Prompt diagnosis and treatment of acute heart failure will reduce mortality and morbidity

In people aged more than 65 years acute heart failure is one of the more common causes of hospital admission in which a better prognosis is achievable if the condition is diagnosed and treated early. In this article Alison Warren describes some of the diagnostic features of acute heart failure and the pharmacological strategies used to manage the condition according to its aetiology.

Introduction

Acute heart failure is a leading cause of hospitalisation in people aged more than 65 years. In some cases this will be a result of new onset acute heart failure while in many cases it will be the result of decompensation in a patient with pre-existing chronic heart failure. Whichever category the patient falls into the prognosis is poor with high in-hospital and one-year mortality, and a high probability (40–50%) of one or more re-admissions over the next 12 months.[1–3] In addition, many of these patients may have or may develop renal dysfunction — the cardio-renal syndrome — complicating the management and adversely affecting the longer-term outcome.

Aetiology

Acute heart failure is defined by the European Society of Cardiology as: 'The rapid onset of symptoms and signs secondary to abnormal cardiac function, which may occur with or without prior cardiac disease'.[4] There are many causes of acute heart failure (see Table 1) — with decompensation of chronic disease, acute coronary syndromes (ACS) and coronary heart disease, arrhythmias, hypertension and valvular disease being the more common aetiologies. The clinical syndrome is characterised by a reduction in cardiac output, reduced perfusion of tissues and increased tissue congestion. This results in the myocardium being unable to maintain sufficient cardiac output to meet the demands of the peripheral circulation.

Signs and symptoms

Most patients have significant volume overload and congestive symptoms will predominate — pulmonary oedema and shortness of breath associated with left-sided failure and peripheral oedema, raised venous pressure with or without ascites with right-sided failure (often a combination of the two will be seen). There will commonly be increased body weight, reduced urine output, fatigue and muscle weakness. There may be haemodynamic compromise with hypotension and poor tissue perfusion resulting in worsening renal function, hepatic dysfunction and cardiac compromise. In the most severe form the patient will be in cardiogenic shock.

Table 1. Aetiology of acute heart failure[1,2,4]

- ☐ Decompensated chronic heart failure (up to two-thirds of cases)
- ☐ Acute coronary syndromes, such as myocardial infarction, angina, mechanical complications of infarction
- ☐ Hypertension (often associated with preserved systolic function)
- ☐ Acute arrhythmia, such as ventricular tachycardia or fibrillation, atrial fibrillation
- ☐ Valvular disease, such as mitral regurgitation, aortic stenosis
- ☐ Cardiomyopathy (including post-partum) or myocarditis
- ☐ Cardiac tamponade
- ☐ Aortic dissection
- ☐ Infection — particularly in known heart failure
- ☐ Lack of compliance with medication, or fluid intake, or use of alcohol or NSAIDs

Diagnosis

The diagnosis is based on a summary of symptoms and the clinical findings. Initial investigations will include an ECG, chest X-ray and blood tests for renal function and electrolytes, blood glucose, haemoglobin, platelets and clotting parameters, and cardiac enzymes. In severe cases arterial blood gases will be required.

In acute heart failure the ECG is rarely normal and although it often does not show any significant abnormalities it may be a useful diagnostic tool to help determine aetiology (for example, ACS or arrhythmias). The chest X-ray will give information relating to cardiac size and the presence of pulmonary congestion, and may allow differentiation between cardiac and lung pathology. However, the essential tool for evaluation of the patient is the echocardiogram, which is used to evaluate and monitor regional and global left and right ventricular function, valvular structure and function, pericardial pathology and mechanical complications of infarction. The echocardiogram thus directs the clinician to the aetiology and/or severity of the problem, which in turn will direct the treatment plan.

Brain natriuretic protein (BNP) is released

Unlike the situation with chronic heart failure, in acute heart failure there is a lack of controlled clincial trial data to define the optimum treatment.

from the cardiac ventricles in response to increased wall stretch and volume overload.[4] Although there are no consensus reference values for BNP in people with healthy hearts or cardiac pathologies there has been interest in the use of BNP — or N-terminal pro-BNP — levels as a negative predictor of heart failure. Therefore, even though BNP levels may be potentially useful to exclude heart failure they are not routinely used in the evaluation of acute heart failure.

Goals of treatment

The immediate goals of treatment are to improve symptoms and stabilise the haemodynamic condition, but successful treatment involves identifying the aetiology and putting into place a comprehensive treatment plan.[4,5]

Initially the main priorities are to achieve adequate oxygen levels and relieve distress. Subsequently, treatments are given to reduce preload (volume returning to the heart) and afterload (the volume against which the heart pumps). These will include vasodilators, diuretics and in some cases inotropes. Once the patient has been stabilised further treatments will be required for the longer term management of the disease. Reviewing the aetiology will determine whether there are any underlying correctable causes (for example, valvular disease, revascularisation of coronary disease, control of rhythm and/or rate disorders). In addition, introduction of medications for the management of chronic heart failure will be needed. The longer term management is beyond the scope of this article but is guided by numerous randomised controlled trials that form the basis of recommendations from NICE,[6] SIGN[7] and the international cardiology community.[8,9]

Pharmacological treatments for acute heart failure

Unlike the situation with chronic heart failure, in acute heart failure there is a lack of controlled clinical trial data to define the optimum treatment — and the few trials that have been undertaken have focussed on symptom relief rather than on patient-oriented outcomes. The recommendations outlined below are drawn from the available evidence base and consensus expert opinion presented in recently published international guidelines.[4,5]

Oxygen

Prescription of oxygen is needed to improve and maintain the oxygen saturation to 95–98%. This may be done by increasing the fraction of inspired oxygen delivered. If it is not possible to achieve this via nasal administration alternative non-invasive techniques may be used, which include:[10]

© Timothy Large/ istockphoto

- Continuous positive airways pressure (CPAP). Using a face mask this method results in a reduction in the work of breathing and a decrease in metabolic demand.
- Non-invasive positive pressure ventilation (NIPPV) which uses a ventilator and a face mask or nasal administration set.

These techniques have been shown to improve oxygenation without the need for endotracheal intubation. They therefore reduce the need for mechanical ventilation (which is reserved for patients who cannot tolerate the above or those who have respiratory muscle fatigue).

Opiates

Small bolus doses (2–3mg) of morphine are used if the patient is restless or short of breath. Symptom relief results from a combination of venodilatation, mild arterial dilation and a reduction in heart rate thus reducing oxygen demand.

Vasodilators

Vasodilators are a first-line treatment if hypoperfusion is associated with an adequate blood pressure.[4,5] Nitrates are available by the sub-lingual, buccal, oral or intravenous routes. Low dose nitrates result in venodilatation. As the dose is increased they will also produce arterial and coronary vasodilatation, thus improving preload, afterload and coronary blood flow. Therefore, in the acute phase, the dose should be up-titrated to the maximum tolerated with careful monitoring of the blood pressure. In many cases dosage may be limited by hypotension — with a decrease in dose needed if the systolic blood pressure drops below 90–100mmHg.

Typical doses of intravenous nitrates are:

- glyceryl trinitrate 20–200micrograms/ minute
- isosorbide dinitrate 1–10mg/hour.

Prolonged use of nitrates is limited by the rapid development of tolerance — within 24 hours. Sodium nitroprusside offers an alternative treatment, which is of particular use in the setting of acute hypertensive heart failure or valvular regurgitation where prolonged administration of vasodilators may be needed. Care should be taken during administration (because the administration sets must be covered to protect them from

exposure to light) and in the presence of renal insufficiency (accumulation and risk of cyanide toxicity with prolonged administration can occur).

The newer agent nesiritide, a recombinant form of human BNP, is given intravenously and results in venous, arterial and coronary vasodilatation. Early clinical trials demonstrated that in acute decompensated heart failure nesiritide improved symptoms and appeared to be safer than dobutamine. However, the safety of nesiritide compared with diuretics and conventional vasodilator therapy is less clear, with short term increases in the risk of death and worsening of renal function, and thus further research is needed to clarify its place, if any, in the management of this patient group.[11,12]

Diuretics

Although lacking trial data with 'hard' clinical outcomes, it is clear from clinical experience that diuretics give rapid symptomatic relief of breathlessness and thus, for reducing fluid retention diuretics are a mainstay of treatment.[13] Diuretics increase urinary volume by increasing the excretion of water and sodium chloride. Consequent reduction of the plasma and extracellular volume reduces right and left heart filling pressure reducing both peripheral and pulmonary congestion.

Because of their relative potency loop diuretics (furosemide, bumetanide) are the principal agents used. Given orally the superior bioavailability of bumetanide (80–95%) versus furosemide (45–70%) may influence choice.[14] However, in the acute phase the intravenous route, with the added advantage of offering some vasodilatory effects, will be required. In this case bumetanide offers no advantage over furosemide, and because of familiarity of dosing and ease of administration furosemide is generally considered the first choice drug.

© Tomaz Bercic/istockphoto

Doses need to be titrated to effect taking into account the patient's pre-existing diuretic regimen (if any) and renal function (higher doses are required in reduced renal function). Careful dosing is mandatory to ensure adequate diuresis without over diuresis. Dosing must be guided by symptoms and signs of fluid overload, fluid balance measurements and daily weights with careful monitoring of renal function and electrolyte status (particularly sodium, potassium and magnesium levels). Similarly, attention must be given to signs of fluid depletion such as worsening renal function, symptomatic hypotension and muscle cramps, and doses altered accordingly. In some cases achieving an adequate response may be difficult and several strategies have been suggested to improve diuresis or overcome diuretic resistance, which may involve giving thiazide diuretics and/or spironolactone in combination with loop diuretic therapy. Table 2 outlines some of the commonly used strategies.[4,15]

Although lacking trial data with 'hard' clinical outcomes, it is clear from clinical experience that diuretics give rapid symptomatic relief of breathlessness and thus, for reducing fluid retention diuretics are a mainstay of treatment.

New agents that act by antagonism of the vasopressin (V2) receptor are under development. The V2 receptor is located in the renal collecting tubules and antagonism leads to reduced free water absorption without resulting in hyponatraemia. Two short term studies of tolvaptan were promising in terms of symptom relief without worsening renal function but, disappointingly, a subsequent longer term trial showed no reduction in mortality or morbidity at one year.[16]

Inotropes

Inotropes may be needed early in the management of acute heart failure, such as in cardiogenic shock associated with acute myocardial infarction (AMI) requiring urgent coronary revascularisation. Their use may be less urgent in other patients such as those with peripheral hypoperfusion (hypotension and decreased renal output) who are refractory to diuretics and vasodilator therapy as outlined above. The most commonly used agents are dobutamine, dopamine and the phosphodiesterase inhibitors enoximone or milrinone.[4,5,17]

Dobutamine, usually the first choice agent, exerts its inotropic effects via the beta 1-adrenoreceptor and is administered as a continuous infusion at a rate of 2–10 micrograms/kg/minute. The positive inotropic effects improve cardiac output and consequently improve tissue perfusion and

Table 2. Strategies for overcoming diuretic resistance[4]

- ☐ Increase dosage
- ☐ Consider changing the drug, such as furosemide to bumetanide or *vice versa*
- ☐ Change to intravenous route
- ☐ Administer by continuous infusion
- ☐ Add thiazide (such as bendroflumethiazide) or thiazide-like diuretic (such as metolazone) for synergistic effect (Note that thiazides, with the exception of metolazone, are ineffective if CrCl <30ml/minute)
- ☐ Add aldosterone antagonist (spironolactone, eplerenone after acute myocardial infarction)
- ☐ Limit fluid intake (typically to 1000–1500ml/24hours)
- ☐ Limit sodium intake (≤2g/day)
- ☐ Reduce dose of ACE inhibitor
- ☐ Ultrafiltration[15]

renal output. Blood pressure may increase slightly but more commonly little or no change is seen. Rarely, higher doses may be used but these are generally avoided because of dose-related increases in heart rate, which may be dose limiting, particularly in patients with underlying atrial fibrillation. Short term use is desirable because there is some tolerance and partial loss of effect after only 48 hours of therapy.

Historically, 'renal dose dopamine' (2–4 micrograms/kg/minute) has been used in combination with dobutamine to preserve renal function. At these low doses effects through the dopamine receptors predominate and small, uncontrolled studies support this theory demonstrating that dopamine increases sodium and water excretion. However, use has fallen out of fashion because trials in the intensive care setting in which dopamine was given to limit renal dysfunction failed to show a benefit and highlighted potential adverse effects associated with use.[18]

In patients who have preserved blood pressure phosphodiesterase inhibitors offer an alternative regimen. These drugs exert their effect by inhibiting the breakdown of cyclic AMP producing inotropic effects with vasodilatation (hence they are often referred to as inodilators). The two agents available are enoximone and milrinone.

More recently there has been interest in a new class of agent known as calcium sensitizers, which act by stabilising the conformational change to troponin C when it binds to calcium, which facilitates myocardial cross-binding and, as a result, improves contractility. Levosimendan, currently unlicensed in the UK, is the most studied compound in this class. Most data from trials involved treatment for 6–24 hours given as a loading dose followed by a continuous infusion. However, because the half-life is in the region of 80 hours haemodynamic effects are prolonged and last 48 hours or more after stopping the infusion. In phase II trials beneficial effects were seen compared to dobutamine and thus larger phase III trials (REVIVE and SURVIVE) were undertaken. The results did not show the benefits anticipated and the future development of this agent is unclear.[19]

Introduction of chronic therapy

Once the patient has stabilised in the acute phase it is important to consider the longer term management. This will include the introduction and subsequent up-titration of evidence-based strategies for chronic heart failure. Having a treatment plan in place is essential for the close monitoring and follow-up that the majority of these patients require to reduce the mortality and morbidity associated with heart failure.[6,7,8,9]

Conclusion

Acute heart failure is a common reason for hospital admission. Prompt diagnosis and treatment is essential to reduce the mortality and morbidity associated with this condition. Pharmacological intervention is an important part of this treatment package and although there is not an extensive evidence base, recent international guidelines exist to guide patient management. Newer agents are sought but to date limited benefits on mortality and morbidity have been seen. Once over the acute event ongoing management of these patients, in line with guidelines for chronic heart failure, is required.

Declarations of interest

The author has no interests to declare.

Alison Warren, lead cardiac pharmacist, Brighton and Sussex University Hospitals NHS Trust

Series editors:

Jonathan Underhill, National Prescribing Centre, Liverpool, UK

Scott Pegler, principal pharmacist, medicines information manager, Morriston Hospital, Swansea NHS Trust, UK

John Bane, medicine information/clinical trial pharmacist, Pharmacy Dept, Sheffield Childrens NHS Foundation Trust, Sheffield, UK

References

1. Nieminen M, Bratsaert D, Dickstein K *et al*. EuroHeart failure survey II (EHFS II) a survey on hospitalised acute heart failure patients: a description of the population. *Eur Heart J* 2006; **27(22):** 2725–36.
2. Yancy C, Lopatin M, Stevenson H *et al*. Clinical presentation, management and in-hospital outcomes of patients admitted with acute decompensated heart failure and preserved systolic function. *JACC* 2006; **47:** 76–84.
3. Siirilia-Waris K, Lassus J, Melin J *et al*. Characteristics, outcomes and predictors of 1 year mortality in patients hospitalised with acute heart failure. *Eur Heart J* 2006; **27(24):** 3011–7.
4. The Task Force of Acute Heart Failure of the European Society of Cardiology. Executive summary on the guidelines for the diagnosis and treatment of acute heart failure. *Eur Heart J* 2005; **26(4):** 384–416. (Full text available on website only: www.escardio.org/knowledge/guidelines.)
5. American Society of Heart Failure. Evaluation and management of patients with acute decompensated heart failure. *J Card Fail* 2006; **12:** e1–e122. (www.hfsa.org/hf_guidelines.asp).
6. National Institute for Health and Clinical Excellence. *Chronic heart failure: management of chronic heart failure in adults in primary and secondary care*. Clinical guideline number 5 July 2003. Available from www.nice.org.uk/page.aspx?o=CG005.
7. Scottish Intercollegiate Guidelines Network. *Management of chronic heart failure. A national clinical guideline.* Clinical Guideline number 95 February 2007. Available from www.sign.ac.uk/pdf/sign95.pdf.
8. The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure: full text (update 2005). *Eur Heart J* 2005; **26(11):** 1115–1140. Also available from www.escardio.org/knowledge/guidelines or www.eurheartj.org.
9. McMurray J, Cohen-Solal A, Dietz R *et al*. Practical recommendations for the use of ACE inhibitors, beta-blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. *Eur J Heart Fail* 2005; **7:** 710–21.
10. British Thoracic Society Standards of Care Committee. Non-invasive ventilation in acute respiratory failure. *Chest* 2002; **57:** 192–211.
11. Sackner-Bernstein JD, Kowalski M, Fox M *et al*. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA* 2005; **293(15):** 1900–1905.
12. Yancy C. Benefit-risk assessment if nesiritide in acute decompensated heart failure. *Drug Safety* 2007; **30(9):** 765–81.
13. Farris R, Flather MJ, Percell M *et al*. Diuretics for heart failure. *Cochrane Database Systematic Review* 2006; 1 00003838.
14. Thompson healthcare products. Micromedex website www.thomsonhc.com/home/dispatch.
15. Costanzo M, Guglin M, Saltzberg M. Ultra filtration versus intravenous diuretics for patients hospitalised for acute decompensated heart failure. *JACC* 2007; **49:** 675–83.
16. Konstam M, Gheorghiade M, Burnett J *et al*. Effects of oral tolvaptan in patients hospitalised with worsening heart failure: The Everest Outcome Trial. *JAMA* 2007; **297(12):** 1319–1331.
17. Petersen JW. Inotropes in the management of acute heart failure. *Crit Care Med* 2008; **36:** S106–11.
18. Belloma R, Chapman M, Finfer S. Low dose dopamine in patients with early renal dysfunction: a placebo controlled randomised trial — Australia and New Zealand Intensive Care Society (ANZICS) clinical trials group. *Lancet* 2000; **356:** 2139–43.
19. De Luca L, Colucci W, Nieminen B. Evidence base on the use of levosimendan in different clinical settings. *Eur Heart J* 2006; **27(16):** 1908–1920.