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Management of heart failure and the role of the new inotrope levosimendan

NICHOLAS IOANNOU, DUNCAN LA WYNCOLL

Abstract

Despite the availability of an array of medical therapies for the treatment of heart failure, quality of life is often poor for the majority of patients, and the mortality remains high. In addition, treatment is regularly not well tolerated and this results in frequent hospital admissions for some patients. This article reviews the management and medical treatment of acute heart failure, focusing on the emerging role of levosimendan.

Levosimendan is currently licensed in 10 European countries (Simdax, Orion Pharma, Finland) for the treatment of acute heart failure. It is a new inotropic drug with a dual mechanism of action: sensitisation of the cardiac myofilament to calcium, thus enhancing cardiac contractility, and vasodilation of vascular smooth muscle. The published clinical studies so far have utilised intravenous levosimendan. However, the agent is also well absorbed orally, and phase two trials of its use in stable patients with less severe heart failure are underway.[1]

Key words: acute heart failure, chronic heart failure, levosimendan, myocardial infarction, calcium sensitiser.

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Introduction

With an estimated prevalence of 1–2%, chronic heart failure is a major public health problem. It accounts for approximately 1–2% of healthcare expenditure in developed countries;[2] in the US chronic heart failure has an incidence of 2.2/1,000, which makes it more frequent than breast, cervix and colon cancer combined.[3] Furthermore, it has been estimated that heart failure accounts for 5% of acute hospital admissions, and re-admission rates in this population are also high. The prevalence is increasing since most new cases occur in the elderly population.[4]

Royal Free Hospital, Royal Free Hampstead NHS Trust, London, NW3 2QG.
Nicholas Ioannou, Cardiology Registrar
St Thomas' Hospital Adult Intensive Care, Guy's & St Thomas' NHS Trust, London, SE1 7EH.
Duncan LA Wyncoll, Consultant Intensivist
Correspondence to: Dr N Ioannou
(email: nioannou@doctors.org.uk)

Table 1. The aetiology of heart failure

- Coronary artery disease
- Hypertension
- Valvular heart disease
- Cardiomyopathy e.g. dilated, hypertrophic, alcoholic
- Cardiac arrhythmias such as atrial fibrillation
- Infiltrative disease e.g. amyloid, sarcoid, malignancy
- Infective e.g. viral myocarditis, rheumatic fever, HIV
- Metabolic and endocrine e.g. thyroid disease, acromegaly
- Constrictive pericarditis

Heart failure is a progressive clinical syndrome with multiple aetiologies, and may occur as a result of many different structural or functional cardiac abnormalities. In the developed world the most common cause is coronary artery disease, either alone or in combination with hypertension. Table 1 lists the common underlying conditions involved in the aetiology of heart failure. Other predisposing factors, such as diabetes mellitus, hypercholesterolaemia, obesity and smoking, may increase the risk of developing this syndrome.

Symptoms of heart failure include fatigue, limited exercise tolerance, anorexia and dyspnoea. Clinical signs include pulsus alternans, an elevated jugular venous pressure, a third heart sound, pulmonary crepitations, peripheral oedema and ascites. The classification of chronic heart failure can be staged according to guidelines published by the American College of Cardiology and the American Heart Association.[5] This can be used in conjunction with the more traditional functional classification provided by the New York Heart Association[6] (table 2).

Those patients with chronic heart failure who experience symptoms on mild exertion or at rest are at greatest risk for recurrent or prolonged hospital admissions for acute decompensation. This often results from myocardial ischaemia, arrhythmias, non-compliance with treatment and/or intercurrent infection. Acute heart failure may also arise suddenly following a cardiac insult in a patient without previous evidence of overt cardiovascular disease, e.g. following acute myocardial infarction (MI). Whatever the aetiology, the morbidity and mortality remain high despite maximal medical therapy.

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Table 2. Classification of heart failure

ACC/AHA stage		NYHA functional classification	
A	At high risk for heart failure but without structural heart disease or symptoms of heart failure	None	
B	Structural heart disease but without symptoms of heart failure	**I**	Asymptomatic during ordinary physical activity
C	Structural heart disease with prior or current symptoms of heart failure	**II**	Slight limitation of ordinary physical activity
		III	Marked limitation of ordinary physical activity
D	Refractory heart failure requiring specialised interventions	**IV**	Symptoms present at rest

Key: ACC = American College of Cardiology; AHA = American Heart Association; NYHA = New York Heart Association

Management of chronic heart failure

The decline in the effective functioning of the heart as a pump characterises the syndrome of heart failure. It usually occurs as a result of left ventricular systolic dysfunction (reduced contraction), although diastolic dysfunction (increased ventricular stiffness) may be evident in some patients.[7]

The complex reflex mechanisms that are initiated to improve cardiac output in the failing heart ultimately contribute to further cardiac dysfunction. Left ventricular pump failure results in reduced blood pressure and reduced renal perfusion. The fall in blood pressure is detected by baroreceptors, resulting in activation of the sympathetic nervous system. This mechanism causes vasoconstriction, in an attempt to improve tissue perfusion: systemic vascular resistance, and thus afterload, are increased. Reduced renal perfusion results in salt and water retention and vasoconstriction, secondary to activation of the renin-angiotensin-aldosterone axis, further increasing pre-load.

Other neuroendocrine mechanisms result in raised levels of noradrenaline, vasopressin and endothelin, and these all contribute to vasoconstriction and increased peripheral resistance. The elevated afterload and pre-load have further deleterious effects on the already failing heart. These neurohumoral mechanisms also result in left ventricular remodelling, resulting in altered ventricular size, shape and function.[8] Other mechanisms such as ventricular dyssynchrony and malignant cardiac arrhythmias may further compromise cardiac performance.[9]

There are several important goals in the treatment of heart failure:

- Improvement of the force of cardiac contraction
- Reduction of the resistance to ejection of blood from the ventricles (the afterload)
- Reduction of the pre-load, i.e. the end-diastolic ventricular filling volume
- Reversal of the process of ventricular remodelling
- Restoration of the atrial contribution to ventricular filling (if compromised)

Optimisation of medical therapy is of utmost importance to improve symptoms and quality of life, in addition to reducing hospital admissions and enhancing long-term outcome. Recent guidelines published in the UK by the National Institute for Clinical Excellence (NICE) have set out recommended therapies in the management of chronic heart failure.[10] The following classes of drug are currently in use.

Diuretics

In combination with salt and water restriction, diuretics such as bendrofluazide and frusemide are a mainstay treatment for the management of the fluid overload associated with heart failure. Diuretics decrease pre-load by causing a natriuresis in the kidney. Loop diuretics such as frusemide also have venodilatory effects, resulting in symptomatic improvement before the onset of diuresis.

Vasodilators

Vasodilators such as glyceryl trinitrate (GTN) and hydralazine reduce both pre-load and afterload, thus lowering filling pressures and improving stroke volume. This results in an enhanced cardiac output.

Angiotensin-converting enzyme (ACE) inhibitors

ACE inhibitors should be given to almost all patients who have heart failure due to left ventricular systolic dysfunction (including asymptomatic patients). These agents act by antagonising the activation of neuroendocrine mechanisms such as the renin-angiotensin-aldosterone axis: this results in peripheral vasodilatation and reduction of afterload. ACE inhibitors also act to reverse the process of ventricular remodelling and promote a return to normal ventricular size, shape and function. Several large-scale clinical trials have demonstrated significant mortality, morbidity and quality of life benefits associated with ACE inhibitors.[11,12]

Patients intolerant of ACE inhibitors may tolerate angiotensin receptor blockers (ARBs). Although they are not currently licensed in the UK for use in heart failure, their role as additive therapy in patients already taking an ACE inhibitor is under investigation.

Beta blockers

Beta blockade has been shown to improve survival, symptoms and quality of life in several trials.[13] The beneficial effects occur by several mechanisms, including antagonism of the activation of the sympathetic nervous system resulting in reduced afterload, and slowing of the heart rate, thus prolonging diastolic filling time and optimising coronary flow. Moreover, beta blockers have anti-arrhythmic and anti-ischaemic properties, and they improve ventricular function by reversing the remodelling process.

Digoxin

Digoxin is often used as a first-line treatment in elderly patients who have heart failure associated with atrial fibrillation, but can

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be adjunctive therapy for patients in sinus rhythm. Digoxin enhances cardiac contractility, improves symptoms and reduces the frequency of hospital admissions; however, it has not been shown to reduce mortality.[14]

Aldosterone antagonists

The elevated aldosterone levels in heart failure result in salt and water retention. Aldosterone antagonists, such as spironolactone, improve mortality and morbidity when used in moderate to severe heart failure as adjunctive therapy.[15]

Thiamine (vitamin B_1)

Thiamine deficiency has negative effects on myocardial function, and patients with heart failure receiving long-term diuretic therapy may be thiamine deplete as a result of thiamine wasting. Supplementation of thiamine in patients with moderate to severe heart failure is an often-overlooked therapeutic option.[16]

Acute decompensated heart failure

Acute decompensated heart failure describes a severe episode of cardiac dysfunction requiring emergency medical treatment and hospitalisation. The initial aims are to stabilise the patient by improving symptoms, enhancing cardiac function and maximising organ perfusion; the ultimate goals are to enable hospital discharge and achieve a survival benefit.

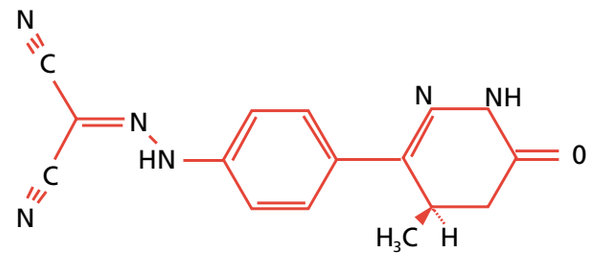
Established early treatment strategies include:

- Oxygen administration and positive airway pressure to correct hypoxaemia
- Opioids (such as morphine or diamorphine) to reduce anxiety, sympathetic drive and pre-load
- Nitrates to reduce both pre-load and afterload
- Diuretics to effect venodilation and a diuresis[17]

Refractory cases may require intravenous inotropic drugs to reverse haemodynamic compromise. Traditional inotropes in the acute setting include the beta adrenergic agonists (such as adrenaline, dobutamine, dopexamine and dopamine) and phosphodiesterase inhibitors (such as milrinone and enoximone). Stimulation of beta adrenoreceptors results in increased activity of adenylate cyclase, thus increasing production of cyclic adenosine monophosphate (cAMP). Alternatively, phosphodiesterase inhibition reduces pre-existing cAMP breakdown. Both classes of inotrope exert their effects via increased levels of cAMP. This results in increased levels of calcium ions within the cardiac myocyte, hence increased cardiac contractility.

Although beta agonists and phosphodiesterase inhibitors have positive effects on cardiac contractility, the deleterious effects of raised intracellular calcium on the failing myocardium limit their use. Thus, myocardial oxygen demand is increased, ischaemia potentially exacerbated, diastolic relaxation is impaired, and tachycardia and malignant arrhythmias may occur. The effect of beta agonists is attenuated by the use of beta blockers: this is clinically relevant since the use of beta blockers as an effective evidence-based therapy in heart failure is becoming more widespread. In addition, beta agonists also exhibit tachyphylaxis (drug tolerance).

Figure 1. The molecular structure of levosimendan



Although these positive inotropic drugs produce short-term haemodynamic improvements in acute heart failure, their effect on long-term patient outcome has not been clearly established. Interestingly, the common adverse effects and lack of efficacy of these drugs, have not prevented their widespread use in clinical practice. In fact, the use of traditional inotropes such as milrinone[18,19] and dobutamine has frequently been associated with adverse outcomes and increased mortality.[20]

Levosimendan: a new inotrope

Levosimendan is a novel inotropic agent that can be administered intravenously in the treatment of acute decompensated heart failure. It is a pyridazinone-dinitrile derivative. Figure 1 illustrates the molecular structure. Levosimendan exhibits linear pharmacokinetics, with approximately 97–98% bound to plasma proteins. It has an elimination half-life of approximately one hour and it appears to be completely metabolised. The active metabolites of levosimendan have longer half-lives and may account for the prolonged haemodynamic effects of this drug, which sometimes persist for up to one week. Impaired renal function does not significantly alter plasma concentrations, though the elimination of the active metabolites may be affected. In contrast, the elimination of levosimendan may be slightly prolonged in the presence of hepatic impairment.[21,22]

Mechanism of action

Levosimendan has two important mechanisms of action. Its primary action is to enhance cardiac contractility. This is achieved via a pharmacological mechanism known as calcium sensitisation.

The role of calcium ions in the contractile process of cardiac myocytes is well established. The cardiac myofilament is the subunit of contraction within cardiac muscle cells. It consists of actin and myosin protein filaments plus regulatory proteins – tropomyosin, troponin C and troponins I and T. Electrical excitation of the cardiac myocyte results in the entry of calcium ions into the cell and subsequent mobilisation of calcium ions from the sarcoplasmic reticulum. Calcium binds to cardiac troponin C, resulting in a conformational change in the tropomyosin regula-

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tory protein which is closely associated to the actin helix. This conformational change unlocks the active sites that exist on the actin-myosin proteins, enabling the formation of adenosine triphosphate (ATP)-dependent cross-bridges and contraction of the myocyte.

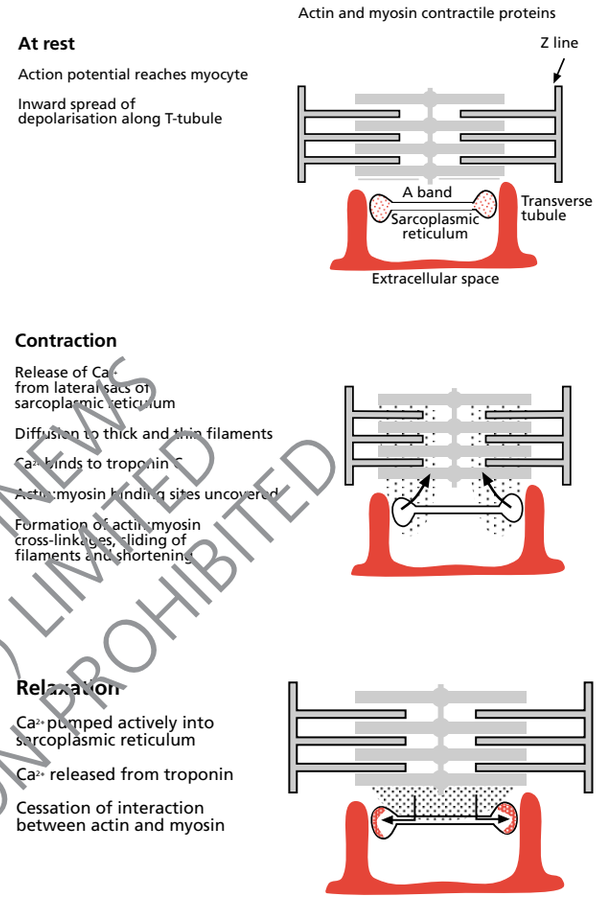
Contraction is followed by relaxation and recovery of the contractile apparatus; this is an active process achieved by pumping calcium ions into the sarcoplasmic reticulum and loss of actin-myosin cross-bridges. These calcium ion shifts within the cardiac myocyte are highly energy-dependent processes. The contraction and relaxation of the cardiac myofilament is illustrated in figure 2.

Traditional inotropes enhance contractility by increasing the available intracellular calcium that can bind to cardiac troponin C, at the expense of increasing myocardial energy and oxygen demand and increasing the risk of arrhythmias. In contrast, levosimendan exerts its inotropic effect by binding to cardiac troponin C, thus stabilising calcium ion-induced conformational changes in the tropomyosin regulatory protein. As a result, actin-myosin filament protein cross-bridge formation is facilitated and prolonged. The contractile apparatus is sensitised to the available calcium ions without increasing the influx of calcium ions into the cell.[23] Cardiac performance and contractility are improved without a significant increase in total myocardial energy demand and oxygen consumption. The potential for arrhythmias is also reduced as total intracellular calcium levels are not raised.

An additional benefit of calcium sensitisation is that the stabilisation effect on cardiac troponin C is calcium-dependent. Levosimendan only exerts its effects during systole; it does not bind to cardiac troponin C during the relaxation phase of the contractile process, when the intracellular calcium ion concentration is low. The clinical effect of this phenomenon is that the duration of diastole is not affected and hence ventricular relaxation is not impaired.[24] Consequently, adequate ventricular filling and optimal coronary perfusion still occur.

Levosimendan has an important secondary action – vasodilation of vascular smooth muscle. It acts upon ATP-sensitive potassium channels found in the myocardium, peripheral blood vessels and coronary arteries.[25,26] This widespread vasodilation has the beneficial effect, in the failing heart, of reducing cardiac pre-load and afterload in addition to improving coronary flow, reducing ischaemia and improving renal blood flow. Dose-dependent hypotension may occur, however.

Figure 2. Myofilament contraction and relaxation



The actin and myosin contractile proteins are illustrated in these diagrams, with the calcium ions represented as black dots

Evidence for clinical use of levosimendan

Levosimendan is administered to patients with acutely decompensated heart failure via central or peripheral intravenous infusion. The typical treatment regimen involves a loading dose of 6–12 µg/kg over 10 minutes, followed by a continuous 24-hour infusion of 0.05–0.2 µg/kg/min. Levosimendan has been assessed clinically in more patients than any other intravenous inotrope. More than 1,300 patients with heart failure have taken part in trials conducted in Europe and the US.

Following initial dose-finding[27] and dose-escalation studies,[28] two major clinical studies involving levosimendan have investigated its haemodynamic effects in addition to its effects on symptoms, morbidity and mortality.[29,30] The relevant features of these studies are compared in table 3. Since coronary artery disease is the leading cause of heart failure, new inotropic agents need to be comprehensively evaluated in this group. A high proportion of the patients included in trials with levosimendan had ischaemic heart disease.

The LIDO study

The LIDO study (levosimendan infusion versus dobutamine in severe low-output heart failure) was an international, multicentre, double-blind, randomised controlled trial of patients with severe, low-output, decompensated heart failure.[29] They were randomised to receive intravenous levosimendan (a loading dose of 24 µg/kg followed by a 24-hour infusion of 0.1 to 0.2 µg/kg/min) or intravenous dobutamine (5 to 10 µg/kg/min for 24

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Table 3. Comparison of major trials involving levosimendan

Study	No. of patients	No. of patients treated with levosimendan	Comparative therapy	NYHA class	LVEF	Aetiology of heart failure	Beta blockers used
Dose-finding[27]	151	95	Placebo/dobutamine	II-IV	< 40%	IHD 100%	28%
Dose-escalation[28]	146	98	Placebo	III/IV	≤ 30%	IHD 60% DCM 40%	Not reported
LIDO[29]	203	103	Dobutamine	III/IV	< 35%	IHD 47% Other 53%	38%
RUSSLAN[30]	504	402	Placebo	IV	Not reported	Acute post-MI	39%

Key: IHD = ischaemic heart disease; MI = myocardial infarction; DCM = dilated cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

hours). One hundred and three patients were assigned to receive levosimendan and 100 patients were assigned to receive dobutamine.

Patients were monitored in an intensive care setting. The primary end points at 24 hours were haemodynamic and defined as: an increase in cardiac index by ≥ 30% compared to baseline and a reduction in pulmonary artery occlusion pressure (PAOP) of ≥ 25%. Secondary end points included symptomatic improvement, and mortality and morbidity at 30 days and six months after randomisation.

After 24 hours, 28% of levosimendan-treated patients achieved sustained haemodynamic improvement (the primary end point) compared to only 15% in the dobutamine group (p=0.022). In addition, there was a lower mortality in the levosimendan group at both 30 days (8% *vs.* 17%; p=0.049) and six months (26% *vs.* 38%; p=0.029). This translates into a number-needed-to-treat (NNT) of 12 to save one life at 180 days.

Levosimendan was well tolerated and caused significantly fewer cardiac adverse events when compared to dobutamine. Chest pain indicating myocardial ischaemia was reported less frequently in the levosimendan group (p=0.013). There were significantly fewer rhythm disturbances in the levosimendan group (3.9% *vs.* 13%; p=0.023). The most commonly reported adverse events in the levosimendan-treated group were headache and hypotension. Levosimendan was also reported to improve symptoms such as dyspnoea and fatigue to a greater extent than dobutamine, but this finding was not statistically significant.

The use of beta blockers attenuates the effects of beta adrenergic agonists such as dobutamine, as discussed previously. In the LIDO study, 37% of patients in the levosimendan group and 39% of patients in the dobutamine group were taking beta blockers prior to randomisation. Analysis of this subgroup demonstrated that the use of beta blockers did not attenuate the effects of levosimendan. However, the use of beta blockers might have attenuated the actions of dobutamine and perhaps even subjected these patients to predominantly alpha adrenergic actions. (Dobutamine is a racemic mixture of L- and D-dobutamine: the former is a potent alpha agonist and the latter a potent beta agonist.) At baseline, 90% of the patients were receiving ACE inhibitors.

Table 4. Comparison of properties of levosimendan, dobutamine and milrinone

	Levosimendan	Dobutamine	Milrinone
Mechanism of action	Calcium sensitiser	Beta adrenergic agonist	Phosphodiesterase inhibitor
Increased intracellular Ca^{2+}	No	Yes	Yes
Increased cAMP	No	Yes	Yes
Increased cardiac contractility	Yes	Yes	Yes
Increased O_2 demand	No	Yes	Yes
Tachyphylaxis	No	Yes	No
Antagonised by beta blockers	No	Yes	No
Adverse effects	Hypotension, headache	Tachycardia, arrhythmias	Hypotension, arrhythmias

The LIDO study provides data from a well-designed small trial to support the use of levosimendan as a safe and efficacious inotropic agent, and to suggest that it is significantly more effective than dobutamine therapy. Levosimendan enhances cardiac output and reduces PAOP without increasing cardiac workload. However, it is acknowledged that the haemodynamic improvements and mortality benefits of levosimendan were obtained in comparison to dobutamine, a beta adrenergic agonist for which there have been no previous randomised controlled trials assessing clinical efficacy and safety. Table 4 summarises the properties of levosimendan compared with dobutamine and milrinone.

The RUSSLAN study

The RUSSLAN study (randomised study on safety and effective-

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ness in patients with left ventricular failure after an acute myocardial infarction) was another multicentre, randomised, double-blind but placebo-controlled study.[30] Five hundred and four patients with acute symptomatic heart failure occurring despite conventional therapy, within five days of an MI, were randomised to placebo or to one of four levosimendan treatment groups. Only 16% of patients had received thrombolysis and 45% were receiving ACE inhibitors. Levosimendan was administered intravenously as a loading dose of 6, 12, 24 or 24 µg/kg followed by an infusion of 0.1, 0.2, 0.2 or 0.4 µg/kg/min, respectively. Total duration of treatment was only six hours. The primary end points were evidence of hypotension and myocardial ischaemia, and secondary end points included worsening heart failure and all-cause mortality. Exclusion criteria included systolic blood pressure < 90 mmHg.

In this study levosimendan at doses of 0.1–0.2 µg/kg/min did not exacerbate hypotension or myocardial ischaemia, although a higher frequency of adverse cardiac events was reported in the highest levosimendan dose group.

Patients treated with levosimendan had a significantly reduced risk of death and worsening heart failure compared with those in the placebo group, both at six hours (2% *vs.* 5.9%; p=0.033) and at 24 hours (4% *vs*. 8.8%; p=0.044). In addition all-cause mortality at 14 days was reduced in patients treated with levosimendan (11.7% *vs.* 19.6%; p=0.031). This reduction in mortality appeared to be maintained at six months' retrospective follow-up regardless of the dose of levosimendan used, translating to a NNT of 8 to save one life at 180 days.

The RUSSLAN study was not originally powered for mortality as a primary end point but it provides further impressive data for the safe use of levosimendan in high-risk patients; it is also the largest study of levosimendan published to date.

Current licence and future uses

Intravenous levosimendan is currently licensed in 10 European countries (Sweden, Finland, Spain, Italy, Iceland, Greece, Luxembourg, Norway, Portugal and Austria). However, a licence has not yet been granted in the UK, France or Germany. Phase three clinical studies are currently ongoing in the US and Europe. Additional trials are required to broaden the therapeutic indications for levosimendan in clinical practice safely. Considering the mechanism of action of levosimendan, patients with cardiogenic shock, diastolic heart failure or low cardiac output states following coronary artery bypass surgery may be groups that also benefit. The combination of levosimendan with beta blockers may prove useful in chronic heart failure. In addition, the sustained haemodynamic effects of levosimendan suggest a role for repeated and intermittent use of this drug in patients with refractory chronic heart failure.

Conclusion

The calcium sensitiser, levosimendan is a novel inotropic agent with additional vasodilator properties that has been evaluated in several clinical trials. In comparison with traditional inotropic agents used in acute heart failure, levosimendan is effective and well tolerated, and appears to offer substantial therapeutic benefits with minimal adverse effects. It increases cardiac contractility without increasing myocardial oxygen demand, and in clinical trials it has been shown to decrease morbidity and mortality.

Further trials are underway to ascertain the effects of this exciting new drug on haemodynamic parameters, symptoms and mortality in patients with severe acute heart failure. Levosimendan has the potential to become a routine first-line inotropic agent in the management of acute heart failure.

Key messages

- Heart failure accounts for 5% of hospital admissions
- Optimisation of medical therapy is important to improve quality of life in heart failure
- The long-term effect of traditional inotropes has not been established
- Levosimendan increases cardiac contractility without increasing myocardial oxygen demand
- In clinical trials of acute heart failure, levosimendan was shown to decrease morbidity and mortality

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CASE REPORT

Obstruction of the superior vena cava secondary to right atrial plasmocytoma

SAHRKAW AZAT MUHYALDEEN, NICOLA SYME-GRANT, STUART DAVID PRINGLE, GRAEME PETER MCNEILL, TERENCE HAROLD PRINGLE

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Introduction

Plasma cell neoplasia has three distinct manifestations – extramedullary plasmocytoma, solitary plasmocytoma and multiple myeloma.[1,2] Extramedullary plasmocytoma is found most often in soft tissue, usually in the submucosa of the upper airways. Extramedullary plasmocytoma of the heart is extremely rare, with only 11 cases reported in the literature. We report the case of an 80-year-old man with multiple myeloma. He presented with superior vena caval obstruction secondary to a combination of extravascular compression and right atrial plasmocytoma.

Walsall Manor Hospital, Department of Cardiology, Moat Road, Walsall, West Midlands, WS2 9PS.
Sahrkaw A Muhyaldeen, Specialist Registrar in Cardiology
Ninewells Hospital, Dundee, DD1 9SY.
Nicola Syme-Grant, Specialist Registrar in Pathology
Stuart David Pringle, Consultant Cardiologist
Graeme Peter McNeill, Consultant Cardiologist
Terence Harold Pringle, Consultant Cardiologist
Correspondence to: Dr SA Muhyaldeen
(email: sarkaw@doctors.org.uk)

Case report

An 80-year-old Caucasian man was admitted to the acute medical ward with a four-month history of progressively increasing dyspnoea, paroxysmal nocturnal dyspnoea and swelling of the face and ankles. His past medical history included angina, hypertension, right hemicolectomy for Duke's stage B carcinoma of the colon, multiple myeloma (with lesions in the neck, chest, arm and stomach, treated by deep radiotherapy), and repeated courses of melphalan. Two months previously he had been admitted with a microcytic anaemia secondary to colonic polyps, which was treated with a blood transfusion.

On admission, he was in atrial fibrillation with a ventricular response of 80 beats per minute, his blood pressure was 128/66 mmHg, his jugular venous pressure was raised and he had mild pitting oedema of the ankles. Heart auscultation revealed a grade II ejection systolic murmur. Abdominal examination revealed a smooth superficial mass 2 cm x 3 cm in the lower abdomen.

Investigations revealed a normochromic, normocytic anaemia with haemoglobin (Hb) 6.9 g/dL. His urea was 8.6 mmol/L and his creatinine 78 µmol/L. Liver function tests, creatine kinase, corrected calcium, C-reactive protein and plasma viscosity were all normal but his paraprotein band 2 was elevated at 11 g/dL.

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Figure 1. Transoesophageal echocardiogram showing a mass attached to the right atrium

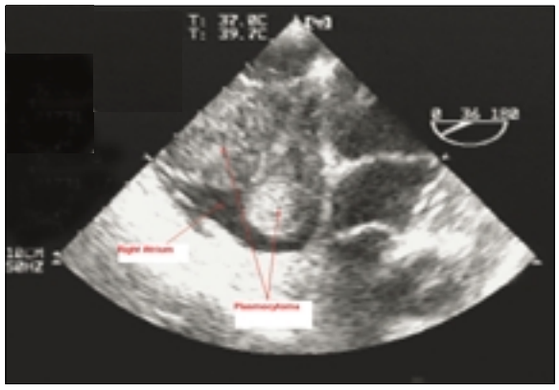
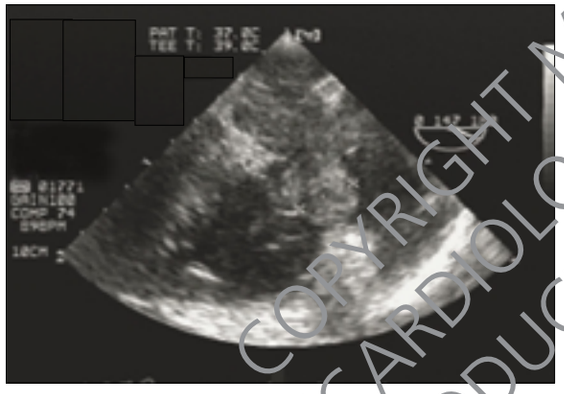


Figure 2. Echocardiogram showing a 2 cm x 2 cm mobile mass attached to the interatrial septum



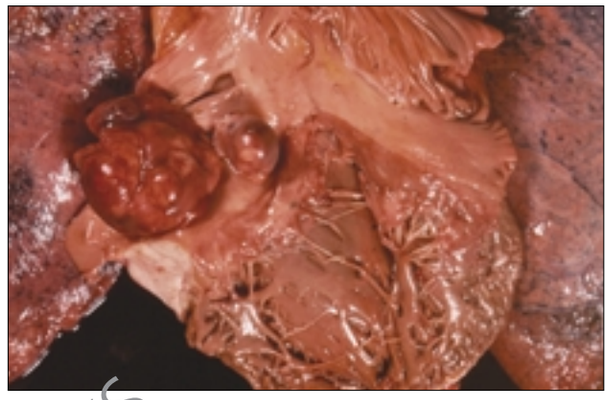
Transthoracic echocardiography was performed: although only poor views were obtained, there was no valvular heart disease and his left ventricular systolic function appeared poor.

The patient was treated with a blood transfusion. Treatment for heart failure, including frusemide and an angiotensin-converting enzyme inhibitor, was started. Upper gastrointestinal endoscopy and sigmoidoscopy failed to reveal a source of bleeding. The patient made slow progress and was discharged home.

Two days later he was readmitted with more swelling of the face and arms plus dilated veins on the anterior chest wall, suggesting obstruction of the superior vena cava (SVC). A left cephalic venogram showed a filling defect in the right atrium. Transoesophageal echocardiography revealed a 3 cm x 3 cm mass attached to the upper part of the right atrium, obstructing the drainage of the SVC (figure 1). A 2 cm x 2 cm round mobile mass was seen attached to the interatrial septum; it prolapsed through the tricuspid valve during diastole (figure 2).

Computerised tomography scanning of the abdomen and thorax showed that the SVC was narrowed and virtually occluded by a large mediastinal mass. In addition, there was a large irregular-filling defect in the right atrium extending to the left atrium. There was a large oval mass approximately 8 cm in diameter of intermediate attenuation above the bladder and a subcutaneous soft tissue mass approximately 2 cm in diameter in the left anterior abdominal wall.

Figure 3. Post mortem findings, showing two masses adjacent to the tricuspid valve



The patient was treated with a one-week course of palliative radiotherapy, and the signs of superior vena caval obstruction improved. His haemoglobin level continued to fall and he received repeated blood transfusions. His condition gradually deteriorated, and he died three and a half months after his acute admission.

Autopsy findings

At post mortem, the patient was found to have multiple tumour deposits, bilaterally in the perinephric fat, around the left adrenal gland, in the left para-aortic area, and within the pelvis and the mesentery of the small bowel.

The right atrium contained two polypoid masses measuring 30 x 25 x 20 mm and 15 x 10 x 8 mm, respectively. These were firmly adherent to the posterior atrial wall just superior to the valve ring and they were obstructing the tricuspid valve even though they were not adherent to it (figure 3). Their cut surfaces had a variable appearance, with pale and haemorrhagic areas. On further sections, both masses were found to be in direct communication with an area of solid pale tumour within the valve ring itself and extending into the myocardium of the right ventricle (figure 4). The right coronary artery was compressed by this tumour. The atrial appendages were free of thrombus.

Histology of all the masses was similar. They were composed of a diffuse infiltrate of plasma cells with varying levels of maturation.

Discussion

Extramedullary plasmocytoma of the heart is extremely rare: only 11 cases have been reported in the literature.[3,4] One common

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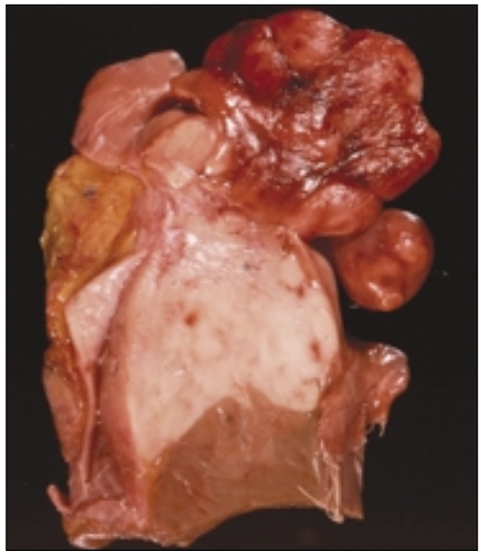
Figure 4. Post mortem findings, showing a mass of solid pale tumour extending into the myocardium of the right ventricle



finding in all these cases has been the predominant involvement of the right atrium. Clonal immunoglobulin gene rearrangement studies have suggested that malignant cells from the primary site travel in the venous blood and are deposited in the right atrium.[5,6]

Plasmocytoma involvement of the coronary arteries has been reported only once before, by Champeaux and colleagues: they reported a 57-year-old man with multiple myeloma and metastatic plasmocytoma involvement of the myocardium, compressing the right coronary artery and infiltrating the coronary sinus.[4] In our case the right coronary artery was compressed by plasmocytoma within the tricuspid valve ring.

This case presented with superior vena caval obstruction secondary to mediastinal and right atrial plasmocytoma. However, multiple myeloma and extramedullary plasmocytoma can cause other cardiovascular pathology such as hyperviscosity, cardiac amyloidosis, various dysrhythmias, myocardial infarction[7] and high output cardiac failure secondary to extensive bony involvement.

In the literature there are no specific guidelines for the treatment of cardiac plasmocytoma, since the number of cases is so small and the survival data so limited. Localised extramedullary plasmocytoma usually responds to deep radiotherapy, and the overall relapse rate is generally less than 30%.[3] Chemotherapy is the treatment of choice for more advanced cases with widely disseminated disease. Our case responded to a one-week course of radiotherapy with improvement in the signs of superior vena caval obstruction. Chemotherapy was not considered a suitable option for this patient because he had multiple pathology and his prognosis was poor. Surgical treatment is usually only indicated as a life-saving measure in patients who are haemodynamically unstable secondary to tumour obstruction of the right side of the heart.

Key messages

- Secondary cardiac tumours are reported in as many as 10–15% of patients with metastatic tumours
- Clinicians should have a low threshold for performing echocardiography in patients with widespread malignancy who present with cardiac symptoms
- Transoesophageal echocardiography is more sensitive than transthoracic in detecting structural abnormalities of the heart

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Note from author

At the time that the case report was written Dr Muhyaldeen was working at Ninewells Hospital, Dundee.

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