REVIEW
New and emerging drug therapies for the management of acute heart failure
H. Krum and D. Liew
National Health and Medical Research Council Centre of Clinical Research Excellence in Therapeutics, Departments of Medicine, and Epidemiology and Preventive Medicine, Monash University Central and Eastern Clinical School, Alfred Hospital, Melbourne, Victoria, Australia

Abstract
In recent times, there have been many developments in therapies for acute heart failure, in contrast to the preceding 20 years. These have been mainly fuelled by new and expanding knowledge about the pathophysiology of heart failure, which has allowed for insight into potential therapeutic strategies. This review will examine the key emerging therapies for acute heart failure, in light of available pathophysiological and clinical evidence. (Intern Med J 2003; 33: 515–520)

Key words: acute heart failure, nesiritide, levosimendan, tezosentan, review.

BACKGROUND
Epidemiology of acute heart failure in Australia
In Australia, there are no specific data on the incidence of acute heart failure, nor the number of people affected, for many of whom episodes will be recurrent. The estimated overall prevalence of chronic heart failure is 1.5% (300 000 persons affected), and the incidence is 0.0015 per person-year (30 000 new cases each year).1 In 1998–1999, heart failure (not further specified) was the principal diagnosis in 41 900 hospitalizations, which represented 0.7% of all hospitalizations and 10% of hospitalizations for cardiovascular disease.2 Approximately 3700 (9%) of these resulted in patients dying in hospital.2 During the same period, approximately 2600 deaths (2% of total) were ascribed to heart failure.3

In 1993–1994, the direct cost of treating cardiovascular disease in Australia was $A3.9 billion, representing 12% of total health-care expenditure. Heart failure accounted for $A420 million, excluding that of downstream complications.4

Pathophysiology of acute heart failure
The pathophysiological hallmark of acute heart failure is a sudden decrease in cardiac output causing activation of neurohormonal pathways, particularly the renin-angiotensin-aldosterone, sympathetic nervous and endothelin systems.5 The combined effects of elevations in angiotensin II, aldosterone, adrenergic hormones and endothelin include avid sodium and water retention, peripheral vasoconstriction, tachycardia and renal vasoconstriction. These result in an increase in cardiac workload, which further exacerbates low output, and a ‘vicious cycle’ ensues (Fig. 1).

Endogenous vasodilating systems are those which oppose the effects of vasoconstricting and antinatriuretic neurohormones, and comprise natriuretic peptides, nitric oxide and prostaglandins. Their effects include: (i) natriuresis and diuresis, (ii) arterial and venous dilatation, (iii) increased stroke volume and (iv) inhibition of renin, aldosterone and noradrenaline synthesis.5 In decompensated heart failure, the endogenous vasodilating systems are overwhelmed by the effects of the activated renin-angiotensin-aldosterone, sympathetic nervous and endothelin systems.

STANDARD TREATMENT OF ACUTE HEART FAILURE
I. Drug therapies
Until very recently, there have been very few randomized controlled clinical trials of drug therapies in acute heart failure, and therefore no pharmacological strategy is currently mandated by high-level evidence. (Acute heart failure is defined in this setting as reduction in ventricular function causing rapid deterioration in clinical status and necessitating hospitalization in most cases; and either arises de novo or is caused by acute decompensation of chronic heart failure.)

With this caveat in mind, current guidelines from the American College of Cardiology and the American Heart Association are based on therapies aimed at
reducing intraventricular filling pressures, improving cardiac output and achieving euvoalaemia in the volume-overloaded patient. General supportive care includes the judicious use of diuretics (particularly loop diuretics), supplemental oxygen and anticoagulation. Anticoagulation is particularly indicated if patients are required to rest in bed for prolonged periods of time. Vasodilator therapies and inotropic agents currently represent the main treatment options for patients with acute heart failure who require additional cardiac support despite the above measures.

**Vasodilator therapies**

The mainstays of vasodilator therapy for acute heart failure are nitroglycerin and sodium nitroprusside. These agents are used for preload reduction and, thus, diminution of intracardiac pressures. They also have modest effects on afterload due to limited actions on the arterial circulation. The pharmacological actions of nitroglycerin and sodium nitroprusside are vasodilation induced by exogenous nitric oxide donation. The drawbacks to these agents are mainly tolerance, headache and hypotension. Occasionally, there is rapid development of tachyphylaxis with i.v. administration.

**Inotropic agents**

Conventional inotropic agents increase cyclic adenosine monophosphate (AMP) within the myocardium, thus permitting enhanced entry of calcium into cells and enhanced actin–myosin coupling. These agents act either via activation of β-adrenergic receptors (i.e. dobutamine and dopamine) or via inhibition of specific cardiac phosphodiesterase type III (i.e. milrinone), and are parenterally administered.

Dobutamine and dopamine are catecholamines which stimulate β1-adrenoceptors within the myocardium to increase cardiac output. However, at moderate to high doses, dopamine also evokes systemic vasoconstriction. A major disadvantage of β1-agonists is that patients currently receiving beta-blockers (such as those with background chronic heart failure) may display resistance to their pharmacological effects. Conversely, concomitant use of β1-agonists makes the introduction of beta-blockade somewhat more difficult.

Milrinone has greater vasodilating properties than dobutamine. Therefore its actions are both the enhancement of contractility and reduction of afterload by systemic vasodilation. Its other advantage is that, being ‘downstream’ of the β1-adrenoceptor, it permits continuation of beta-blocker therapy among those already on it, or it may serve as a bridge to introduction of long-term beta-blockade.

The main adverse effects of both these classes of agents are significant hypotension and, more sinisterly, an increased propensity to lethal arrhythmias. In fact, available evidence suggests that long-term inotropic therapy increases the risk of mortality in patients with heart failure, regardless of the agent used. Furthermore, the

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**Figure 1** Pathophysiological pathways of acute heart failure (‘vicious cycles’), and the main sites of action of nesiritide, levosimendan and tezosentan.
II. Non-drug therapies

A variety of non-drug therapies have been advocated in the treatment of patients with acute heart failure, particularly in those with refractory volume overload. Ultrafiltration increases urinary output and absorption of excessive extravascular fluid, and may mitigate neurohumoral activation. In addition, renal impairment frequently accompanies acute heart failure. These provide the biological basis for accumulating data which suggest that the judicious application of ultrafiltration techniques may represent an efficacious adjunct to conventional therapies in acute failure, at least with regard to short-term clinical improvements.13

In the severely hypotensive patient with cardiogenic shock, intra-aortic balloon pump and variations of counter-pulsion support are often used as short-term therapy. Because of problems with line infection, this approach cannot be used long-term. However, it may be useful for bridging patients to more definitive procedures such as insertion of a ventricular assist device or cardiac transplantation.14

There has also been renewed interest in non-invasive positive pressure ventilation for the treatment of acute heart failure, with a recent trial showing that continuous positive airway pressure (CPAP) ventilation led to more rapid clinical improvement compared to placebo.15 CPAP may represent useful adjunctive treatment for the early management of acute heart failure.

NEW DRUG THERAPIES FOR ACUTE HEART FAILURE

Acute heart failure has been somewhat of a barren testing area for new drug therapies over the last 10–20 years. However, recent times have seen the emergence of a number of new agents, offering potentially significant advantages over current therapies.

To summarize, the limitations of current therapies are:

- increased arrhythmogenicity
- increase in risk of sudden death with prolonged use
- requirement for monitoring
- hypotension
- difficulty with ongoing use of background therapies such as beta-blockers (some agents)

Agents currently either just reaching the market, or currently being evaluated in late-phase trials, include nesiritide, levosimendan and tezosentan. Figure 1 indicates their main sites of action within the pathophysiological pathways of acute heart failure. A fourth class of agents, vasopressin antagonists, are in earlier stages of development.

Nesiritide

Of the novel agents, nesiritide is in the most advanced stages of development. The structure of nesiritide is identical to endogenously produced human B-type natriuretic peptide, one of a family of four presently known natriuretic peptides (A-type to D-type). The agent is manufactured from the bacterium *Escherichia coli* via recombinant DNA technology.16

Nesiritide binds to both A- and B-type natriuretic peptide receptors on endothelial and vascular smooth muscle cells, causing intracellular cyclic guanosine monophosphate production, subsequent systemic venous and arterial vasodilation and the reduction of preload and afterload. It also exerts diuretic and natriuretic effects and causes coronary vasodilation. Nesiritide has neither inotropic nor chronotropic effects and the vasodilation caused by nesiritide does not lead to reflex tachycardia or increased levels of noradrenaline.17

Phase II studies of nesiritide in heart failure included approximately 150 patients, using infusion and bolus doses, and varying durations of treatment. In general, haemodynamic parameters were significantly improved.

In an efficacy study,18 127 patients with acute decompenated heart failure were randomized to placebo or one of two regimens of nesiritide (each a bolus followed by infusion for up to 7 days). Nesiritide decreased both pulmonary capillary wedge pressure and systemic vascular resistance in a dose-dependent fashion, while cardiac index was increased (without an increase in heart rate, implying an increase in stroke volume). Clinical status was also improved and the drug was generally well tolerated.

A comparative study evaluated 305 acute heart failure patients randomized to either open-label ‘standard care’ or one of two double-blinded doses of nesiritide (each a bolus followed by infusion for up to 7 days).19 By 6 h, both nesiritide doses produced significant clinical improvement in global clinical status and dyspnoea and fatigue, which were still sustained until the end of therapy. In a substudy, it was found that, compared to the nesiritide group, ventricular arrhythmias occurred significantly more frequently among the 68 patients assigned to dobutamine within the ‘standard care’ group.20

The Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy (PRECEDENT) study involved 246 patients and compared two doses of nesiritide to dobutamine. Nesiritide and dobutamine were comparable in improving signs and symptoms of heart failure. Use of baseline and on-treatment Holter monitors, however, indicated significant arrhythmogenicity associated with use of dobutamine and lack of any arrhythmogenic or tachy-cardic effects of nesiritide.21

The Vasodilation in the Management of Acute Congestive heart failure (VMAC) trial, which recruited 489 patients, demonstrated that nesiritide was superior at reducing filling pressures compared to nitroglycerin and placebo, when added to standard care.22 Patients with acute coronary syndromes, advanced renal disease, significant arrhythmias, diastolic dysfunction, beta-blocker treatment, and those unable to be weaned off dobutamine and dopamine, were all safely managed with nesiritide. Furthermore, patients receiving beta-blockers responded to nesiritide at least as well as patients not on...
beta-blockers, without higher incidences of hypotension or bradycardia. Fewer adverse events occurred on nesiritide compared to nitroglycerin, and the incidence of symptomatic hypotension was similar for the two drugs.

In total, 1700 subjects have been involved in phase III trials of nesiritide, 1000 of whom received active drug. Based on the combined evidence for efficacy and safety, nesiritide was approved by the Food and Drug Administration in August 2001 for i.v. treatment of patients with acute decompensated heart failure.

The major adverse effect of nesiritide is dose-dependent hypotension. Nesiritide is contraindicated in patients hypersensitive to any of its components, and should not be used as primary therapy for patients with cardiogenic shock, or in patients with systolic blood pressures of less than 90 mmHg.

Currently, there are two ongoing phase IV studies of nesiritide. The Prospective Randomized Outcome Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor (PROACTION) study is a randomized, double-blind, placebo-controlled pilot trial of approximately 250 patients with decompensated heart failure that will evaluate the safety and tolerability of nesiritide used as first-line therapy in the emergency department, compared to standard care. The Follow-Up Serial Infusions of Natrecor (FUSION) study is a randomized, controlled, pilot trial designed to evaluate the utility of short, intermittent infusions of two doses of nesiritide in patients with acute heart failure at high risk of being readmitted to the hospital.

**Levosimendan**

Levosimendan acts by increasing myocyte sensitivity to calcium. The advantage of this approach is that, at least in theory, contractile performance is improved without increasing energy demand and without activation of cyclic AMP. Therefore, there is no increase in arrhythmogenicity. Levosimendan also induces vasodilatation via ATP-dependent potassium channel opening. Furthermore, calcium sensitization is reduced during diastole, thus permitting normal diastolic relaxation without diastolic calcium overload. The net result is improved inotropy as well as vasodilator activity with increased cardiac output, but without concomitant increase in oxygen demand.

The clinical efficacy and safety of levosimendan have been evaluated in two major trials. In a randomized, placebo-controlled, double-blind study of left ventricular failure due to an acute myocardial infarction (RUSSLAN), 504 patients were randomized (within 48 h of infarction) to a 6 h infusion of one of four doses of levosimendan or placebo. Although this was designed as a safety study (the primary end-point was hypotension or myocardial ischaemia of clinical significance), levosimendan-treated patients experienced lower risk of death and worsening heart failure than patients receiving placebo, both during the 6-hour infusion (2.0% vs. 5.9%; \( P = 0.03 \)) and over 24 h (4.0% vs. 8.8%; \( P = 0.04 \)). A reduction in all-cause mortality in the active treatment groups compared to placebo was also noted over 14 days (11.7% vs. 19.6%; \( P = 0.03 \)). There was no increase in hypotension or ischaemia with the different doses of levosimendan used in comparison to placebo (\( P = 0.32 \)).

In the Levosimendan Infusion versus Dobutamine (LIDO) trial, 203 patients were assigned to levosimendan or dobutamine in a multicentre, randomized, double-blind clinical trial. The primary end-point was improvement in haemodynamic parameters (defined as an increase of \( \geq 30\% \) in cardiac output and a decrease of \( \geq 25\% \) in pulmonary capillary wedge pressure) at 24 h. Twenty-eight per cent of subjects in the levosimendan group reached the primary end-point, compared with 15% in the dobutamine group (\( P = 0.02 \)). At 180 days, the mortality rates were 26% and 38% within the levosimendan and dobutamine groups, respectively (\( P = 0.03 \)).

However, the results of the LIDO study should be interpreted with caution because use of dobutamine may be associated with excess mortality and it is unclear whether levosimendan would be associated with an overall increased or decreased risk of mortality, if compared to placebo.

The Randomized, Multicentre Evaluation of Intravenous Levosimendan Efficacy versus Placebo in the Short Term Treatment of Decompensated Chronic Heart Failure (REVIVE) study, which is currently ongoing in the USA and focused on efficacy, will hopefully address many of the outstanding issues with levosimendan.

Lefosimendan is currently approved as a positive inotropic agent in the setting of acute heart failure in many countries and is available in Australia and New Zealand under special access for patients who are refractory to standard acute heart failure therapies.

**Tezosentan**

Endothelin is a 21 amino acid peptide which acts not only as a potent vasoconstrictor, but also as a profibrotic, pro-inflammatory and a comitogen. It is implicated in a variety of cardiovascular diseases characterized by vasoconstriction, cardiac dysfunction and ischaemia. In the setting of acute myocardial infarction, endothelin levels rise and coronary vasoconstriction contributes to worsening myocardial function.

Against this background, a variety of interventions that reduce the activity of the endothelin system have been tested for treatment of heart failure. Tezosentan is termed a dual endothelin receptor antagonist because it blocks both types of endothelin receptors (ET-A and ET-B) located on vascular smooth muscle cells and endothelial cells. It has a short half-life, allowing rapid up-and-down titration.

Two earlier studies showed that short-term infusions of tezosentan safely improved haemodynamic parameters among patients with advanced heart failure, and these were followed by four phase III studies, collectively known as the Randomized Intravenous Tezosentan Trials (RITZ). The two pivotal trials were RITZ-2 and RITZ-1, whereas RITZ-4 and RITZ-5 were supportive pilot studies. RITZ-2, which involved 285 subjects with acute heart failure, compared the haemodynamic effects of two doses
of tezosentan (50 mg/h and 100 mg/h) to placebo on top of conventional therapy over 24 h. There was a statistically significant change from baseline in cardiac index at 6 h with both doses of tezosentan relative to placebo (50 mg/h, 21.4%; 100 mg/h, 21.5%; placebo, 2.0%; P < 0.0001). Significant improvements were also observed in secondary haemodynamic parameters, including decreases in pulmonary capillary wedge pressure (50 mg/h, 18.4%; 100 mg/h, 18.8%; placebo, 2.3%; P < 0.0001).31

However, RITZ-1 – a 669-subject study which examined the effect of tezosentan (50 mg/h) plus standard treatment on symptoms of acute heart failure – failed to meet its primary objective of significantly improving dyspnoea. Secondary end-points, including time to death and worsening of heart failure, also failed to reach statistical significance.32 This may have been: (i) because the dose studied was too high, as suggested by the relatively high incidence of hypotension and/or (ii) because RITZ-1 subjects were comparatively healthier than those in other tezosentan trials. A lower dose of 25 mg/h may have conferred a more favourable risk–benefit ratio.

On this basis, a large phase III outcome trial, the Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Study (VERITAS), is currently ongoing with tezosentan at a lower dose, hoping to maintain near maximal haemodynamic benefit without an increase in adverse events.

Vasopressin antagonists

Vasopressin is another potential target for therapeutic blockade, as this hormone is activated in the acute, decompensated heart failure setting. The cardiovascular effects of vasopressin are mediated via two major receptor sub-types.33 The V_1A receptor is found in blood vessels and mediates vasoconstriction. The V_2 receptor mediates the effects of vasopressin on water excretion. Agents have been developed which block either or both receptor sub-types.

Selective V_2 and dual V_1A/V_2 receptor antagonism strategies have been found to substantially increase free water excretion, reduce body weight and improve symptoms of congestion in fluid overloaded patients.34 These effects have been found to occur without the worsening of renal function and potassium depletion that frequently characterises use of loop diuretics. The two main agents studied in this regard are: (i) tolvaptan (OPC-41061), a selective vasopressin V_2 receptor antagonist and (ii) conivaptan (WM-087), a dual V_1A/V_2 receptor antagonist.

Thus, these agents may be particularly useful in the treatment of patients with heart failure who experience volume overload and decompensation, and also have hyponatraemia. Phase III studies with vasopressin antagonists are currently being conducted in both the acute and chronic heart failure settings.

SUMMARY AND CONCLUSIONS

Evidence is accumulating for the efficacy and safety of nesiritide, levosimendan, tezosentan and vasopressin antagonists as therapies for acute heart failure, but currently remains insufficient to support their use beyond those patients recalcitrant to standard therapies, such as initial diuretic therapy followed by i.v. inotropic or vasodilator agents as required.

Another limiting factor for their listing on the Australian Pharmaceutical Benefits Schedule will be cost, and more specifically, cost-effectiveness. These agents will be unlikely to gain listing until a strong pharmacoeconomic argument can be made in their favour. This will require robust Australian data on morbidity (especially hospitalizations) and mortality due to acute heart failure, which are not presently available.

Nesiritide, levosimendan, tezosentan and vasopressin antagonists are currently at the forefront of a growing body of therapeutic research in acute heart failure that is being fuelled by rapidly expanding knowledge about relevant pathophysiology. In contrast to the paucity of new agents for acute heart failure over the last 20 years, the near future may observe many new developments in the drug management of this condition.

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