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New aspects of pharmacotherapy in acute heart failure

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Abstract

Acute heart failure is an important clinical problem. In the USA approximately one million patients are hospitalised annually for acute heart failure, and about 50% of these require readmission within 6–12 months of discharge. Acute heart failure accounts for most hospital admissions among patients over 65 years of age in the USA.

The prognosis in heart failure patients is poor. Mortality at five years is 25% and is higher than in patients with myocardial infarction and some cancers. Despite major progress in chronic heart failure management (Evidence Based Medicine) the treatment of acute heart failure is still empirical. Large multi-centre studies on the pharmacotherapy of acute heart failure are still lacking. The authors discuss management in acute heart failure concerning guidelines of the European Society of Cardiology from 2005 and modern pharmacotherapy.
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acute heart failure, pharmacotherapy of acute heart failure

Introduction

Acute heart failure is an important clinical problem. In the USA approximately one million patients are hospitalised annually for acute heart failure, and about 50% of these require readmission within 6–12 months of discharge. Acute heart failure accounts for most hospital admissions among patients over 65 years of age in the USA [1–3].

The prognosis in heart failure patients is poor. Mortality at five years is 25% and is higher than in patients with myocardial infarction and some cancers [3]. Although in-hospital mortality in patients with worsening chronic heart failure is relatively low, mortality or rehospitalisation within 60 days stands at about 60% [3].

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The underlying causes of acute heart failure syndrome include structural changes in the heart and vessels. The ageing of the population and effective treatment of more patients with acute coronary syndromes have markedly increased the number of patients with myocardial injury which results in the development of heart failure.

Recent advances have greatly improved understanding of the physiology and risk factors for the development of acute heart failure. It is increasingly widely accepted that both acute and chronic heart failure syndromes are caused by an interplay of haemodynamic factors, activation of neurohormones and cytokines, fluid retention and redistribution within the cardiovascular system [4, 5]. Knowledge of the pathophysiological mechanisms has provided new directions in clinical trials with chronic and acute heart failure patients.

Definition and pathophysiology of acute heart failure

The European Society of Cardiology (ECS) defines acute heart failure as a sudden onset of signs

and symptoms of abnormal heart function [6]. It may occur during or without preceding heart disease. Heart failure may be associated with systolic or diastolic failure, arrhythmia or pathological alterations in preload or afterload. It is frequently a life-threatening condition and requires immediate treatment. Acute heart failure may develop as a new onset condition or acute decompensation of chronic heart failure [3, 6]. Patients with acute heart failure may present with a spectrum of illnesses:

— acute heart failure which does not fulfil the criteria of cardiogenic shock, pulmonary oedema or hypertensive crisis;
— hypertensive acute heart failure in which the symptoms of acute heart failure occur with high blood pressure values and relatively normal left ventricular function and with the presence of radiological signs of pulmonary oedema;
— radiological signs of pulmonary oedema with severe respiratory failure, pulmonary crepitations, orthopnoea and arterial blood saturation below 90%;
— cardiogenic shock: a state of inadequate tissue perfusion due to cardiac dysfunction caused by heart failure despite normal (corrected) preload; there are no strict haemodynamic criteria to account for differences in its incidence and clinical course; cardiogenic shock is usually characterised by low blood pressure values (systolic blood pressure < 90 mm Hg or mean blood pressure decrease by > 30 mm Hg) and/or low diuresis (< 0.5 ml/kg/h) at heart rate > 60 bpm with or without vital organ failure; cardiogenic shock is frequently related to low output syndrome;
— markedly decreased cardiac output, usually with accompanying tachycardia (arrhythmia, thyrotoxicosis, anaemia, Paget's disease etc.), warm extremities, pulmonary congestion and possibly low arterial blood pressure similar to septic shock [6].

Acute heart failure may develop suddenly as a complication of myocardial infarction, myocarditis and valve defects. In over 70% of patients the acute event occurs in the course of chronic heart failure, for instance in the course of infection, stress, inappropriate pharmacotherapy, rhythm disorders, arterial hypertension or hormonal changes (such as in thyrotoxicosis) [1, 3]. This situation is sometimes referred to as worsening chronic heart failure. Acute heart failure should not be regarded as shock, which may be due to many factors. If the shock is of cardiac origin, acute heart failure should be taken into account, as these two clinical entities may co-exist [4].

Advances in invasive cardiology and cardiac surgery have significantly reduced mortality in patients with cardiogenic shock, but it remains high nevertheless (35% on average) [1].

In acute heart failure left atrial pressure rises suddenly, leading to pulmonary oedema. Venous congestion ensues, leading to peripheral oedema and hepatomegaly. The clinical manifestations of acute heart failure include dyspnoea, orthopnoea, cough and reduced exercise tolerance. Fluid retention increases body mass. There may be symptoms related to low cardiac output, such as increased creatinine, weakness, loss of consciousness, pallor, cyanosis, nausea and vomiting [1].

Despite major progress in chronic heart failure management (EBM, Evidence Based Medicine) the treatment of acute heart failure is still empirical. Large multi-centre studies on the pharmacotherapy of acute heart failure are still lacking [3].

The treatment of acute heart failure differs from long-term medical care in patients with chronic heart failure and requires admission to intensive care units.

It is important to monitor vital signs: pulse, blood pressure, blood oximetry, diuresis, haemodynamic parameters such as pulmonary capillary wedge pressure, left ventricular filling pressure, systemic and pulmonary resistance and cardiac index. Pharmacological treatment of acute heart failure focuses on reducing myocardial oxygen demand, improving contractility, reducing preload and afterload and maintaining normal tissue perfusion [2]. In decompensated heart failure the following drugs are used: diuretics, positive inotropic drugs, vasodilators and drugs enhancing renal perfusion (Table 1) [3, 8, 9]. In acute heart failure an important objective is to treat the underlying diseases and to remove the cause of the worsening of symptoms. Patients with ST-segment elevation myocardial infarction and cardiogenic shock should undergo reperfusion treatment (percutaneous coronary intervention or, if this is impossible, thrombolysis). Patients with low output syndrome or structural changes in the heart (for instance mitral valve regurgitation or ventricular septal rupture) may need surgical intervention [4, 8, 9].

The non-pharmacological management of acute heart failure and its benefits are summarised in Table 2.

In acute heart failure an important treatment target is to establish an adequate blood oxygen level. The oxygen saturation should be between 95% and 98% (a class I recommendation in the ESC Guidelines 2005) [6]. In order to improve tissue

Table 1. Pharmacotherapy of acute heart failure

Type of therapy	Drugs
Intravenous diuretics	Furosemide, torasemide, bumetanide
Intravenous vasodilators	Sodium nitropruside, nitroglycerin, nesiritide
Intravenous positive inotropic drugs	Dobutamine, dopamine, milrinone, enoximone, epinephrine, norepnephrine, digoxin, levosimendan
Intravenous drugs enhancing renal perfusion	Dopamine

Table 2. Non-pharmacological treatment of acute heart failure

Type of therapy	Benefits
Oxygen therapy, artificial ventilation	Increased oxygen delivery
Intra-aortic counterpulsation	Decreased left ventricular end-diastolic pressure, increased stroke volume, improved cardiac output
Biventricular pacing	Ventricular contraction synchrony, improved pump function of the heart
Mechanical left ventricular support devices	Reduced ventricular work, unloading the heart
Interventions: percutaneous transluminal coronary angioplasty, mitral valvuloplasty	Recanalisation, improved perfusion, removal of the mechanical obstacle
Emergent cardiac surgery: coronary artery bypass grafting, surgery for heart valve defects, heart transplant	Improved perfusion, improved valve function

oxygenation it is necessary to deliver oxygen to the patients using mechanical ventilation, if indicated, through face or nasal masks. In the early stage of acute heart failure it is recommended that intravenous morphine be administered (a class IIb recommendation), usually with an anti-vomiting drug and, in the case of fluid retention, intravenous diuretics (class I recommendations) [6]. This approach is effective as proved in long-term studies, although there has been no confirmation in controlled or randomised clinical trials. The anxiolytic effects of morphine reduce sympathetic activation in the central nervous system, leading to a marked reduction in preload and afterload [4]. Morphine and its derivatives relieve anxiety and pain and reduce myocardial oxygen demand [2, 10].

Intravenous diuretics and nitroglycerin reduce preload and filling pressure [3, 6]. Loop diuretics (furosemide, bumetanide and torasemide), apart from their diuretic effects, increase the production of vasodilating prostaglandins, thus reducing preload [2, 10]. Intravenous diuretics are recommended in acute decompensated heart failure and accompanying fluid retention (class I recommendation). Diuretics normalise loading conditions and decrease neurohormonal activation in a short time. Thiazides and spironolactone may be combined with loop diuretics [6]. In acute left ventricular failure it is necessary to reduce fluid intake and maintain fluid balance.

Vasodilators such as sodium nitroprusside, nitroglycerin and enalaprilate reduce preload and afterload [2, 3, 6]. Sodium nitroprusside is recommended in patients with acute heart failure and increased afterload, in other words in the presence of a hypertensive crisis and mitral regurgitation (class I recommendation) [6]. However, its chronic use may lead to an accumulation of toxic metabolites (Table 3).

Widely used nitrates may cause tachyphylaxis within 48 hours of administration. Other negative effects include the development of tolerance to high-dose nitrates after 16–24 h intravenous infusion [6]. There is a lack of data on the safety and efficacy of diuretics and nitrates in acute heart failure [3, 6].

Two randomised trials have shown the efficacy of intravenous high-dose nitrates combined with low-dose furosemide (class I recommendation) [6].

Positive inotropic drugs are recommended in patients with peripheral hypoperfusion (hypotension, renal impairment) (class IIa recommendation) [6].

Table 4 summarises the doses of positive inotropic agents in compliance with the ESC guidelines.

Table 3. Recommended dosage of vasodilators in patients with acute heart failure according to the guidelines of the European Society of Cardiology 2005

Vasodilator	Recommended intravenous dose
Nitroglycerin	Initially 20 μg/min, may be up-titrated to 200 μg/min
Isosorbide dinitrate	Initially 1 mg/h, may be up-titrated to 10 mg/h
Sodium nitroprusside	0.3–5 μg/kg/min
Nesiritide	Bolus 2 μg/kg + infusion 0.015–0.03 μg/kg/min

Table 4. The European Society of Cardiology recommended dosage of positive inotropic drugs in acute heart failure

Positive intropic drug	Recommended intravenous dose
Dobutamine	2–20 μg/kg/min (β+)
Dopamine	< 3 μg/kg/min: renal effect (δ+) 3–5 μg/kg/min: positive inotropic action (β+) > 5 μg/kg/min (β+), vasopressor (α+)
Milrinone	Bolus 25–75 μg/kg over 10–20 min followed by 0.375–0.75 μg/kg/min
Enoximone	Bolus 0.275–0.75 mg/kg, followed by 1.25–7.5 μg/kg/min
Levosimendan	Bolus 12–24 μg/kg over 10 min, followed by 0.1 μg/kg/min (max 0.2 μg/kg/min)
Norepinephrine	0.2–1 μg/kg/min
Epinephrine	Bolus 1 mg, followed by 0.05–0.5 μg/kg/min

The following positive inotropes are used: digoxin, dobutamine, isoproterenol, ibopamine, prenalterol, xamoterol, epinephrine, norepinephrine, amrinone, milrinone, enoximone, piroximone and vesnarinone [3, 6, 7]. However, positive inotropic agents cause side effects. They increase myocardial oxygen demand and have pro-arrhythmic effects and a negative influence on the long-term prognosis [3, 6, 7]. Dobutamine may be ineffective in patients who have been receiving beta blockers. In a recent OPTIME — CHF study (the Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) milrinone used for the treatment of decompensated heart failure insignificantly increased the incidence of arrhythmias and hypotension as compared to placebo [7, 11].

Dobutamine and milrinone do not shorten the hospital stay of patients with acute heart failure but they may increase mortality, especially in patients with ischaemic heart disease [3]. The benefits of digoxin in acute heart failure include an increased cardiac index (CI), a reduced heart rate (CO), left ventricular filling pressure and right atrial pressure [3].

Acute heart failure is a condition requiring prompt intervention to improve the circulatory haemodynamics. The available treatments are associated with various side effects, such as neurohormonal activation, hypotension, arrhythmias and increased myocardial ischaemia [2, 7]. Newer and safer drugs may soon be used for the treatment of acute heart failure, including calcium sensitisers, recombinant B-type natriuretic protein, vasopeptidase inhibitors, endothelin antagonists and vasopressin antagonists [1, 3, 4, 6, 7, 12–25].

Calcium sensitisers

Levosimendan and nesiritide are used for the treatment of decompensated heart failure in many countries.

Levosimendan increases the sensitivity of troponin C to calcium and activates ATP-dependent potassium channels. It inhibits phosphodiesterase III (PDE III) and is characterised by vasodilating and positive inotropic properties [7, 12]. Levosimendan dilates coronary and peripheral vessels through the activation of ATP-dependent potassium channels. It improves myocardial contractility with no effect on intracellular calcium concentration. The drug increases cardiac output and decreases pulmonary capillary wedge pressure. Levosimendan does not increase myocardial oxygen demand and is not associated with an increased risk of arrhythmias or myocardial ischaemia. Nor is there a reduction in

long-term survival in patients with acute heart failure [3, 6]. Levosimendan also has positive lusitropic affects, improving both systolic and diastolic function. It reduces pulmonary capillary wedge pressure by as much as 50% and increases cardiac output by 40% in a dose-dependent manner. High doses of levosimendan slightly increase the heart rate [12, 17, 23]. The safety profile of levosimendan seems more advantageous than that of dobutamine. A multi-centre randomised study demonstrated that a six-hour infusion of levosimendan improved circulatory haemodynamics in patients with acute heart failure [17].

Levosimendan may be used in combination with beta blockers. It has been found to be safer than dobutamine [7].

In a multi-centre randomised LIDO study (Efficacy and Safety of Intravenous Levosimendan Compared with Dobutamine in Severe Low-Output Heart Failure) haemodynamic improvement was achieved in 28% of patients with acute heart failure receiving levosimendan and in 15% of patients treated with dobutamine ($p = 0.022$). At one month after acute heart failure mortality was halved in patients receiving levosimendan (8% vs. 17%; $p = 0.49$). At 180 days mortality in patients receiving levosimendan was 26% in contrast to 38% in patients receiving dobutamine, the difference being statistically significant ($p = 0.029$). Levosimendan was more efficacious than standard dobutamine [7].

In the RUSSLAN study (Randomised Study on the Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarct) levosimendan was also more advantageous in patients with myocardial infarction and concomitant heart failure [7, 24].

An ongoing REVIVE II study (Randomised, Multi-centre Evaluation of Intravenous Levosimendan Efficacy Versus Placebo in the Short Term Treatment of Decompensated Heart Failure) has been designed to evaluate the efficacy of intravenous levosimendan in patients with decompensated heart failure. Levosimendan is recommended in patients with the symptoms of low cardiac output, in the absence of arterial hypotension (class of recommendations II) [6].

Natriuretic peptides in acute heart failure

There are four major natriuretic peptides: atrial natriuretic peptide (ANP), which is synthesised in the atria, brain natriuretic peptide (BNP), which is synthesised in the ventricles, C-type natriuretic peptide (CNP), which is synthesised in the brain and the recently discovered Dendroaspis, which is detectable in blood serum and the atrial myocardium [26]. In patients with heart failure plasma ANP and BNP levels are markedly increased. The natriuretic, diuretic, vasodilating and fibrosis-inhibiting effects of natriuretic peptides provide attractive possibilities in the treatment of heart failure. In contrast to loop diuretics and many vasodilators, natriuretic peptides inhibit rather than stimulate the renin-angiotensin-aldosterone system, which appears to have a major effect on the long-term efficacy of heart failure treatment. Natriuretic peptides reduce myocardial ischaemia and modulate vessel growth. A model of acute heart failure in dogs showed that exogenous BNP protected against an increase in plasma renin activity in contrast to control animals [4, 25].

Administered intravenously nesiritide, a recombinant form of B-type natriuretic protein, increases intracellular cGMP concentration. The drug has diuretic, natriuretic and vasodilating properties. It dilates veins and arteries, including the coronary vessels and decreases pulmonary capillary wedge pressure [26]. Nesiritide also has beneficial effects on hormonal activity as it decreases aldosterone and endothelin-1 levels. The drug does not increase myocardial oxygen demand, has no positive inotropic effects and does not influence heart rate. It has no pro-arrhythmic properties [2, 26]. Nesiritide improves the echocardiographic parameters of diastolic function and relieves symptoms in patients with acute heart failure. It also increases glomerular filtration, inhibits the renin-angiotensin-aldosterone system and induces natriuresis [4, 25, 26].

A multi-centre randomised PRECEDENT study (The Prospective Randomised Evaluation of Cardiac Ectopy with DobutaminE or Natrecor Therapy) was designed to compare the effects of Natrecor (nesiritide) and dobutamine on the incidence of ventricular arrhythmia in a group of 255 patients with severe heart failure requiring intravenous vasoactive medication. After 24 h Holter monitoring the patients were given nesiritide (0.015–0.03 μg/kg/min) or dobutamine (5 μg/kg/min). Dobutamine was found to increase the number of premature ventricular beats and mean heart rate. In the dobutamine group there were significantly more complex ventricular arrhythmias than in the nesiritide group ($p < 0.05$) [22]. Nesiritide, in contrast to positive inotropes (such as dobutamine), has no pro-arrhythmic effect. In a recently published VMAC study (Vasodilator in the Management of Acute Congestive Heart Failure) nesiritide reduced pulmonary capillary wedge pressure faster and to

a greater extent than did nitroglycerin. Nesiritide was also better than placebo at reducing dyspnoea. The reduction in dyspnoea was not statistically significant as compared with nitroglycerin [3]. The side effects of nesiritide included a marked decrease in arterial blood pressure. In earlier studies with higher doses of nesiritide hypotension was found in 6–12% [8]. In VCAM study, in which nesiritide was used in the currently recommended doses, symptomatic hypotension occurred in 4% of patients, similar to those receiving nitroglycerin. Nesiritide improves haemodynamics to a greater extent than nitroglycerin and produces fewer side effects. It does not lead to the tachyphylaxis observed in patients receiving nitroglycerin [2, 7, 26]. The drug is efficacious and safe in patients with renal failure [26]. Nesiritide was approved in the USA in 2001 for the treatment of acute decompensated heart failure. The ongoing BELIEVE study (B-type Natriuretic Peptide and Post-myocardial Infarction Left Ventricular Remodelling) is the first clinical trial to analyse the cardioprotective properties of nesiritide. Nesiritide inhibits fibroblast proliferation, affects endothelial cells and inhibits aldosterone activity, thus preventing cardiac remodelling in patients after acute myocardial infarction. Nesiritide, as a multi-directional agent without serious side effects, is promising in patients with acute heart failure. The safety and efficacy of nesiritide in acute heart failure have been demonstrated in a phase III study [26].

Endothelin receptor antagonists in heart failure

Endothelin plays an important physiological role as a regulator of cardiovascular function [27]. The endothelium possesses the ability to modulate vascular tone by the release of vasodilators (such as endothelium-derived relaxing factor, bradykinin and prostaglandins) and vasoconstrictors (such as angiotensin II and endothelin). The interaction of these locally produced factors with other systemic vasoconstricting reflexes, and especially with the sympathetic and RAA systems, results in the increase of vascular tone which is typical of heart failure. Endothelin-1 increases pulmonary artery pressure and pulmonary vascular resistance [1, 27]. The concept of endothelial dysfunction in heart failure is widely accepted.

Preliminary data show that *endothelin antagonists* may improve left ventricular function, delay or reverse unfavourable remodelling, decrease systemic and pulmonary vascular resistance, improve central haemodynamic parameters and prognosis [4, 13].

The effects of endothelin-1 are mediated by two receptors: ETA and ETB. ETA receptors are expressed in vascular smooth muscle cells, and their activation causes vasoconstriction. ETB receptors are expressed in vascular endothelial cells, and they induce nitric oxide-dependent vasodilation. Some ETB receptors on vascular smooth muscle cells may cause vasoconstriction. Understanding of the role of endothelin-1 in heart failure has contributed to the discovery of endothelin-1 receptor antagonists. Endothelin-A and endothelin-B receptor antagonists such as bosentan and tezosentan increase left ventricular stroke volume [13]. Bosentan, a non-selective ETA/ETB antagonist, dilates systemic and pulmonary vessels in patients with acute heart failure. Kiowski et al. used intravenous bosentan or placebo in a randomised study in 24 patients with NYHA class III heart failure. Bosentan was found to decrease arterial blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, pulmonary and systemic vascular resistance and to increase the cardiac index [14, 15]. Tezosentan is another non-selective ETA/ETB receptor antagonist.

Torre-Amione et al. [16] demonstrated that tezosentan rapidly improved peripheral and central perfusion and was well tolerated. The effect of tezosentan on the cardiac index was seen as early as at 30 minutes. Tezosentan decreased pulmonary capillary wedge pressure, pulmonary artery pressure, pulmonary and systemic vascular resistance and peripheral pressure and did not affect the heart rate.

In a multi-centre RITZ-2 study (The Randomised Intravenous TeZosentan Study) 292 patients were randomised to receive tezosentan 50 mg/h or 100 mg/h or placebo for 24 hours after admission for acute heart failure. The primary endpoint was the change in cardiac index six hours after the start of treatment, while secondary endpoints included dyspnoea, worsening of heart failure at 24 hours and death. Both doses of tezosentan increased the cardiac index and decreased pulmonary capillary wedge pressure significantly more than placebo ($p < 0.0001$). Tezosentan was also associated with a dose-related decrease in arterial blood pressure and no changes in heart rate. Patients who received tezosentan were less likely to experience a worsening of dyspnoea, and more likely to show clinical improvement ($p = 0.048$). The safety profile of low dose tezosentan was similar to that of placebo. In the RITZ-1 and RITZ-2 study the side effects of tezosentan resulted from vasodilation (hypotension, headache and renal injury) and were probably associated with the higher dose [19].

A recently completed large, multi-centre international VERITAS study (Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Study) was designed to evaluate the short-term efficacy of tezosentan in patients with severe heart failure. The study was discontinued for futility. The results of the study were surprising: there were no differences between tezosentan and placebo in dyspnoea reduction over the first 24 hours of treatment. No differences were seen in the course of heart failure or mortality at 7 and 30 days. Nor was there was any effect on six-month survival either in patients receiving active treatment or those receiving placebo. Tezosentan was not associated with any clinical benefit despite clear haemodynamic improvement (systolic blood pressure decreased by 6 mm Hg, improved cardiac index and reduced systemic vascular resistance). The reasons for this remain to be elucidated [28].

Other drugs

Vasopressin receptor antagonists, such as OPC-41061 block the antidiuretic action of endogenous vasopressin, thus increasing free water clearance. Patients with heart failure have an increased level of antidiuretic hormones [21]. The ACTIV-CHF study was designed to evaluate the effects of a selective vasopressin inhibitor (tolvaptan) in patients hospitalised for heart failure with ejection fraction < 40%. An important symptom of worsening heart failure is water retention, as manifest by rapid body mass growth. In the ACTIV-CHF study body weight at 24 hours decreased rapidly with tolvaptan. At 60 days water loss was 2 l higher than after placebo. Sodium concentration, as expected, increased in patients receiving the active drug. There were no changes in heart rate or blood pressure and renal function was preserved. The rate of readmission and worsening heart failure over 60 days was similar to placebo [21]. Vasopressin inhibitors may be indicated in patients at high risk of death who have hyponatraemia, increased creatinine levels and symptoms of progressive congestion while staying in a hospital. The ongoing EVEREST study (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) is expected to provide a new insight into the treatment of heart failure with antidiuretic hormone antagonists.

Vasopeptidase inhibitors such as omapatrilat inhibit neutral endopeptidase (NEP).

Omapatrilat also inhibits angiotensin-converting enzyme ACE, thus causing vasodilatation. It decreases the level of angiotensin II and inhibits the degradation of bradykinin and natriuretic peptides. The drug increases natriuresis, decreases vascular wall tone, and inhibits proliferation of smooth muscle cells. Attempts have been made to use omapatrilat in heart failure [18].

Adenosine receptor antagonists such as BG9717 are candidate drugs for the treatment of acute heart failure. Mechanisms involve dilation of afferent renal arterioles, increased glomerular filtration and improved renal function. Adenosine receptor antagonists decrease sodium resorption in the proximal and distal renal tubules, leading to diuresis. In a randomised double-blind study patients with NYHA class II/III heart failure and pulmonary oedema were given parenterally an adenosine receptor antagonist combined with furosemide. Controls received only furosemide. The combined treatment with BG9717 and furosemide enhanced diuresis and creatinine clearance as compared with the controls. Those receiving only furosemide showed reduced creatinine clearance. For this reason BG9717 may be especially beneficial in patients with renal failure.

The development of new technologies in pharmacology has resulted in the discovery of drugs that may improve the prognosis and survival of patients with acute heart failure. Further multi-centre and randomised studies with these new drugs, if found efficacious and safe, will provide the opportunity to use them in the treatment of acute heart failure.

References

1. Rodgers JE, Patterson JH. Nesiritide's role in acute decompensated heart failure (www.CaseStudyRx.com). Heart Failure, 1: 1–5.
2. Fonarow GC. Pharmacologic therapies for acutely decompensated heart failure. Rev Cardiovasc Med, 2002; 3 (suppl. 4): 18–26.
3. Gheorghiade M, Zannad F. Modern management of acute heart failure syndromes. Eur Heart J, 2005; Suppl. 7: B3–B7.
4. Poole-Wilson PA, Xue SR. Nowe metody leczenia ostrej niewydolności serca. Kardiologia po Dyplomie, 2004; 3: 34–49.
5. Nessler J. Niewydolność serca — nowe spojrzenie na patogenezę i leczenie. Nowa Klin, 2001; 8: 308–313.
6. Nieminen MS, Böhm M, Cowie MR et al. Guidelines on the diagnosis and treatment of acute heart failure — full text. The Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J, 2005 (doi:1093/eurheartj/ehi117).
7. Trikas AG, Fourlas CA, Stephanadis CI. Inotropes in heart failure: novel aspects. Hellenic J Cardiol, 2003; 44: 326–331.

8. Bristol MR, Lowes BD. Management of heart failure. In: Braunwald E, Zipes DP, Libby P ed. Heart disease. A textbook of cardiovascular medicine. W.B. Saunders Company, Philadelphia 2005; 603–624.
9. Bristol MR, Linas S, Port JD. Drugs in the treatment of heart failure. In: Braunwald E, Zipes DP, Libby P ed. Heart Disease. A Textbook of cardiovascular medicine. W.B. Saunders Company, Philadelphia 2005; 569–601.
10. Millane T, Jackson G, Gibbs CR, Lip GYH. ABC heart of failure. Acute and chronic management strategies. BMJ, 2000; 320: 559–562.
11. Cuffe MS, Calif RM, Adams KF et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA, 2002; 287: 1541–1547.
12. Nieminen MS, Akila J, Hasenfuss G et al. Hemodynamic and neurohormonal effects of continuous infusion of levosimendan in patients with congestive heart failure. J Am Coll Cardiol, 2000; 36: 1903–1912.
13. Givertz MM, Colucci WS, LeJemtel TH et al. Acute endothelin a receptor blockade causes selective pulmonary vasodilatation in patients with chronic heart failure. Circulation, 2000; 101: 2922–2927.
14. Kiowski W, Sutsch G, Hunziker P et al. Evidence for endothelin-1-mediated vasoconstriction in severe chronic heart failure. Lancet, 1995; 346: 732–736.
15. Sutsch G, Kiowski W, Yan X-W et al. Short-term oral endothelin-receptor antagonist therapy in conventionally treated patients with symptomatic severe chronic heart failure. Circulation, 1998; 98: 2262–2268.
16. Torre-Amione G, Durand J-B, Nagueh S. A pilot safety trial of prolonged (48h) infusion of the dual endothelin-receptor antagonist tezosentan in patients with advanced heart failure. Chest, 2001; 120: 460–466.
17. Slawsky MT, Colucci WS, Gottlieb SS. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Circulation, 2000; 102: 2222–2227.
18. Persson J, Morsing P, Grande PO. Vasopeptidase inhibition with omapatrilat increases fluid and protein microvascular permeability in cat skeletal muscle. J Hypertens, 2004; 22: 637–644.
19. Clinical Trials Update: CAPRICORN, COPERNICUS, MIRACLE, STAF, RITZ-2, RECOVER and RENAISSANCE and cachexia and cholesterol in heart failure. Highlights of the Scientific Sessions of the American College of Cardiology, 2001. Eur J Heart Failure, 2001; 3: 381–387.
20. Kondo K, Ogawa H, Yamashita H et al. 7-Chloro-5--hydroxy-1-[2-methyl-4-(2-methylbenzoyl--amino)benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine (OPC-41061): a potent, orally active nonpeptide arginine vasopressin V2 receptor antagonist. Bioorg Med Chem, 1999; 7: 1743–1754.
21. Gheorghiade M, Gattis WA, O'Connor CM et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA, 2004; 291: 1963–1971.
22. Silver MA, Horton DP, Ghali JK, Elkayam U. Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acutely decompensated heart failure. J Am Coll Cardiol, 2002; 39: 798–803.
23. Ukkonen H, Saraste M, Akkila J et al. Myocardial efficiency during levosimendan infusion in congestive heart failure. Clin Pharmacol Ther, 2000; 68: 522–531.
24. Moiseyev VS, Poder P, Andrejevs N et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). Eur Heart J, 2002; 23: 1422–1432.
25. Colucci WS, Elkayam U, Horton BP et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. N Engl J Med, 2000; 343: 246–253.
26. Burnett JC. Nesiritide: new hope for acute heart failure syndromes? Eur Heart J, 2005; 7 (Suppl): B25–B30.
27. Nessler J, Piwowarska W, Nessler B, Kitliński M, Mroczek-Czernecka D, Stępniewski M. Stężenie endoteliny 1 (ET-1) u chorych z niewydolnością serca o etiologii niedokrwiennej. Folia Cardiol, 2003; 10: 169–175.
28. Teerlink JR, McMurray JJV. VERITAS: Value of endothelin receptor inhibition with tezosentan in acute heart failure studies. American College of Cardiology 2005 Annual Scientific Session, March 6–9, 2005; Orlando, Florida. Medscape (http:www.medscape.com/viewarticle/501428).