, these are discharge rather than admission diagnoses. The EuroHeart Failure survey suggested that only 40% of patients with a discharge diagnosis of heart failure had severe breathlessness at rest at the time of admission, that up to one-third of people discharged with heart failure were admitted for a reason unrelated to heart failure and about another one-third had no prior diagnosis of heart failure.[4] In addition, many patients admitted with heart failure also had an acute coronary syndrome, rapid AF or infection.

Khand *et al* suggest that NHS discharge statistics may grossly underestimate total heart failure-related activity.[7] An analysis of discharge statistics showed substantial misclassification rates, with missed diagnoses considerably outweighing false-positive classifications. This suggests that using official statistics actual rates of heart failure-related admissions may be underestimated by 30% or more. Clearly, this entails an enormous diagnostic as well as management burden. As the proportion of the population aged over 60 years grows, the incidence of heart failure in the overall population will increase,[1] and the prevalence of heart failure will increase as effective treatment extends the lives of people who have sustained major cardiac damage. An organised and systematic approach to diagnosis, management and monitoring is required.

In summary, although heart failure is common, there is considerable uncertainty about the incidence of ACPOE. The best guess is that a district general hospital serving 300,000 people should expect to see at least one case each day.

Aetiology of acute heart failure

About two-thirds of patients with AHF have a prior diagnosis of heart failure. Many admissions reflect worsening in underlying heart function, but myocardial ischaemia, arrhythmias (especially AF), hypertension, infection, changes in medication (including low adherence) and excessive dietary salt or alcohol may all precipitate acute deterioration of chronic heart failure or cause the new onset of heart failure (Table 1). Probably only about 50% of cases are associated with a reduced left ventricular ejection fraction (LVEF). Many

Key Points

Fluid retention or high vascular resistance leading to fluid translocation may lead to acute cardiogenic pulmonary oedema (ACPOE)

Always search for a potential reversible cause for acute hear failure (AHF)

Most cases of pulmonary oedema respond symptomatically to a combination of oxygen, opiates and diuretics. Vasodilators might help. Inotropic agents are of unproven additional safety or benefit

Discharging patients into a structured long-term management plan is key to improving the prognosis of acute heart failure

KEY WORDS: heart failure, prognosis, pulmonary oedema, treatment

Table 1. Precipitating factors for acute heart failure.

Ref.	No. of patients	Population characteristics	Leading cause	%
8	48,612	Age 73 years Women 52% Mean LVEF 39%	Multiple Respiratory infection Ischaemia Arrhythmia	61 15 15 14
9	150	Age 75 years Women 40% Moderate to severe reduction in LV function 67%	Myocardial ischaemia Arrhythmia Hypertension Infection Anaemia Drug omission Salt excess	51 31 29 18 13 8 8

LVEF = left ventricular ejection fraction.

cases are associated with a normal ejection fraction, especially patients with rapid AF or valve disease.

Diagnosis

The differential diagnosis of ACPOE in the emergency room is often difficult. The typical patient is pale, cool to touch and sweaty, reflecting intense sympathetic activation, obviously breathless and sitting upright. Coughing up pink frothy sputum is relatively uncommon. Patients may have a central or peripheral cyanosis and reduced oxygen saturations. The venous pressure is often clinically normal and the jugular venous pressure hard to estimate. Most patients do not have peripheral oedema. Auscultation of the chest should reveal bilateral fine basal pulmonary crepitations that do not clear on coughing and there may be high-pitched expiratory rhonchi. Circumstantial evidence, such as a previous history of myocardial infarction (MI) or the presence of concomitant heart disease such as the murmurs of mitral or aortic valve disease or rapid AF provides useful diagnostic pointers.

Patients should have blood taken for haematology, electrolytes and renal function, albumin and glucose. Venous rather than arterial blood gases suffice to assess acid-base balance, provided transcutaneous oxygen saturations are available. A chest X-ray should be done to exclude pulmonary causes of breathlessness (pneumonia, lung cancer, pneumothorax) and to identify pulmonary congestion. An ECG will confirm heart rhythm and any evidence of conduction abnormalities or of ventricular hypertrophy or myocardial ischaemia.

Many also have potential non-cardiac reasons for breathlessness. Until recently the gold standard for confirming a diagnosis has been cardiac imaging, usually echocardiography, showing a reduced LVEF. However, some people have all the features of heart failure, respond to treatment with diuretics and yet have a normal LVEF. This appears to be a heterogeneous group of patients, for example[10]:

- rarer causes of heart failure such as constrictive pericarditis
- paroxysmal disease (ischaemia or arrhythmia)
- forme fruste of systolic dysfunction (long-axis dysfunction)[11] or
- genuine diastolic dysfunction.[12]

Cardiac imaging, especially in unsophisticated hands, has a high rate of misclassification. Alternative means of confirming or refuting a diagnosis have been sought.

Biomarkers

The most promising recent approach to diagnosis has been the use of biomarkers, especially brain natriuretic peptide (BNP or NT-proBNP).[13] The diagnosis can be refuted with some confidence if peptide levels are low, although levels may not be elevated in constrictive pericarditis (a group of patients who should not develop ACPOE). If levels are markedly elevated, the patient is in sinus rhythm and renal function not grossly abnormal, the diagnosis of AHF may be made with confidence. Levels of BNP and NT-proBNP are increased in patients with AF even in the absence of other evidence of heart failure, suggesting that a higher diagnostic threshold is required in this group.[14] Some patients have intermediate levels, potentially leading to diagnostic uncertainty. However, if a patient has equivocal symptoms and signs combined with a modest elevation in NT-proBNP, it is most likely to represent cardiac dysfunction. Severe symptoms combined with a slight elevation in NT-proBNP suggest the main diagnosis is not heart failure. As always, clinical judgement is required.

BNP/NT-proBNP is the best prognostic marker in patients with heart failure.[15] A divergence between BNP/NT-proBNP and clinical assessment usually reflects a deficiency in the accuracy of clinical diagnosis. Although BNP and NT-proBNP may appear disproportionately elevated in patients with renal dysfunction or AF, these patients also have a worse prognosis.[16,17]

ESC guidelines now suggest that NT-proBNP above 400 pg/ml is required for the diagnosis of heart failure.[3] This refers mainly to outpatients with chronic symptoms and signs. Patients with symptoms at rest due to heart failure usually have levels of NT-proBNP over 1,500 pg/ml. In a study of BNP, a value of over 100 pg/ml was found most useful in confirming the presence of heart failure.[18] Grossly elevated BNP/NT-proBNP indicates a bad prognosis but not the reason why. This requires investigation of both renal and cardiac function.

Treatment of ACPOE

The reason for ACPOE should be sought and managed. Many patients are hypertensive and have high LAPs but normal cardiac output. Treatment of ACPOE has changed little over 40 years.[9] Most

patients receive intravenous (iv) diuretics and high-flow oxygen, some are given opiates and vasodilators, and even fewer assisted ventilation. Conventional treatment is highly effective – to the relief of patients and doctors but to the great frustration of those trying to develop new treatments. This may be an example of a largely satisfied need. A few patients do not respond to conventional therapy and require advanced treatment that might include mechanical ventilation, inotropic therapy or circulatory support.

Conversely, patients with progressive exertional breathlessness and worsening oedema who often have pulmonary hypertension, a low cardiac output and worsening renal dysfunction are often difficult to manage. Mixing these two patient populations has probably led to the failure of many clinical trials in AHF. These trials have also lacked a consistent methodology for assessing symptoms.[19]

Oxygen and ventilation

ACPOE can lead to hypoxaemia which can be relieved by increasing inspired oxygen concentration. Hypoxaemia, in turn, leads to pulmonary vasoconstriction, increasing the load on the right ventricle. However, overcorrection may lead to systemic vasoconstriction and could be harmful.[20] There is no scientific evidence that high-flow oxygen therapy improves symptoms or outcome in ACPOE, but it is routinely given and anecdotally often helps symptoms, although distress is increased in some patients when given by mask. It can usually be given very quickly, even before the patient reaches hospital. Care is required when giving oxygen if the patient has lung disease as oxygen can reduce respiratory drive causing hypercapnia (respiratory failure). Ideally, use of oxygen should be restricted to patients with an arterial oxygen saturation below 95%. When high-flow oxygen is unable to correct hypoxaemia, non-invasive ventilation (NIV) should be considered. A large trial has shown that NIV does not improve outcome but may improve symptoms not responding to first-line measures.[6] If hypercapnia develops, the patient may require invasive ventilation (Table 2) unless a decision for palliative care only is made, in which case sufficient morphine to relieve distress is warranted after discussion with relatives.

Opiates

Opiates rapidly relieve distress and slow respiratory rate, but there is little evidence that they have any haemodynamic benefit in AHF. Morphine (2.5–5.0 mg iv) should be given with metoclopramide (5–10 mg) to reduce nausea and vomiting. One recent large study reported that only 3% of patients were treated with opiates. It is not clear whether this is an advance or deficiency in care.[6,21]

Intravenous diuretics

Although diuretics are not a logical treatment for many cases of ACPOE they are usually given. There is inconclusive evidence of clinically worthwhile venodilator effects.[22] The dose given should vary according to the patient's usual daily dose. Diuretic-naive patients should receive 40 mg of furosemide or 1 mg of bumetanide as a bolus. Patients already taking diuretics may be given double their usual daily dose. If the dose of furosemide exceeds 120 mg, an initial bolus of 80–120 mg should be followed by a short iv infusion. Continuous infusion should be reserved for difficult cases requiring several days of iv therapy. Patients with difficulty passing urine lying down should have a urinary catheter.

Table 2. Indications for invasive ventilation (usually more than one factor required).

Indication	Threshold level
Exhaustion	
Hypoxaemia despite high-flow O_2	<8 kPa (arterial saturation <93%)
Hypercapnia	>8 kPa
Acidosis	pH <7.2
Failure to respond to NIV	

NIV = non-invasive ventilation.

Vasodilators

The evidence that vasodilators are safe and/or effective in patients with ACPOE is not robust. Nitrates are used in 20–50% of cases in reports of AHF[9,23–25] and are recommended as routine by some authorities.[6] Vasodilators may cause hypotension that can exacerbate myocardial perfusion deficits, which may be lethal. Nitrates are the greatest culprit. In hypertensive patients, nitrates may be used without invasive haemodynamic monitoring provided blood pressure (BP) is monitored carefully. In patients with an arterial systolic BP under 120 mmHg consideration should be given to invasive haemodynamic monitoring to avoid excessive reductions in LV filling pressures and hypotension. When such monitoring is not possible, vasodilators should be used cautiously and BP checked every 15 minutes.

Inotropic agents

There is no obvious role for inotropic agents in the management of ACPOE. If the patient is hypotensive and developing shock, the alternatives are reversing the underlying problem, usually by surgery or percutaneous intervention or reverting to palliative care. There is no evidence that renal-dose dopamine is effective. Levosimendan is both an inotropic agent and a vasodilator. It appears effective for patients with severe chronic, low output heart failure but there is no convincing evidence of benefit for patients with ACPOE. This agent is not available in the UK.[24]

Other interventions

Ultrafiltration is best targeted at patients with gross fluid overload. Intra-aortic balloon pumping can be useful as an interim measure in patients with a surgically remediable problem such as mitral regurgitation. Patients with rapid AF should receive iv digoxin and/or amiodarone.[26] Care should be taken to avoid phlebitis with the latter agent. Patients with ACPOE cannot lie flat so, unless the patient is ventilated, MI should be managed with thrombolysis, and unstable angina with judicious doses of nitrates. Infection will require antibiotics.

All patients should receive heparin prophylaxis for deep venous thrombosis or full-dose heparin if in AF.

Monitoring

Patients should have heart rate and rhythm, respiratory rate, BP and transcutaneous oxygen saturations monitored until they have recovered. Biochemistry and blood gases should be repeated after two hours if there is poor response to initial therapy or sooner if concomitant respiratory disease or initial blood gases are grossly abnormal.

Further treatment

Long-term treatment is complex and should be managed by someone with expertise in managing this deadly condition who can appropriately select patients for treatment with diuretics, angiotensin converting-enzyme inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone antagonists, cardiac resynchronisation devices, defibrillators, digoxin and anticoagulation, and also select patients who will benefit from revascularisation or valve or myocardial surgery. A management plan for ACPOE is given in Table 3.

Outcome and risk stratification

The overall inhospital mortality from heart failure is about 5% but may be higher for ACPOE (about 12%).[9] One-year mortality among those who survive until discharge is about 40%. Greater emphasis on post-hospital care is required to improve long-term outcomes. Concomitant MI, diabetes, low BP, renal dysfunction, more severe LV dysfunction and, more recently, elevated BNP or troponin predict an adverse outcome in patients with ACPOE.[9,27–29] In clinical trial populations of AHF, six-month mortality has ranged between 14% and 26%.[23–25]

Table 3. Management plan for acute cardiogenic pulmonary oedema.

Treatment step	Treatment
1	Sit upright and give high flow (60–100%) O_2 (caution if severe chronic respiratory disease)
2	iv bolus diuretic: at least 40 mg furosemide or 1 mg bumetanide if diuretic naive or 80–120 mg if on chronic diuretic therapy. Use infusion if higher doses required *Note*: patients unable to pass urine in a bedpan should have a urinary catheter
3	Diamorphine initially 2.5 mg (caution if severe respiratory disease) and metoclopramide (10 mg) iv. May be repeated after 15 min if required
4	Sublingual nitrate spray, followed by iv nitrate infusion, initially GTN 20 μg/min or ISD, initially 2 mg/hour titrated up to 10-fold at 15 min intervals. BP monitoring essential. Caution with both if systolic BP <120 mmHg
5	CPAP if patient exhaustion or failure to respond within 60 min *OR*
6	Mechanical ventilation if failure to tolerate CPAP and need for ventilation
7	Circulatory support – an ominous sign, generally successful only as a bridge to a rescue procedure (surgery or percutaneous cardiac procedure)

Note: at all steps a reminder should be given to treat the cause.

Atrial fibrillation: digoxin, 500 μg iv over 1 min, can be repeated once after 10 min but often not very effective. May be supplemented by amiodarone 450 mg iv as a bolus, ideally through a long line, but may be given in a peripheral vein provided confidence that there will be no extravasation and flushed with normal saline. A further 300 mg can be given after 30 min. Amiodarone and digoxin combined may be superior to either alone. iv esmolol should also be considered, although no evidence base.
Myocardial ischaemia: consider nitrates, perhaps cautious use of esmolol if this fails and the patient has a tachycardia.
Myocardial infarction: thrombolysis.

BP = blood pressure; CPAP = continuous positive airway pressure; GTN = glyceryl trinitrate; ISD = isosorbide dinitrate; iv = intravenous.

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