

Current Concepts in the Management of Heart Failure

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ABSTRACT

Objective: *To review current concepts in the management of patients with heart failure.*

Data sources: *A review of articles reported on acute and chronic heart failure.*

Summary of review: *Heart failure has been defined as that state which occurs when the heart fails to maintain the needs of the body despite a satisfactory venous return. While it has been divided functionally into high-output failure and low-output failure, it is often used to describe patients with left ventricular low-output failure and is divided into systolic or diastolic heart failure, depending on left ventricular ejection fraction. The clinical features are due largely to venous congestion and reduction in cardiac output with symptoms of fatigue, orthopnoea, paroxysmal nocturnal dyspnoea and peripheral oedema being common complaints. Plasma natriuretic peptide levels are elevated in patients with symptomless left ventricular failure and have been useful in diagnosing heart failure in patients admitted with acute dyspnea.*

Treatment of heart failure is aimed at correcting both the underlying disorder as well as the precipitating cause (e.g. ischaemia, valvular heart disease, anaemia, thyrotoxicosis, etc), as well as reducing cardiac work, enhancing myocardial contractility and treating the complications (e.g. reducing salt and water retention, and neurohumoral activation). Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, β -blockers and spironolactone have all been associated with a reduction in mortality in patients with chronic heart failure. While digoxin and diuretics are used to reduce the number of episodes of pulmonary oedema, they have not been associated with a significant reduction in mortality. Surgery (e.g. transplantation, mechanical assist devices) has a definite place in young patients with chronic dilated cardiomyopathy with severe heart failure although other therapeutic agents (e.g. growth hormone, thyroxine and antioxidants) are yet to be shown to be of benefit.

Conclusions: *Heart failure is a common condition caused by many disorders leading to left ventricular dysfunction. Management of the underlying disorder (e.g. ischaemia, valvular disease, hypertension) maintenance of sinus rhythm, as well as reducing excessive neurohumoral activation (ACE inhibitors, angiotensin receptor antagonists, β -blockers, spironolactone) can reduce mortality and improve morbidity in patients with chronic heart failure (Critical Care and Resuscitation 2004; 6: 31-53)*

Key words: Heart failure, pulmonary oedema, cardiomyopathy

Heart failure may be defined as that state which occurs when the heart fails to maintain an adequate circulation for the needs of the body, despite a

satisfactory venous return. It should be distinguished from vascular congestion which occurs in patients who have normal cardiac function and an increase in

intravascular volume caused by the administration of excessive fluids, particularly in patients with renal failure.

PATHOPHYSIOLOGICAL TYPES

While heart failure may be described morphologically as left ventricular and right ventricular failure or functionally as high-output failure and low-output failure, the term heart failure is often used to describe patients with left ventricular low-output failure and is divided into systolic or diastolic heart failure, depending on left ventricular ejection fraction.

Low-output failure. This is associated with a low cardiac output and high filling pressures and, depending on the clinical features, is described as either 'forward failure' or 'backward failure'. When a reduction in cardiac output occurs (i.e. 'forward failure'), the body sets into motion various reflexes which retain sodium and water (e.g. activates renin-angiotensin-aldosterone and antidiuretic hormone systems), in an attempt to increase cardiac output by increasing venous return, leading in turn to peripheral and pulmonary oedema (i.e. 'backward failure').

High-output failure. This is associated with a high cardiac output, fluid retention and (apart from anaemia) an elevated mixed venous haemoglobin oxygen saturation. It is caused by any condition with a severely lowered peripheral resistance (e.g. beriberi, anaemia, arteriovenous fistula, Paget's disease, hyperthyroidism, autonomic neuropathy and severe sepsis). High-output failure from a dialysis shunt is uncommon as it usually requires a flow averaging 1.5 litres per minute, and at least one other contributing factor (i.e. coronary artery disease).¹ The diagnosis may be confirmed by observing a reduction in pulse rate when the AV dialysis shunt is compressed.

Right ventricular failure. This is associated with the clinical features of systemic venous congestion, (e.g. peripheral oedema, hepatic congestion, ascites).

Left ventricular failure. This is associated with the clinical features of pulmonary congestion (e.g. pulmonary oedema, dyspnoea, orthopnoea, cough) and is divided into:

Systolic failure: which is a clinical syndrome of heart failure (i.e. low cardiac output, pulmonary oedema) associated with a reduction in the left ventricular ejection fraction (< 0.5) and an enlarged left ventricular chamber,² and

Diastolic failure: which is a clinical syndrome of heart failure associated with a preserved left ventricular ejection fraction (0.50 or more) and a small left ventricular chamber.²⁻⁵

AETIOLOGY

Heart failure is always caused by an underlying cardiovascular abnormality, which often becomes overt following a precipitating event. In evaluating heart failure, both the underlying cause and the precipitating event should be identified (Table 1). The role of revascularisation procedures (e.g. coronary artery bypass grafting, coronary angioplasty) in patients with heart failure (without angina) caused by ischaemic heart disease is yet to be defined.⁶

Table 1 Causes of heart failure

<i>Underlying cause</i>	
Myocardial disease	(e.g. ischaemic heart disease, cardiomyopathy)
Valvular disease	(e.g. mitral or aortic stenosis or regurgitation)
Pericardial disease	(e.g. constrictive pericarditis, cardiac tamponade)
Vascular defect	(e.g. atrioventricular malformation)
<i>Precipitating cause</i>	
Myocardial ischaemia, infarction	
Hypertension	
Pulmonary embolism	
Anaemia	
Tachycardia	
Infection, sepsis	
Heat exhaustion	
Arrhythmia	
Drugs	(e.g. β -adrenergic blockers, corticosteroids, calcium-channel blockers, antiarrhythmic agents, oestrogens)
Respiratory failure	
Pregnancy	
Hyperthyroidism, hypothyroidism	

SYSTOLIC FAILURE

Systolic failure is usually caused by disorders that are associated with dilated cardiomyopathies. A cardiomyopathy is defined as a diffuse disorder of the heart that leads to heart failure.⁷⁻⁹ Cardiomyopathies usually have a reduced cardiac index and are classified depending on their left ventricular ejection fraction (LVEF) and whether they are dilated, non dilated or hypertrophic (Table 2).^{7,8,10,11}

Dilated cardiomyopathies are characterised by a profound reduction in the left ventricular ejection fraction (i.e. less than 0.40).⁷ There is also a reduction in noradrenaline stores, a down-regulation of β -adrenergic receptors (i.e. a 30% decrease in

responsiveness of the β receptor¹² and a 50% reduction in β receptor density) and a nitric oxide induced attenuation of the positive inotropic effect of catecholamines.¹³

The normal myocardial cell contains 80% β_1 and 20% β_2 receptors. The β receptor loss in dilated cardiomyopathies is characteristically a selective β_1 receptor loss.¹² Some data also suggest that activation of the inhibitory (i.e. negative inotropic) β_3 receptor (which is resistant to chronic agonist-induced desensitisation)¹⁴ may also play a role in the reduction of myocardial contractility.¹⁵ Pathologically, all four chambers are dilated and the disorder is progressive. Factors which have been proposed to cause the change in myocardial morphology and function include noninflammatory mechanisms of myocyte apoptosis (i.e. programmed cell death, which is distinguished from cell necrosis by occurring in isolated cells and without an inflammatory response),¹⁶ and inflammatory mechanisms with chronic TNF- α stimulation causing left ventricular contractile dysfunction and dilation.¹⁷

Table 2 Causes of cardiomyopathy

Dilated cardiomyopathies

(LVEF < 0.40)

- Ischaemic heart disease, diabetes, uraemia
- Idiopathic, tachycardia induced
- Alcoholic, connective tissue disorders
- Secondary to mitral or aortic valve disease
- Postpartum, nutritional deficiencies
- Haemochromatosis, heavy metals
- Drugs
 - doxorubicin, daunorubicin, amphetamines, cocaine
 - sulphonamides, phenylbutazone
- Phaeochromocytoma
- Sarcoid, others (e.g. glycogen storage disease)
- Infective
 - Coxsackie A, B, Influenza A, B, herpes, rubella
 - Cytomegalovirus, hepatitis A, B and C,
 - Toxoplasmosis, mycoplasma, psittacosis

Nondilated (restrictive) cardiomyopathies

(LVEF 0.40 - 0.70)

- Idiopathic, amyloid, scleroderma, sarcoid
- Radiation, neoplastic infiltration
- Drugs (e.g. methysergide, busulfan)
- Endomyocardial fibrosis

Hypertrophic cardiomyopathies

(LVEF 0.45 - 0.95)

- Familial, Friedreich's ataxia

LVEF = left ventricular ejection fraction.

CLINICAL FEATURES

The clinical features associated with heart failure are due largely to venous congestion or reduction in cardiac output, although some patients may present with embolic phenomena or sudden death due to spontaneous ventricular tachycardia (VT) and ventricular fibrillation (VF).

The symptoms include fatigue and weakness (due to a reduced capacity to increase cardiac output in response to exercise), orthopnoea, nocturnal coughing or dyspnoea, paroxysmal nocturnal dyspnoea, breathlessness, wheezing and haemoptysis (due to pulmonary venous congestion), anorexia and nausea (due to visceral congestion), and ankle oedema and leg oedema (due to systemic venous congestion).

The signs include cyanosis, raised JVP, triple rhythm, pulmonary crackles, pleural effusion, Cheyne-Stokes respiration, swelling of ankles, hepatomegaly, jaundice and ascites, although ascites occurs more commonly with constrictive pericarditis or tricuspid regurgitation.

INVESTIGATIONS

The investigations often performed in patients with heart failure include:

Chest X-ray. This allows an accurate assessment of the cardiac size and shape, and confirms the presence of pulmonary congestion and pleural effusions.

ECG. This is performed to review the cardiac rhythm and evidence of an underlying myocardial disorder. With dilated cardiomyopathies the ECG commonly reveals LBBB, left ventricular hypertrophy, poor precordial R wave progression, T wave and ST segment changes, low voltage QRS complexes (particularly in the limb leads) and atrial fibrillation.

Echocardiography. This allows an assessment of myocardial, pericardial and valve function, and, by assessing the left ventricular ejection fraction, whether the predominant defect is diastolic heart failure or systolic heart failure.²

Plasma enzymes and biochemistry. Creatinine kinase (MB isoenzyme), lactate dehydrogenase (LDH), and troponin levels are elevated in the presence of acute myocardial injury. Patients with heart failure may develop an ischaemic hepatitis due to an elevated systemic venous pressure, causing hepatic congestion, associated with a reduction in hepatic arterial blood flow. The hepatic injury is characterised by centrilobular necrosis and is often associated with acute renal impairment with an elevated plasma urea, creatinine and uric acid (particularly with diuretic use).^{18,19} There is a mild elevation of plasma bilirubin, prothrombin time and alkaline phosphatase (ALP), and a characteristically greater increase in plasma LDH

compared with plasma alanine amino transferase (ALT) or aspartate amino transferase (AST).¹⁹⁻²¹ One study found that the mean serum ALT/LDH ratio in patients with ischaemic hepatitis was 0.87, compared with 1.46 in paracetamol hepatitis and 4.65 in viral hepatitis, and that a serum ALT/LDH ratio of < 1.5 differentiated ischaemic hepatitis from paracetamol hepatitis and viral hepatitis, with a sensitivity of 94% and a specificity of 84%.²⁰ With the correction of heart failure, the enzyme changes usually resolve rapidly (i.e. > 50% decrease within 72 hr).^{18,22,23}

Plasma A-type and B-type natriuretic peptide. Atrial natriuretic peptide (ANP) is secreted as N- and C-terminal fragments (i.e. NT-ANP and CT-ANP, respectively) in response to an elevation in right atrial pressure. B-type natriuretic peptide (BNP) is secreted from the ventricular myocardium in response to elevation in ventricular diastolic pressure. Both BNP²⁴ and NT-ANP²⁵ are elevated in symptomless left ventricular failure and may be early markers of New York Heart Association (NYHA) class I heart failure,²⁶ and therefore indicators for angiotensin converting enzyme (ACE) inhibitor therapy following acute myocardial infarction.^{27,28} One study reported a diagnostic accuracy for congestive cardiac failure of 83.4% with B-type natriuretic peptide levels of 100 pg/mL or greater (with a negative predictive value of 96% with B-type natriuretic peptide levels of 50 pg/mL or less), in patients admitted with acute dyspnea.²⁹ Concentrations of BNP are also consistently raised in patients with diastolic dysfunction (e.g. aortic stenosis, hypertrophic cardiomyopathy, restrictive cardiomyopathy), and levels reflect the response to therapy. Plasma BNP levels are also independently associated with mortality in patients with heart failure. As NT-ANP provides the same information as BNP and accurate commercial assays are currently available for the former, NT-ANP levels are often used in clinical practice.³⁰

Non-specific inflammatory markers. The ESR is characteristically low in patients with heart failure although it is not a pathognomonic feature. Elevation in plasma C-reactive protein and leucocytosis indicate an inflammatory response. Auto-antibodies (e.g. antinuclear factor, etc) indicate an autoimmune process.

Radionuclide ventriculography. This may be used to provide an accurate assessment of the left ventricular ejection fraction.

Cardiac catheterisation. This may be performed to assess coronary artery disease, valve function, atrial and ventricular pressures, cardiac output, ventricular stroke work, and mixed venous oxygen concentrations.³¹

Other tests. Other tests may also be performed to confirm the presence of a precipitating cause (e.g. lung scan, thyroid function studies).

A 6 minute walk test has been used to assess the severity of heart failure, although prognostication using this test alone has a low sensitivity.³²

TREATMENT

In a patient with heart failure the treatment is aimed at correcting the underlying and precipitating cause (e.g. ischaemic heart disease, valvular heart disease, pericardial constriction, ventricular aneurysm, etc), as well as reducing cardiac work (e.g. using vasodilators and neurohumoral inhibitors), enhancing myocardial contractility (e.g. using digoxin, sympathomimetic amines, phosphodiesterase inhibitors, calcium sensitisers) and treatment of complications (e.g. reducing salt and water retention, thromboembolism, arrhythmias). Surgery (e.g. transplantation, mechanical assist devices) has a definite place in young patients with chronic dilated cardiomyopathy with severe (NYHA IV) heart failure although other therapeutic agents (e.g. growth hormone, thyroxine and antioxidants) are yet to be shown to be of consistent benefit. As chronic heart failure is associated with an activation of circulating neurohumoral factors and proinflammatory cytokines that may contribute to the progression of the disease, agents that inhibit or block their effects may have a beneficial effect on mortality.

Reduction of cardiac work

This includes rest (particularly after meals), weight loss and a reduction in myocardial afterload. The latter may be achieved by arterial or venous dilators.

Vasodilators

Venodilators. Nitrates reduce ventricular filling pressures and diastolic volumes, and therefore reduce afterload. However, long-term therapy with nitrates has been disappointing as oral isosorbide dinitrate at 40 mg 6-hourly does not increase the exercise capacity of patients with chronic heart failure more than that observed with a placebo, nor does it consistently relieve symptoms of heart failure.^{33,34}

Arterial vasodilators. These consist of direct vasodilators and calcium channel blockers

Direct vasodilators include agents that liberate nitric oxide (e.g. hydralazine, nitrates) and agents that open K_{ATP} channels (e.g. minoxidil). While the principal haemodynamic effect of the direct vasodilators is a reduction in systemic vascular resistance, and therefore a reduction in afterload, neither hydralazine or minoxidil alone consistently alleviate symptoms or improve the exercise tolerance of patients with heart

failure.³³ However, in patients with mild to moderate heart failure (NYHA class II and III), therapy with hydralazine and isosorbide dinitrate added to digoxin and diuretics has been shown to reduce mortality from 38% to 25% at 2 years, compared with no reduction in mortality when a placebo or prazosin were added to digoxin and diuretic therapy.³⁵ Nevertheless, the combination of isosorbide dinitrate and hydralazine has many side-effects, causing poor patient compliance and tolerance.³³ A trial comparing isosorbide dinitrate and hydralazine with enalapril in patients with mild to moderate heart failure who were treated with digoxin and diuretics, showed a significantly lower mortality after two years in the enalapril group (18%) when compared with the isosorbide and hydralazine group (25%).³⁶

Calcium-channel blockers (e.g. verapamil, nifedipine, diltiazem, felodipine, nifedipine). These agents reduce afterload by reducing systemic vascular resistance, although they have not been associated with an enhanced exercise tolerance or symptomatic benefits in patients with heart failure.³³ Furthermore, they exert important negative inotropic effects which have been implicated in adversely affecting the haemodynamic and clinical status of patients with severe left ventricular dysfunction,³³ and have also been reported to increase mortality in patients with heart failure who have suffered recent myocardial infarction.³⁷ While amlodipine does not increase cardiovascular morbidity or mortality in patients with severe heart failure it has not yet been shown to reduce morbidity or mortality.³⁸

Neurohumoral inhibitors

Angiotensin converting enzyme (ACE) inhibitors. These agents interfere with the formation of angiotensin II (thereby reducing smooth muscle constriction, catecholamine release, vasopressin release, renal tubular sodium reabsorption, aldosterone release and inhibiting baroreceptor sensitivity)^{39,40} causing a reduction in left ventricular filling pressure, a decrease in peripheral resistance and a reduction in pulse rate.^{41,42} They produce both short- and long-term clinical improvements in patients with chronic heart failure which are superior to other vasodilator drugs (an effect that is not reduced by the coadministration of aspirin)⁴³ which may be due to a reduction in the growth factor effect of angiotensin II on cardiac 'remodelling',⁴⁴ and bradykinin induced regression of vascular hypertrophy⁴⁵ and preconditioning of myocardium against ischaemia.⁴⁶

In patients with mild, moderate or severe heart failure, dyspnoea is relieved, exercise tolerance is improved, and the incidences of myocardial infarction and mortality are reduced.⁴⁷⁻⁴⁹ Angiotensin converting enzyme inhibitors reduce the need for diuretics and

potassium supplementation and act to correct hyponatraemia and hypokalaemia commonly associated with severe heart failure. They should be used initially at a low dosage, increasing up to the maximum tolerable effect. The patient is observed closely for hypotension, particularly when diuretics are used and an elevation in plasma creatinine (which may indicate bilateral renal artery stenosis).⁵⁰

Angiotensin converting enzyme inhibitors are now considered as first-line treatment for patients with chronic heart failure.⁵¹

Angiotensin receptor antagonists. The selective AT₁ receptor inhibitor losartan potassium may also be useful in the management of heart failure.⁵² In one double-blind, randomised captopril-controlled trial in 722 patients over 65 with heart failure, losartan (beginning with 12.5 mg and titrated to 50 mg daily) was associated with a lower all-cause mortality, better tolerance, and no difference in renal dysfunction when compared with captopril (beginning with 6.25 mg and titrated to 50 mg 8-hourly).⁵³ This effect may be due to a greater reduction of cardiac tissue noradrenaline at the neuroeffector junction with losartan compared with captopril (as production of non ACE angiotensin II and high bradykinin levels - both of which enhance the release of cardiac noradrenaline - occurs with captopril).⁵⁴ However, in a larger study (3152 patients) losartan was not superior to captopril in improving survival in elderly heart failure patients, although it was significantly better tolerated. (i.e. lower rate of discontinuation due to adverse effects).⁵⁵

Combination of an angiotensin converting enzyme inhibitor and angiotensin receptor antagonist. In one trial of 601 patients with heart failure randomised to candesartan, enalapril or the combination of both, there was no significant difference in the rate of mortality or hospitalisation between the three groups at 43 weeks of follow-up.⁵⁶ In another trial, where valsartan (160 mg per day) was administered to patients with NYHA class II - IV heart failure treated with β adrenergic receptor blockers and ACE inhibitors, there was a significant increased mortality compared with the group given placebo, with the authors concluding that extensive blockade of multiple neurohormonal systems in patients with heart failure may be deleterious,⁵⁷ although the result may have occurred by chance.⁵⁸ However, in a recent large randomised placebo controlled trial in patients with NYHA class II - IV heart failure (patients were excluded if the creatinine was > 0.265 mmol/L, potassium was > 5.5 mmol/L or if there was bilateral renal artery stenosis or critical aortic valve stenosis), candesartan led to a 1.6% absolute reduction in mortality and 4.3% absolute reduction in incidence of cardiovascular mortality and hospitalisation for heart

failure. The reduction in mortality occurred in patients who were treated with other agents (e.g. β -blockers, digoxin, diuretics, spironolactone, aspirin, statins), optimal doses of ACE inhibitors and in patients who were intolerant of ACE inhibitors, although in patients with ejection fractions of $> 40\%$ the mortality reduction was not significant.⁵⁹⁻⁶²

Beta-adrenergic antagonists (β blockers). Chronic sympathetic stimulation has adverse effects on myocardial function, causing vasoconstriction, arrhythmogenesis, an increase in renin secretion and noradrenaline release.⁶³ Myocardial β_1 -adrenoreceptor down-regulation with relative preservation of β_2 -adrenoreceptor density and function occurs, which is thought to be a consequence of the increased β_1 -adrenoreceptor stimulation by the sympathetic neurotransmitter noradrenaline. However, the reason for a differential down-regulation of β -adrenoreceptor subtypes remains largely obscure as exogenous catecholamine stimulation generally down-regulates the β_2 -adrenoreceptor to a greater extent than the β_1 -adrenoreceptor.⁶⁴

High levels of noradrenaline are directly toxic to myocardial cells, mediated through increased levels of intracellular calcium, apoptosis or both.⁶⁵ This effect can be blocked by nonselective β -adrenergic blockade (although β_1 blockade provides the predominant beneficial effect in patients with heart failure) or combined β - and α -adrenergic blockade. Generally, β -adrenergic antagonists have been avoided in patients with heart failure (as well as in patients with asthma, shock, or bradycardia), but recent studies have been performed which have shown a favourable outcome when these agents are used carefully (i.e. increased slowly from extremely low doses) in patients with heart failure.⁶⁶ A meta-analysis of 22 trials involving 10,135 patients with mild to moderate heart failure found a benefit⁶⁷ that translated into a reduction in mortality of 3 and reduction in hospital admissions of 4 for every 100 patients treated per year.⁶⁸ The clinical index of β_1 blockade is the effect on reduction in exercise induced tachycardia.⁶⁹

Carvedilol: Carvedilol is a nonselective β blocker and selective α_1 -adrenergic antagonist, it also has anti-oxidant and anti-apoptotic properties. It is a racemic mixture, with both dextro and laevo forms having α_1 -adrenergic blocking activities but only the laevo form having a nonselective β blocking activity. The ratio of α_1 - to β -adrenoreceptor blockade is 1:10 (c/f 1:4 for labetalol) and carvedilol is about 2 - 4 times as potent as propranolol as a β -adrenoreceptor antagonist.⁷⁰ The drug is rapidly absorbed and undergoes extensive first-pass metabolism in the liver. It reaches a peak concentration 1 to 2 hours post-ingestion and has an

elimination half-life of about 4 to 7 hours. The drug is highly lipophilic and highly protein bound. It is metabolised by the liver, with the bioavailability of the oral medication being greatly increased in patients with liver disease. The pharmacokinetic profile is not altered in patients with renal disease.⁷¹

In patients with heart failure (NYHA class II-III), carvedilol (when used with digoxin, diuretics and ACE inhibitors and when administered carefully, i.e. an initial dose of 3.125 mg 12-hourly and increasing every 7 - 14 days up to 25 mg 12-hourly, if tolerated) has been associated with a reduction in mortality, improvement in symptoms and reduction in the number of cardiovascular hospital admissions.⁷²⁻⁷⁴ While these effects are predominantly observed in patients with mild heart failure (by retarding progression of heart failure), the effect of its indiscriminate use may increase mortality in patients with severe heart failure.⁷⁵ In one large multicentre, randomised controlled trial in patients with severe chronic heart failure (i.e. dyspnoea or fatigue at rest or with minimal exertion and left ventricular ejection fraction $< 25\%$ despite ACE inhibitor, digoxin, spironolactone, amiodarone, nitrate therapy), patients were excluded if they required intensive care or continuous inpatient care, had severe cardiac oedema despite treatment with diuretics, serum creatinine > 0.248 mmol/L, uncorrected valvular disease, primary renal, hepatic or pulmonary disease, asthma, heart rate lower than 68 beats per minute, systolic blood pressure < 85 mmHg, or within the previous two months had an acute myocardial infarct, coronary revascularisation, cerebral ischaemic event or received a β blocker, or received an α -adrenergic blocker, calcium channel blocker, or class I antiarrhythmic within the previous 4 weeks. A slowly increasing dose of carvedilol (to a maximum of 25 mg 12-hourly) reduced morbidity and mortality.⁷⁶

In a recent multicentre, prospective, randomised trial comparing metoprolol (50 mg 12-hourly) with carvedilol 25 mg 12-hourly in heart failure patients (NYHA class II 48%, III 48% and IV 3%), patients who received carvedilol had a 5.7% absolute reduction in mortality (i.e. a mean survival of 8 years compared with 6.6 years).⁷⁷

Bisoprolol: Bisoprolol is a highly selective β_1 -adrenoreceptor antagonist. In one study of patients with mild to moderate heart failure (ejection fraction 35% or less) bisoprolol (1.25 mg daily increasing up to a maximum of 10 mg daily), in association with ACE inhibitors and diuretics, reduced mortality by 34% (with a 44% reduction in sudden death) and reduced hospital admissions by 20%.⁷⁸ The number needed to treat (NNT) was 23 patients for one year to prevent one death.

Bucindolol: Bucindolol is a nonselective β adrenoreceptor antagonist without intrinsic sympathomimetic activity. As it has a strong β_2 -adrenoreceptor blocking effect (blocking noradrenaline release), it causes a profound sympatholytic response. However, in one study of patients with advanced heart failure it did not produce a significant survival benefit.⁷⁹

Metoprolol: In patients with heart failure (NYHA class I to 'stable' IV and an ejection fraction of 40% or less), metoprolol (12.5 - 25 mg daily and titrated up to 200 mg daily over 8 weeks, in association with ACE inhibitors and diuretics) has been reported to reduce the annual mortality (both sudden deaths and deaths due to worsening of heart failure) from 11% to 7.2% (i.e. NNT 27 patients for one year to prevent one death).⁸⁰

Nebivolol: Nebivolol is a selective β_1 -adrenergic blocker with associated vasodilator activity mediated through an increase in NO release (due to a partial β_2 -agonist effect of a metabolite and/or direct effects on the endothelial NO release, although the precise mechanism of action of this effect in humans is still not fully understood).^{81,82} A prospective randomised trial in 26 patients with diastolic heart failure comparing atenolol (50 up to 100 mg daily) with nebivolol (2.5 up to 5 mg daily) for 6 months reported that both agents had equivalent reduction in blood pressure, exercise heart rate and left ventricular mass, although nebivolol was associated with a lower reduction in the cardiac index and a greater reduction in mean pulmonary artery pressure and pulmonary wedge pressure.⁸³

There is now good evidence to suggest that β blockers are beneficial in patients with mild to moderate heart failure⁸⁴ (particularly in NYHA class I, II and III).⁸⁵ However, if β -adrenergic blocking agents are used in patients with severe heart failure (e.g. NYHA class IV) they should be introduced at low doses and used with care.

Endothelin-converting enzyme inhibitors and endothelin receptor blockers. Endothelin-1 is a potent vasoconstrictor with high plasma levels being found in patients with chronic heart failure with the magnitude of elevation corresponding directly to the severity of heart failure.⁸⁶⁻⁸⁸ The mixed endothelin (i.e. ET_A and ET_B) receptor antagonist, bosentan, reduces the systemic and pulmonary artery pressures and increases the cardiac output in patients with chronic heart failure, in addition to the effects of ACE inhibitor therapy.⁸⁹ However, there are no studies that have yet confirmed a reduction in mortality associated with this treatment.⁹⁰ For example, the nonselective endothelin antagonist tezosentan (50 - 100 mg/hr) did not alter 30 day mortality, and the relatively nonselective oral endothelin antagonist enrasentan was associated with a trend to

worsening mortality.⁹¹ In one study, myocardial expression of urotensin II was found to be increased in patients with end-stage congestive cardiac failure, indicating that this peptide may also be important in the development of heart failure.⁹²

Nesiritide. Nesiritide (a recombinant human BNP) is a diuretic with arterial and venodilator and neurohumoral effects (e.g. reduces noradrenaline and aldosterone concentrations) and has been used (6-hour infusion, 2 μ g/kg bolus followed by 0.01 μ g/kg/min and increasing to 0.03 μ g/kg) for treatment of uncompensated heart failure. However, when compared with dobutamine, symptomatic hypotension was more frequent.³⁰

Vasopeptidase inhibitors. The effect of natriuretic peptides (e.g. natriuresis, vasodilation) are reduced if the renin-angiotensin-aldosterone system is not inhibited. The agent omapatrilat inhibits both angiotensin converting enzyme and the natriuretic peptide catalytic enzyme neutral peptididase (NEP), and has been of benefit in patients with chronic heart failure, although in one study omapatrilat had more adverse effects (dizziness, hypotension, diarrhoea, vomiting, constipation, angio-oedema) than the ACE inhibitor lisinopril,⁹³ which may be due to the increase in plasma kinin levels (as both ACE and NEP inactivate bradykinin).⁹⁴

Enhancement of myocardial contractility (positive inotropic agents)

In patients with heart failure there has been only one agent that enhances myocardial contractility that has not increased mortality (i.e. digoxin). While amrinone, milrinone, vesnarinone, pimobendan (a calcium sensitiser with phosphodiesterase inhibiting properties), flosequinan, xamoterol, pirbuterol and prolonged infusions of dopamine and dobutamine had isolated reports of improved outcome, their use in larger trials revealed an increase in mortality.^{95,96} Prolonged β -adrenergic stimulation may increase cell apoptosis by increasing free radical production.⁹⁷

Cardiac glycosides

Digoxin produces immediate and sustained increases in cardiac output and left ventricular ejection fraction and decrease in cardiac filling pressures in patients with chronic heart failure.³³ It improves exercise tolerance and reduces the need for diuretics. These beneficial effects are observed in patients with chronic mild, moderate or severe heart failure if evidence of left ventricular systolic dysfunction (e.g. cardiomegaly, triple rhythm, reduced ejection fraction) is present,⁹⁸ and are additive to the effects of ACE inhibitors.⁹⁹ While patients with heart failure who are in

sinus rhythm and are treated with ACE inhibitors and diuretics have a worsening of heart failure if digoxin is withdrawn from therapy¹⁰⁰ or increased symptoms of heart failure if digoxin is not added to therapy (e.g. digoxin is associated with a reduction by 9 per 1000 patients per year in the rate of hospitalisation due to heart failure),¹⁰¹ digoxin does not alter mortality.¹⁰¹

Digoxin appears to be ineffectual if left ventricular systolic function is preserved (e.g. absence of cardiomegaly, normal ejection fraction) and when heart failure is due to a diastolic function abnormality. Moreover, as cardiac glycosides do not induce a positive lusitropic effect¹⁰² (contrasting to sympathomimetic agents and phosphodiesterase inhibitors) and as they have been reported in animal studies to impair diastolic function,¹⁰³ they may be contraindicated in patients with diastolic heart failure, although this was not confirmed from the data in the Digitalis Investigation Group study.¹⁰¹

Currently, digoxin is indicated for patients who are in atrial fibrillation or sinus rhythm with systolic heart failure to improve quality of life (e.g. by reducing the episodes of acute heart failure requiring hospitalisation).¹⁰⁴

Beta-adrenergic and dopaminergic agonists

Even though catecholamine sensitivity is reduced in chronic heart failure, due to receptor down-regulation, these agents can, in the short term, produce haemodynamic benefits by their positive inotropic effect. Some agents also have peripheral vasodilator effects (due to either β_2 - or dopamine DA₁ receptor stimulation). However, with prolonged use, tolerance often develops and while symptomatology may improve, none have been associated with a reduction in mortality and some have even been associated with an increase in mortality (particularly when used in patients with severe heart failure i.e. NYHA class III and IV).¹⁰⁵

Dobutamine. In a controlled study in patients with stable, moderate to severe, chronic heart failure, a dobutamine infusion (sufficient to increase the pulse rate to 70% - 80% of the patients maximum pulse rate) for 30 minutes a day for 4 days a week for three weeks, enhanced β -receptor up-regulation and chronotropic responsiveness, and improved exercise tolerance and symptoms of heart failure.¹⁰⁶ Furthermore, twice weekly dobutamine infusions have been used successfully to manage patients with severe heart failure, without the development of tolerance.¹⁰⁷ However, a study testing the efficacy and safety of intermittent intravenous dobutamine was stopped early because of an increase in mortality in patients with moderate to severe heart failure.^{108,109}

Xamoterol. Xamoterol has β -agonist and antagonist properties. In one large double-blind study in patients with chronic heart failure,¹¹⁰ oral xamoterol (200 mg twice daily) increased exercise performance and reduced symptoms of breathlessness and tiredness significantly more than digoxin (0.125 mg twice daily).¹¹¹ However, while modest improvements in haemodynamic function, symptoms and exercise tolerance occurred in patients with mild to moderate chronic heart failure,¹¹² in patients with severe heart failure (i.e. NYHA Class III and IV) mortality was increased.¹¹³

Ibopamine. Ibopamine, when taken orally, is hydrolysed to N-methyldopamine (epinine) which stimulates dopamine-1 (DA₁) and dopamine-2 (DA₂) receptors causing renal and peripheral vasodilation seemingly without an inotropic effect. In patients with heart failure it reduces plasma levels of noradrenaline, renin activity and aldosterone, and improves exercise tolerance in patients with mild to moderate heart failure. However, in a large randomised controlled trial, oral ibopamine (100 mg 8-hourly) increased mortality in patients with severe heart failure (NYHA class III - IV) who were already receiving optimum therapy (ACE inhibitors, diuretics and digoxin if indicated).¹¹⁴

Phosphodiesterase inhibitors

Theophylline. Theophylline is a non-specific phosphodiesterase inhibitor as well as a purine receptor antagonist and a time honoured therapy for heart failure with pulmonary oedema, due to its diuretic, vasodilator, respiratory stimulant (it can reverse Cheyne-Stokes respiration),¹¹⁵ and positive inotropic and chronotropic effects. However, there have been no controlled studies that have shown a reduction in mortality associated with theophylline when used in patients with acute or chronic heart failure.

Amrinone and milrinone. Both amrinone and milrinone increase cardiac contractility by inhibiting the cAMP-specific (type III) phosphodiesterase, thereby increasing the normally low levels of intracellular cAMP in the chronic failing heart. While these agents may produce short-term haemodynamic benefits in patients with chronic heart failure, with prolonged use they are associated with an increase in adverse events,¹¹⁶ and mortality,¹¹⁷ and therefore are not recommended in the management of patients with chronic heart failure.

Vesnarinone. Vesnarinone is a phosphodiesterase inhibitor that has other cardiac effects. For example, it prolongs the opening of sodium channels (increasing intracellular calcium by increasing calcium/sodium exchange), delays the inward and outward rectifying potassium currents (prolonging the cardiac action

potential),¹¹⁸ and reduces TNF- α production (probably through its phosphodiesterase inhibiting effect).¹¹⁹ Unlike other phosphodiesterase inhibitors it slows the heart rate. In one study of patients with heart failure, vesnarinone (60 mg/day) reduced the six month risk of worsening of heart failure and reduced mortality in patients with symptoms of NYHA class III disease. However, at 120 mg/day the mortality was increased.^{118,120} Another study (using both 30 mg and 60 mg/day) demonstrated a dose dependent increase in mortality (due to a proarrhythmic effect), although there was an improvement in quality of life.^{121,122}

Calcium sensitisers

Levosimendan. Levosimendan is a calcium sensitiser (sensitises troponin C to calcium in a manner dependent on calcium concentration¹²³) with additional action as a mitochondrial adenosine triphosphate (ATP)-sensitive potassium channel opener.¹²⁴ It has been used with benefit in patients with decompensated heart failure and at therapeutic doses it exhibits enhanced myocardial contractility with no increase in oxygen demands.¹²⁵

Levosimendan produces anti-stunning effects without increasing myocardial intracellular calcium concentrations or prolonging myocardial relaxation. It also causes coronary and systemic vasodilation and has not been shown to be arrhythmogenic. Levosimendan is well tolerated, with the most common adverse events (e.g. headache, hypotension, nausea) being secondary to vasodilation.¹²⁶

In one multicentre, prospective and randomised study of hospital inpatients with severe low-output heart failure (despite optimal oral therapy with vasodilators and diuretics and a left ventricular ejection fraction of less than 0.35, cardiac index of less than 2.5 L/min/m² and a pulmonary capillary wedge pressure of more than 15 mmHg), levosimendan (loading dose of 24 μ g/kg over 10 min followed by a continuous infusion of 0.1 μ g/kg/min for 24 hr) improved haemodynamic performance and was associated with a lower mortality at 180 days compared with dobutamine (infused at 5 μ g/kg/min). The infusion rates were doubled if the response was inadequate at 2 hours.¹²⁷

Treatment of complications

Treatment of salt and water retention

Severe fluid retention may be treated with combination of diuretics (e.g. a thiazide, carbonic anhydrase inhibitor, potassium sparing diuretic, methylxanthines and loop diuretic) and dietary salt restriction. However, diuretics should be monitored with regular plasma electrolyte measurements and renal

and haemodynamic assessment (i.e. sodium, potassium, chloride, bicarbonate, magnesium, urea, and creatinine).

Furosemide. In patients with acute myocardial infarction and pulmonary oedema, intravenous furosemide has been reported to cause direct venodilation, with a reduction in pulmonary artery occlusion pressure (PAOP) within 5 min,¹²⁸ which appears to be mediated by an enhanced local vascular prostaglandin synthesis.¹²⁹ Reflex arterial vasoconstriction with intravenous furosemide has also been reported.¹³⁰ The diuretic effect of intravenous furosemide begins within 5 min, peaks at 30 min and lasts 2 hours.

In patients with chronic congestive cardiac failure, intravenous furosemide may initially worsen pulmonary congestion by causing an acute arterial vasoconstrictive response with a rise in systemic vascular resistance and increase in PAOP (within 10 - 20 min) due to an acute release of renin, increase in sympathetic tone, and release of antidiuretic hormone, which abates after 2 - 4 hours.¹³¹ However, as the neurohumoral stimulation caused by intravenous furosemide is particularly prominent with bolus administration, continuous low-dose furosemide (e.g. 2 - 4 mg/hr for 24 hr) has been used to improve the diuresis without causing the adverse haemodynamic effects.¹³²

Spirolactone. Aldosterone plays an important role in patients with chronic heart failure as it promotes sodium retention (with loss of magnesium and potassium), sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, vascular damage and impairs arterial compliance.¹³³ Initially it was thought that optimal doses of ACE inhibitors would suppress the production of aldosterone (as angiotensin II is a potent stimulus for adrenal aldosterone secretion). However, both angiotensin II and aldosterone ultimately escape the effects of long term ACE inhibition, with aldosterone levels showing a more pronounced rebound (reaching up to 20 times the normal levels in patients with heart failure).¹³⁴ Sustained elevations of angiotensin II and aldosterone concentrations induce abnormal vasomotor reactivity, baroreceptor responsiveness and fibrosis (with ventricular remodelling). While high dose spironolactone (e.g. 50 - 800 mg daily) has a natriuretic effect, low-dose spironolactone (i.e. 25 mg daily) in addition to loop diuretics, ACE inhibitors and digoxin, has been shown to reduce morbidity (i.e. episodes of pulmonary oedema) and mortality in patients with chronic heart failure (ejection fraction < 35%) without a significant rise in plasma potassium.^{133,135-137}

Eplerenone. Eplerenone is an aldosterone antagonist that selectively blocks the mineralocorticoid receptor

(and not the glucocorticoid, progesterone and androgen receptors) and therefore is free of the side effects of painful gynaecomastia and sexual dysfunction that occur with spironolactone. In one large prospective, multicentre, randomised, double-blind placebo-controlled study in patients receiving ACE inhibitors, angiotensin-receptor blockers, β -blockers, diuretics, aspirin, lipid-lowering agents as well as reperfusion therapy (although patients receiving potassium-sparing diuretics, or with a creatinine level of 0.22 $\mu\text{mol/L}$ or potassium greater than 5.0 mmol/L before randomisation were excluded), 3 – 14 days following an acute myocardial infarction with a left ventricular ejection fraction of 40% or less with clinical evidence of heart failure (e.g. pulmonary crackles, chest X-ray signs of congestion or a third heart sound) eplerenone (25 mg daily and titrated to a maximum of 50 mg daily) reduced the relative risk of death by 16% during the 16 month follow-up period and reduced the risk of hospitalisation for heart failure by 15%.¹³⁸

Vasopressin antagonists. Antidiuretic hormone (ADH or vasopressin) acts on the collecting duct of the nephron by binding to the cell membrane V_2 vasopressin receptor, activating adenylate cyclase present on the basolateral cell membrane and increasing intracellular cAMP. The increase in intracellular cAMP causes an increase in intracellular Ca^{2+} concentration, which in turn causes a calmodulin-dependent increase in permeability of the luminal side of the collecting duct cell membrane to water and urea due to the insertion of a highly selective water channel (aquaporin 2, one of a family of ten highly selective water channels)¹³⁹ into the apical membrane.¹⁴⁰ While the collecting ducts are impermeable to water in the absence of ADH, if the distal nephron flow is small enough, then the gradient between the hypotonic luminal fluid and the hypertonic medullary interstitium will allow a moderately hypertonic urine to be formed, even in the absence of ADH.

The arginine-vasopressin antagonist (d(CH₂)₅-D-Tyr(Et)AVVP) has dual activity against V_1 and V_2 receptors and may have a therapeutic role in patients with heart failure.^{141,142} The non-peptide arginine-vasopressin V_2 receptor antagonist (OPC-31260) may also be useful in patients with heart failure and water excess.¹⁴³

Ultrafiltration and haemofiltration. Patients with chronic severe and refractory heart failure with hyponatraemia and oedema have been treated with ultrafiltration¹⁴⁴ and haemofiltration.^{144,145} In one study, 2 - 3 L of fluid was removed in 11 patients at a rate of 500 mL/hr until the right atrial pressure was 'normalised' or the haematocrit became greater than 50%. In all cases the patients' dependent oedema and

dyspnoea improved.¹⁴⁵ Another study which compared a reduction in right atrial pressure by 50% achieved by either ultrafiltration or a frusemide infusion (mean fluid loss with each method approximated 1600 mL), concluded that ultrafiltration improved the functional performance of patients with NYHA class II or III heart failure (which continued 3 months after the procedure) more than frusemide.¹⁴⁶

The advantages of ultrafiltration compared with diuretic therapy in a patient with severe and resistant oedema include removal of a larger amount of sodium and water while correcting electrolyte (e.g. hyponatraemia, hyperkalaemia) and acid-base disturbances.¹⁴⁷

Thromboembolism therapy

The risk of thromboembolic complications in patients with heart failure is increased. Nevertheless, as no controlled trials exist to show the benefit of anticoagulants in patients with heart failure who have not had an embolic episode, in the absence of a mural thrombus and who are in sinus rhythm,¹⁴⁸ some believe that until adequate studies are performed, anticoagulants should not be used routinely¹⁴⁹ and should be used only on an individual basis.^{9,150}

Antiarrhythmic therapy

If the patient with systolic heart failure has had a recorded episode of VT or VF, then amiodarone 100 - 200 mg daily is administered; 24 h Holter monitor recording should be performed after 7 days to review the effect (all other antiarrhythmics have not reduced mortality).

Amiodarone. The antiarrhythmic effects of amiodarone and its effect of slowing the heart rate, vasodilation and non competitive α - and β -adrenergic receptor blockade make it potentially useful in patients with chronic heart failure.¹⁵¹ It also inhibits production of TNF- α by mononuclear cells which may be a mechanism for its beneficial effect in patients with heart failure.¹⁵² In one study, low dose amiodarone (300 mg daily) improved exercise tolerance and mortality (by reducing both sudden death and death due to progressive heart failure) in patients with NYHA class II, III and IV heart failure treated with nitrates, digoxin, ACE inhibitors, diuretics and anticoagulants.¹⁵³ In another study, in patients with severe heart failure, a lower dose of amiodarone (200 mg daily) resulted in fewer side-effects but no reduction in mortality.¹⁵⁴ In a large double-blind, placebo-controlled trial of patients with symptoms of heart failure, cardiac enlargement, 10 or more premature ventricular contractions per hour, and a left ventricular ejection fraction of 40% or less, amiodarone (300 mg per day for up to 4.5 years)

improved ventricular function, suppressed the ventricular arrhythmias and showed a trend toward reducing the mortality in patients with nonischaemic cardiomyopathy. However, it did not reduce the incidence of sudden death or prolong survival in patients with ischaemic cardiomyopathy.¹⁵⁵ Currently, amiodarone is not routinely used in patients with uncomplicated heart failure,¹⁵⁶ although it is indicated in the management of spontaneous ventricular fibrillation in patients with non-ischaemic and ischaemia-induced left ventricular dysfunction as it is associated with a 20% - 30% reduction in the risk of arrhythmic sudden death in these patients.¹⁵⁷

If malignant arrhythmias continue in spite of antiarrhythmic therapy then an implantable cardioverter should be considered. While β -blockers are indicated in hypertrophic cardiomyopathies, they may be hazardous in patients who have dilated cardiomyopathies with severe (NYHA class IV) heart failure as they may increase mortality.¹⁵⁸

In one study of patients with a left ventricular ejection fraction of 0.30 or less after myocardial infarction, mortality was reduced from 19.8% to 14.2% at 20 months when an implantable defibrillator was inserted prophylactically (without prior stratification using electrophysical testing) when compared with a control group.¹⁵⁹

SURGERY

Cardiac transplantation. As most patients with a LVEF less than 25% are dead within 2 years,¹⁶⁰ cardiac transplantation should be considered in patients with unrelenting failure who are under the age of 50,¹⁶¹ as the postoperative 1 year survival is 80% and the 5 year survival is 60%.^{162,163} Contraindications to cardiac transplantation usually include an age greater than 60 years, severe pulmonary hypertension (transpulmonary gradient greater than 15 units and no response to vasodilator therapy), active infection, systemic disease likely to preclude survival or rehabilitation (e.g. severe peripheral vascular disease, terminal neoplastic disease, irreversible hepatic or renal dysfunction) and psychiatric illness likely to interfere with compliance.^{162,164}

Other surgical procedures. Surgical procedures to correct disorders causing heart failure (e.g. repair of valve disease, or akinetic and aneurysmal ventricular abnormalities, and coronary bypass surgery or percutaneous coronary artery reperfusion techniques) can improve cardiac function and reduce heart failure particularly when performed before structural damage (e.g. ventricular dilation, pulmonary hypertension) occurs. Mitral valve repair or replacement, in patients who have a dilated cardiomyopathy with secondary

dilation of the mitral valve ring and severe mitral valve regurgitation, may also improve heart failure.

Myocardial remodelling surgery is aimed at decreasing wall stress and improving myocardial efficiency. Partial left ventriculectomy (the Batista procedure), however, has resulted in an increased mortality rate and high incidence of recurrence.¹⁶⁵ More promising is infarct exclusion surgery (i.e. resection of akinetic areas of both left ventricular free wall and septum),¹⁶⁶ which has resulted in improved myocardial function in areas remote to the surgical site.¹⁶⁷

A new approach to reducing myocardial wall stress is the application of external devices to limit or reduce ventricular volume.¹⁶⁸ The Acorn[®] cardiac support device (Acorn Cardiovascular, St. Paul, Minnesota) is a preformed polyester fabric mesh implant wrapped around the ventricles. The Myocor Myosplint[®] (Myocor, Maple Grove, Minnesota) consists of three devices placed across the ventricle and adjusted to pull the walls of the ventricle together resulting in a shape change from globular to bilobular. Studies of both devices in animals have shown reduced left ventricular wall stress and increased ejection fractions.¹⁶⁹ A clinical study of the Acorn[®] device in 10 patients revealed an improvement in left ventricular ejection fraction and NYHA class.¹⁷⁰

Mechanical circulatory assistance. The role of left ventricular assist devices (LVADs) and total artificial hearts, to date, has been limited to patients with end stage cardiac disease awaiting heart transplantation. LVADs receive blood from the left ventricle via inflow cannulae and pump it, via outflow cannulae, into the aorta. Three devices are currently in clinical use. The Thoratec[®] LVAD is a paracorporeal system with the pump outside the body and inflow and outflow cannulae traversing the skin. Patient mobility is limited and the device can only be used in the hospital setting. The Novacor[®] and Heartmate[®] LVADs are intracorporeal systems that use porcine valves. Both use external controllers and batteries with drive lines traversing the skin. Whilst the pumps are relatively large and only suitable for patients with a body surface area $> 1.5 \text{ m}^2$, the portability of the control boxes and batteries allows discharge from hospital. All these devices carry significant infection risk via the transcutaneous lines and, with the exception of the Heartmate[®], require anticoagulation.

A number of devices are under development and fall broadly into three groups. Totally implantable pulsatile flow devices (e.g. Lionheart[®] LVAD and Abioco[®] implantable replacement heart) do away with the need for lines traversing the skin and thus reduce the infection risk. Continuous flow pumps (e.g.

DeBakey/NASA[®] and Jarvic 2000[®]) are smaller and mechanically less complex than the pulsatile flow devices. However, they have insufficient output to totally replace ventricular function and can only act as boosters. Furthermore, the effect of long term non-pulsatile flow on organ function is not known. Finally, the Abiomed Heart Booster[®] combines a left ventricular volume constraining device with a contractile component. A jacket containing thin walled tubes is placed over the cardiac apex. Hydraulic inflation and deflation augment systole and diastole respectively. This device has the advantage of having no blood contact and not requiring cardiopulmonary bypass for implantation.

The role of LVADs as bridges to transplantation is now established. A study of 264 patients receiving LVADs showed 69% surviving to transplantation. One year survival rates were similar to those patients who had not received an LVAD prior to transplantation. However, rates of infection and cerebral infarction associated with LVAD use were high.¹⁷¹

There is also now some evidence that LVADs can act to rest the native heart allowing a reversal of myocardial remodelling and recovery of function.^{172,173} In one study, 105 patients with dilated cardiomyopathy received LVADs. Of these, 24 patients were successfully weaned from the device and 14 patients demonstrated stable cardiac function during observation periods of up to 4.5 years.¹⁷⁴ The REMATCH trial looked at LVADs as permanent therapy in patients considered unsuitable for transplantation. In this study, 129 patients were randomised to receive an LVAD. The 1 and 2 year survival rates in the LVAD group were 52% and 23% respectively, compared with 25% and 8% in the medically treated group. The commonest causes of death in the LVAD group were infection (41%) and device failure (17%).¹⁷⁵ Technological improvement and the future use of totally implantable devices should decrease these complications.

Cardiac resynchronisation. In approximately 30% of patients with cardiomyopathy an intraventricular conduction delay (e.g. LBBB, RBBB) exists which impairs ventricular coordination, reduces the ability of the failing heart to eject blood and may enhance the severity of mitral regurgitation. In one study of patients with moderate-to-severe symptoms of heart failure associated with an ejection fraction of 35% or less and a QRS interval of 130 msec or more, a dual chamber pacemaker with two ventricular pacing wires (one in the coronary sinus to allow simultaneous left and right ventricular pacing) improved exercise capacity and reduced the rate of hospitalisation for heart failure over a 6 month period.¹⁷⁶ However, as it is not known whether the resynchronisation therapy altered mortality,

currently it is thought that this therapy (in association with an internal cardioverter defibrillator) should probably be limited to patients with low myocardial ejection fractions, wide QRS complexes and who remain symptomatic despite optimal therapy.¹⁷⁷

OTHER THERAPY

While many other therapies for general and specific forms of heart failure have been studied (*vide infra*) neither a consistent improvement in clinical function nor a reduction in mortality have been reported.

Growth hormone. In a study of seven patients with dilated cardiomyopathy, a three month course of recombinant human growth hormone (4 IU subcutaneously on alternate days) increased left-ventricular-wall thickness, reduced chamber size and improved clinical symptoms, exercise capacity and quality of life for the three months following therapy.¹⁷⁸ Two other reports have confirmed these effects.^{179,180} However, a randomised, double-blind, placebo-controlled study of 50 patients, while confirming the increase in left ventricular mass, did not show an improved clinical status (i.e. no change in NYHA functional class) or any difference in left-ventricular systolic wall stress, mean blood pressure, left ventricular ejection fraction, or systemic vascular resistance.¹⁸¹

Thyroxine. In a prospective randomised and placebo controlled study of 20 patients with dilated cardiomyopathy (and no thyroidal illness, amiodarone therapy or complex ventricular arrhythmias), a three month course of oral L-thyroxine (100 µg/day) decreased the left ventricular diastolic volume and systemic vascular resistance, and increased the left ventricular ejection fraction, resting cardiac output and functional capacity.¹⁸²

Intracoronary pyruvate. In one study of 8 patients with dilated non-ischaemic cardiomyopathy, 14 mmol and 28 mmol of pyruvate infused into the left main coronary artery over 15 minutes, resulted in an increase of 23% in cardiac index, 38% increase in stroke volume index, 36% decrease in pulmonary capillary wedge pressure and 11% decrease in heart rate.¹⁸³

Oxpentifylline. In one prospective randomised, controlled study of patients with idiopathic dilated cardiomyopathy, the addition of oxpentifylline (pentoxifylline) 400 mg 8-hourly to treatment with digoxin, ACE inhibitors, and carvedilol was associated with a significant improvement in symptoms and left ventricular function.¹⁸⁴

Antioxidants. With anthracycline therapy the concomitant administration of tocopherol reduces the cardiotoxicity in mice,¹⁸⁵ N-acetylcysteine, 140 mg/kg, 1 hr before doxorubicin therapy, and 70 mg/kg 4 hr

after therapy, protects against the reduction in cardiac guanylate cyclase in vivo and affords the patient cardioprotection against doxorubicin.^{186,187}

Cytokine antagonists. Plasma levels of TNF- α have been found to be elevated in patients with chronic heart failure,¹⁸⁸ with experimental evidence to suggest that this contributes to the disease process.¹⁸⁹ In a study of patients with chronic heart failure the TNF- α receptor fusion protein, etanercept, was associated with an improvement in left ventricular function.¹⁹⁰ However, this study was later stopped as an interim analysis revealed no likelihood of a difference between etanercept and placebo should the study run to completion, casting doubt on the importance of cytokine remodelling as a target for therapy in patients with heart failure.⁹¹

Etomoxir. Etomoxir inhibits myocardial fatty acid oxidation (by inhibiting carnitine palmitoyltransferase-I) thereby increasing myocardial glucose oxidation. It has been used in heart failure to reduce ventricular dilation and hypertrophy (by altering myocardial gene expression) and in one study of patients with NYHA class II and III symptoms of heart failure etomoxir administered for three months improved systolic function.¹⁹¹

OPTIMAL LONG-TERM THERAPY

In the management of patients with chronic systolic heart failure, the direct acting vasodilators, calcium-channel blockers and newer oral sympathomimetic inotropic agents (prelenterol and xamoterol), or the cardiospecific phosphodiesterase inhibitors (amrinone and milrinone), have not been shown to be associated with a reduction in mortality with long-term treatment, and have often been shown to increase mortality.^{33,192-194} Moreover, there are no data at the present time to suggest any therapy improves survival in the patient with NYHA class I cardiac function,¹⁹⁵ although ACE inhibitors alter the course of asymptomatic ventricular dysfunction (NYHA class I) by slowing the progression to overt symptomatic disease.¹⁹⁶ Mortality is reduced in the NYHA class II, III and IV patient, if ACE inhibitors and β -blockers are used or added to the conventional therapy of digoxin and diuretics.^{33,47,98,192,193,195,197} Low dose spironolactone (or eplerenone) and even amiodarone may also reduce mortality in the NYHA class II, III and IV patient when added to ACE inhibitors, digoxin and diuretics and may prove to be a useful addition to therapy.¹⁵¹

Currently, optimal therapy for patients with chronic systolic heart failure (NYHA class II or greater) would seem to be ACE inhibitors and β -blockers, or a combination of ACE inhibitors and β -blockers with intermittent use of diuretics to treat fluid retention,¹⁹⁸

plus digoxin and spironolactone if symptoms of heart failure persist.^{199,200}

TREATMENT OF ACUTE PULMONARY OEDEMA

When left ventricular failure is the underlying cause of acute pulmonary oedema, then reduction in the mean systemic pressure (which is reflected largely by right atrial pressure) by a small amount is required to reduce the left atrial pressure by a large amount (Figure 1). Accordingly, these patients will rapidly respond to diuretics, vasodilators or inotropic agents. In adults, the vascular volume required to be removed is of the order of 300 mL which may be achieved with a 1000 - 2000 mL diuresis.

Systemic hypertension increases the left atrial pressure dramatically in patients with poor left ventricular function, and is often the cause of 'flash' pulmonary oedema. Accordingly, a reduction in mean arterial pressure using vasodilators can rapidly reduce left atrial pressure and is often effective when extracellular fluid (ECF) redistribution rather than ECF excess causes the pulmonary oedema. Inotropic agents (e.g. digoxin) are used in patients with hypotension and poor left ventricular function.

When pulmonary oedema is associated with normal left ventricular function and is due to intravascular volume excess, then a large reduction in the mean systemic pressure is required to reduce the left atrial pressure (Figure 1). These patients are resistant to diuretics, positive inotropic agents and vasodilators and require venesection to reduce the left atrial pressure effectively. In adults, the vascular volume required to be removed in these patients may be of the order of 1500 mL.

Treatment of acute pulmonary oedema due to left ventricular failure requires:

Elevation of the head of the bed.

Oxygen: a high inspired oxygen concentration (50 - 80%) is administered by face mask. If severe hypoxia remains (i.e. PaO₂ < 60 mmHg) then oxygen delivered under pressure (e.g. CPAP) is used. While CPAP via facemask at 10 cm H₂O has been found to be beneficial,²⁰¹ pressure support ventilation with 5 cm PEEP has also been shown to be effective in cardiogenic pulmonary oedema.²⁰² In one study of patients with acute pulmonary edema, non-invasive bilevel positive airway pressure improved ventilation and vital signs more rapidly compared with CPAP although a higher rate of myocardial infarctions was also associated with the use of bilevel positive airway pressure.²⁰³

Morphine: 10 mg intravenously (5 mg i.v. stat followed by 5 mg i.v. after 2 min) reduces venous and

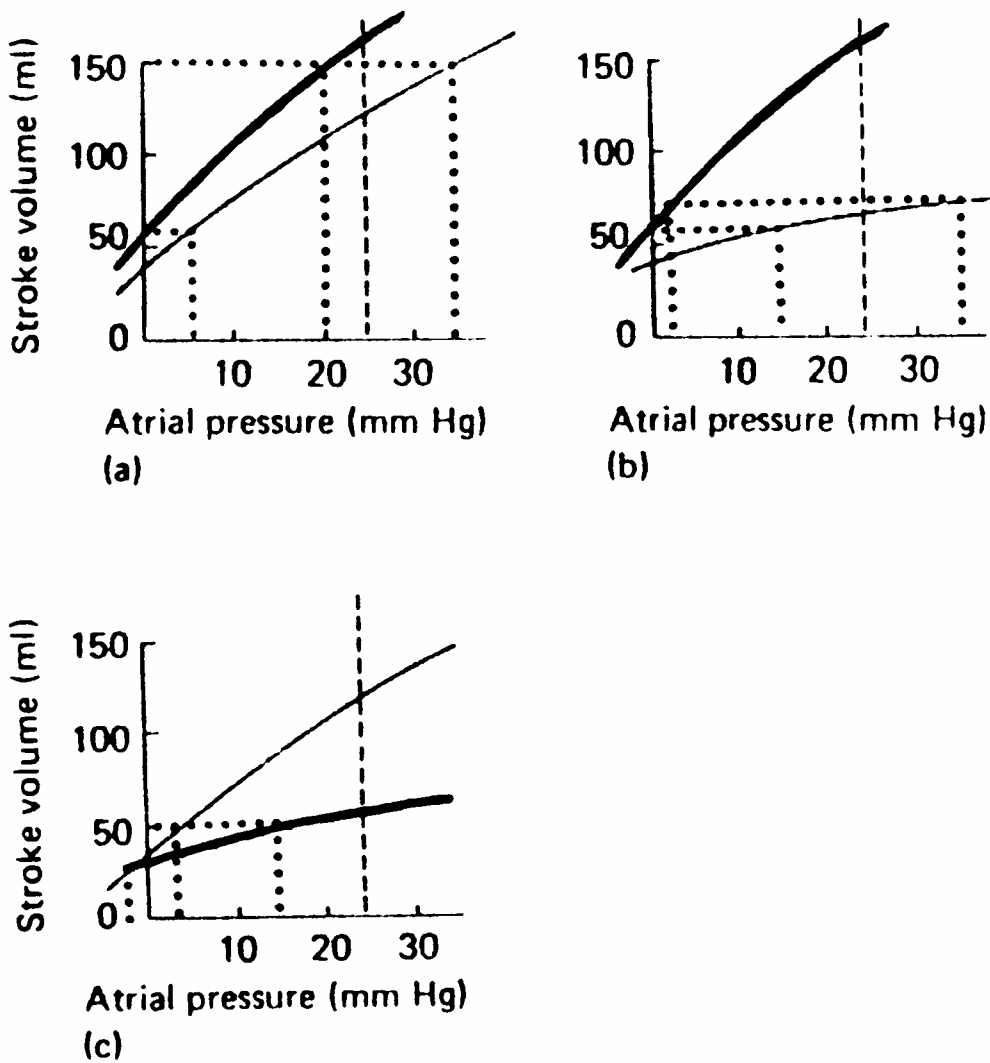


Figure 1. Frank-Starling curves. The relationship between the stroke volume and atrial pressure for the left heart is plotted with a thin line and the right heart is plotted with a thick line. The overt pulmonary oedema ‘line’ (i.e. left atrial pressure of 25 mmHg) is also drawn in.

a. Normal heart. A stroke volume of 60 ml is achieved with a left atrial pressure (LAP) of 7 mmHg and right atrial pressure (RAP) of 0 - 1 mmHg. Increasing the intravascular volume to above the pulmonary oedema line of 25 mmHg (e.g. LAP 35 mmHg) requires a large increase in the RAP (i.e. 20 mmHg). Accordingly, a large reduction in RAP (or intravascular volume) will be required to reduce the LAP.

b. Failing left ventricle. A stroke volume of 60 ml is achieved with a RAP of 0 - 1 mmHg and the LAP of 15 mmHg. Increasing the intravenous volume slightly (i.e. RAP to 1 - 2 mmHg) increases the LAP to 35 mmHg. Accordingly, only a small decrease in intravascular volume is required to produce a large reduction in the LAP.

c. Failing right heart. A stroke volume of 50 ml is achieved with a RAP of 15 mmHg and a LAP of 2 - 3 mmHg. Reducing the RAP reduces the stroke volume with minimal reduction in LAP.

arterial tone directly by releasing histamine and indirectly by reducing sympathetic tone,²⁰⁴ and should be used in all patients with acute pulmonary oedema who are hypertensive and conscious.²⁰⁵

Diuretics: frusemide is often used (40 mg i.v. or double the patient’s normally prescribed dose). While aminophylline 250 mg intravenously has been recommended, tachycardia and nausea have reduced the popularity of this agent.

Nitrates: glyceryl trinitrate may be administered sublingually (0.25 - 0.5 mg) or as a dermal patch (25 - 50 mg) or intravenously (10 - 100 µg/min). Isosorbide dinitrate (3 mg boluses i.v. repeated every 5 minutes until the mean arterial blood pressure had decreased by 30% or is < 90 mmHg) has also been used successfully.²⁰⁶

Other vasodilators: captopril 6.25 - 12.5 mg orally, chlorpromazine 2.5 - 5 mg i.v. and nifedipine 5 - 10 mg sublingually have all been used to reduce the mean

arterial pressure in patients with acute pulmonary oedema and resistant hypertension. While a nitroprusside infusion may be used if the MAP remains above 100 mmHg after maximal vasodilator therapy, it requires direct arterial monitoring.

Digoxin: an intravenous dose of 0.5 - 1.0 mg over 10 minutes is often used, if the patient is hypotensive, in rapid atrial fibrillation and systolic ventricular failure exists.

Venesection: this may be useful in patients who have polycythaemia, removing 500 mL of blood over 30 min via an arterial line. It requires right heart catheterisation to monitor its effect. Ultrafiltration or haemofiltration may also be useful. Rotating tourniquets are of no benefit and should not be used to treat acute pulmonary oedema.²⁰⁷

Mechanical ventilation: endotracheal intubation with CPAP, intermittent positive pressure ventilation (IPPV) or PEEP are used if the patient is in severe respiratory failure unrelieved by the above manoeuvres.²⁰⁸

DIASTOLIC FAILURE

This is often caused by a reduction in myocardial compliance²⁰⁹ and is associated with hypertension, coronary artery disease, myocardial hypertrophy and diabetes.^{210,211} Treatment requires management of precipitating causes (e.g. ischaemia, hypertension), and while captopril, β -blockers, calcium-channel blockers and diuretics are used, the ideal management strategy is yet to be determined.

Rarely diastolic failure may be caused by hypertrophic cardiomyopathy.

Hypertrophic obstructive cardiomyopathy

Hypertrophic obstructive cardiomyopathy (HOCM) is characterised by an asymmetric hypertrophy of the left ventricle and is often transmitted as an autosomal dominant trait (therefore the other family members of the patient should be investigated).²¹² These patients often have hypertrophy of the left ventricle, most striking in the ventricular septum, without dilation of the cavity. The myocardium forming the free wall may be normal, and obstruction to the left ventricular outflow generally occurs when the anterior mitral leaflet abuts onto the hypertrophied septum during systole.²¹³ In contrast to valvular obstruction, the obstruction with HOCM is dynamic and may change from beat to beat. The severity of the obstruction is a function of the width of the outflow tract during systole, which is related to the left ventricular end-diastolic volume, the myocardial contractile state and the afterload. Thus, decreasing afterload, increasing contractility and reducing preload all increase the obstruction. For example, the

obstruction is increased by exercise and isoprenaline (by increasing the contractility and reducing the afterload) and the Valsalva manoeuvre, haemorrhage, glyceryl trinitrate and tachycardia increases the obstruction by decreasing the preload. Squatting decreases the obstruction largely by increasing the afterload.

Dynamic left ventricular outflow tract obstruction has also been described in the absence of asymmetrical septal hypertrophy with acute coronary syndromes,²¹⁴⁻²¹⁶ coronary artery spasm,²¹⁷ catecholamine therapy (particularly with hypovolaemia),²¹⁸ pheochromocytoma,^{219,220} dobutamine stress tests,²²¹ mitral valvuloplasty with atrial fibrillation²²² and with IABP therapy (during aortic valve replacement²²³ and myocardial infarction²²⁴).

Clinical features

The symptoms include dyspnoea, angina, fatigue, impaired consciousness, syncope and sudden death. The latter occurs in 2% - 3% and is due to VT or VF.

The signs include, a prominent 'a' wave, a double or triple apical impulse, and a fourth heart sound. The second heart sound may be paradoxically split, and a systolic ejection murmur (probably due to the aortic obstruction as well as mitral regurgitation) is heard best at the left sternal border or apex rather than at the aortic area or the neck. One sign which is almost pathognomonic for HOCM is the post ectopic beat decrease in systolic pressure (Brockenbrough's sign). The mechanism for normal postectopic potentiation is thought to be due to an increased availability of calcium at the contractile sites, decreased afterload (due to continuing aortic runoff during the prolonged diastolic pause) as well as an increase in fiber length (i.e. preload),²²⁵ all of which are inhibited in the postectopic phase with HOCM.

Investigations

The investigations include an ECG, which reveals left ventricular hypertrophy and broad Q waves, particularly over the left ventricular leads (due to septal hypertrophy) and echocardiography, which reveals the hypertrophied ventricular septum, reopening of the mitral valve during midsystole (i.e. systolic anterior movement) and the juxtaposition of the anterior valve leaflet of the mitral valve at the onset of the obstruction. Echocardiography has reduced the need to perform angiography to demonstrate the subaortic pressure gradient.

Treatment

Beta-adrenergic blockers are administered to reduce angina and syncope, and in 50% are successful. The

beneficial effects appear to be due largely to a decrease in the heart rate which increases ventricular filling during diastole. Verapamil (and diltiazem) may also have beneficial effects, particularly in patients who have not been helped by β -blockers or in whom β blockers are contraindicated (nifedipine, due to its vasodilatory effects, is probably harmful).²²⁶ Treatment of heart failure is by judicious use of β -blockers, verapamil or diltiazem. Every attempt should be made to maintain sinus rhythm,²²⁷ with atrial fibrillation treated by cardioversion then long-term amiodarone to prevent its recurrence. While surgical excision of the hypertrophied portion of the outflow tract has been recommended in individuals who have intractable angina or syncope and who are young and have no left atrial enlargement, surgical myotomy or myomectomy has a high immediate mortality and heart failure is not uncommon in the late postoperative period.²²⁸

Recently, percutaneous transluminal septal ablation has been performed as an alternative to surgical treatment. In this procedure, alcohol is injected into a proximal septal artery to create a localised area of myocardial infarction, resulting in widening of the left ventricular outflow tract with gradient reduction.²²⁹ Follow-up studies show low morbidity (although complete heart block may occur in up to 25% of patients) and mortality (up to 4%) with impressive clinical improvement, as well as further gradient reduction as a result of left ventricular remodelling.²³⁰

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