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Drug Therapy of Heart Failure in the Elderly

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ABSTRACT

Heart failure has many causes, but in the elderly is frequently due to ischaemic heart disease, hypertension or valve lesions. Management principles are similar to those for younger patients. However, in the very elderly, it may not be appropriate to persist with aggressive therapy aimed at mortality reduction at the expense of significant adverse effects. Accurate diagnosis of the mechanism of heart failure is essential to allow rational prescribing and to minimise the adverse effects of inappropriate drug use. This article discusses the approach to diagnosis and the spectrum of agents currently available for treatment of heart failure, and their limitations in the elderly.

Aust J Hosp Pharm 2000; 30: 274-8.

INTRODUCTION

Various cardiovascular diseases may progress to the syndrome of heart failure, most frequently hypertension and ischaemic heart disease.¹ Advancing age in itself is a risk factor for the development of heart failure, in addition to the traditional cardiovascular risk factors of diabetes and hypertension.² It is a common problem in the elderly (those over 65 years of age), with a prevalence of over 10% in those over 80 years old.³ The prevalence is likely to increase as the population ages over the next few decades.

The principles of management in older people are essentially the same as in younger patients. However, the goal of therapy in most younger patients is no longer symptom relief alone. In recent years there has been a shift in emphasis towards prevention of heart failure (e.g. minimising ventricular remodelling post-infarct) and to improving prognosis independent of symptoms (e.g. the use of angiotensin converting enzyme [ACE] inhibitors in patients with minimal symptoms). In older patients who may be subject to comorbidities and polypharmacy, the possibility of adverse drug reactions and drug interactions means that these goals may be achieved only at the expense of unacceptable side effects. Non-compliance with multiple medications may also be an issue for patients in this situation.⁴ In the very elderly with reduced life expectancy, the issue of quality of life may assume a higher priority than aggressive measures to improve long-term prognosis.

DIAGNOSIS OF HEART FAILURE

As in any disease, the cornerstone of management is to make an accurate diagnosis. The clinical syndrome of heart failure has many causes (Table 1), many of which require specific management that would be inappropriate in a patient with a different underlying pathology. For example, the inappropriate treatment of diastolic dysfunction with high dose diuretics frequently leads to further morbidity, such as volume depletion, hypotension and hypokalaemia, which can be avoided by accurate diagnosis. This is particularly important in the elderly who are at increased risk of adverse drug reactions.

Table 1. Causes of heart failure

Mechanism	Potential cause
Left ventricular systolic dysfunction	Ischaemic heart disease Dilated cardiomyopathy Myocarditis
Left ventricular diastolic dysfunction	Hypertensive heart disease Hypertrophic cardiomyopathy Restrictive cardiomyopathy (e.g. amyloidosis) Pericardial effusion or constrictive pericarditis
Valvular heart disease	Aortic stenosis or regurgitation Mitral stenosis or regurgitation
Right ventricular failure	Ischaemic heart disease Pulmonary hypertension Atrial septal defect
'High output' cardiac failure	Anaemia Thyrotoxicosis Sepsis

The diagnosis of heart failure and its cause can usually be ascertained from the history and examination, supported by the investigations outlined in Table 2. The decision to proceed to cardiac catheterisation can be difficult to make in the very elderly. It should be based on the results of preceding investigations and the assessment of the patient's suitability for cardiac surgery, if indicated.

The principles of drug therapy for heart failure are broadly dictated by the classification of the underlying mechanism into systolic or diastolic dysfunction, valvular disease and right ventricular failure, as outlined in Table 1. High output failure responds to management of the underlying cause and will not be further discussed here. The effects of drug therapy may be modified by the

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Table 2. Investigations in heart failure

Investigation	Purpose
Full blood count, biochemistry, thyroid function tests	Exclude underlying causes and detect complications or comorbidities
Electrocardiogram	Detect arrhythmias, evidence of previous infarction, left ventricular hypertrophy
Chest X-ray	Confirm diagnosis of pulmonary congestion or oedema
Echocardiogram	Assess ventricular systolic and diastolic function, valve pathology, congenital heart defects, pulmonary artery pressure
Stress test	Confirm clinical or ECG evidence of ischaemia
Cardiac catheterisation	Further evaluation of coronary anatomy prior to revascularisation; confirmation of presence of valve pathology and congenital heart defects
Ventilation/perfusion scan	Exclude pulmonary embolism as a cause of right ventricular failure with pulmonary hypertension

presence of coexisting conditions, such as renal impairment, hepatic impairment, vascular disease and the requirement for multiple drugs with the potential for interactions. It should be remembered that many agents used in heart failure reduce blood pressure, which may lead to cerebral or myocardial ischaemia in patients with haemodynamically significant stenoses in the carotid, vertebrobasilar or coronary vasculature. Initiation of therapy with low doses, slow upward titration and regular monitoring of renal function and blood pressure helps to prevent the majority of such problems.

SYSTOLIC LEFT VENTRICULAR FAILURE

Drug therapy of heart failure is complemented by a number of non-pharmacological approaches. These include: weight loss; salt restriction to less than 3 g daily; abstinence from alcohol; self-monitoring of fluid balance (e.g. daily weighing); and aerobic exercise programs. General pharmacological measures include therapy for diabetes, hypertension and hyperlipidaemia and control of symptomatic atrial arrhythmias. Drug therapy for asymptomatic ventricular arrhythmias is not indicated.

Specific drug therapy for systolic heart failure can be considered in two broad categories—agents to relieve symptoms and agents to improve prognosis. Diuretics, digoxin and vasodilators are in the former category but do not appear to reduce mortality. In contrast, large studies have shown reduction in mortality with ACE inhibitors, β -blocking agents (such as carvedilol and metoprolol) and spironolactone.

ACE Inhibitors

These agents inhibit the conversion of angiotensin I to angiotensin II. Their beneficial effects in cardiac failure are probably multifactorial, but important mechanisms are the partial inhibition of the renin-angiotensin-aldosterone pathway and reduction in sympathetic activity. This results in vasodilatation, natriuresis and blood pressure reduction. They are useful in reducing dyspnoea, improving exercise tolerance and reducing the frequency of acute exacerbations of heart failure. Importantly,

they have been shown in many studies to reduce morbidity and mortality both in patients with overt heart failure,^{5,6} and in patients with asymptomatic left ventricular dysfunction.⁷ This applies also to patients with recent acute myocardial infarction, either with overt heart failure⁸ or asymptomatic left ventricular dysfunction.^{9,10} Not surprisingly, these agents have become the first-line agents for improving prognosis in heart failure, and should be used in the highest tolerated doses for maximal reduction in morbidity and hospitalisation.¹¹

Adverse Effects

One of the most frequent is a persistent dry cough mediated by potentiation of bradykinin. It appears to be a class effect, is dose related and may respond to dose reduction, but occasionally drug withdrawal is necessary. It is important to establish that the cough is not due to pulmonary congestion before a trial of drug withdrawal. An alternative is to use the newer angiotensin II antagonists which do not potentiate bradykinin. In the recently published ELITE II study, mortality and hospitalisation were not significantly different between patients randomised to losartan or to captopril, while losartan was better tolerated.¹² However, the balance of the available data at this stage favours the use of ACE inhibitors in heart failure, and angiotensin II antagonists should therefore only be used as substitutes when ACE inhibitors have caused intolerable side effects.

Other adverse effects include hypotension which can be severe in patients volume depleted due to high dose diuretics, particularly the elderly in whom baroreceptor control may already be impaired. It can be minimised by reducing the dose of diuretic prior to starting ACE inhibitors; using a small dose of a long-acting agent with slower onset of action; and taking the dose at bedtime. Asymptomatic hypotension is not an indication for reducing or stopping therapy.

Renal impairment and acute renal failure may occur in patients with bilateral renal artery stenosis and renal function should be checked before and again shortly after commencing these drugs. A mild elevation of serum creatinine is a common finding in the elderly, is often multifactorial and is not a contraindication to the use of ACE inhibitors. If it is a reflection of renal hypoperfusion due to severe heart failure it may improve with therapy.

Potassium supplements should not normally be used in combination with ACE inhibitors in view of the risk of hyperkalaemia. Serum potassium should be monitored at regular intervals, particularly when ACE inhibitor therapy is being initiated and titrated and when used in combination with the potassium-sparing diuretic spironolactone (see later).

Diuretics

Diuretics are used to promote sodium and water excretion and hence relieve the symptoms of fluid retention, which include dyspnoea due to pulmonary venous congestion or frank pulmonary oedema. They provide rapid relief of symptoms but are less effective at maintaining long-term freedom from heart failure and appear to have no beneficial effect on mortality. Loop diuretics such as frusemide have a more potent natriuretic effect than thiazide diuretics and maintain their efficacy in moderately severe renal impairment, and are thus the first-line therapy

in symptomatic heart failure. In advanced heart failure, diuretic resistance may necessitate the use of a loop diuretic and a thiazide in combination.

Adverse Effects

Volume depletion and hypotension are of particular concern in the elderly who may already be at risk of falls because of impaired baroreceptor responsiveness, cerebrovascular disease, musculoskeletal problems and polypharmacy. Marked symptomatic postural hypotension (>20 mmHg drop in systolic blood pressure) is an indication to reduce diuretic dosage unless there is still unequivocal evidence of fluid retention. The combination of hypotension and persistent fluid retention, particularly with deterioration in renal function, suggests worsening heart failure and the need for additional therapy, which may include intravenous diuretics and possibly inotropic support. Potassium and magnesium depletion secondary to diuresis may predispose the patient to potentially lethal ventricular arrhythmias and should be avoided with the use of either potassium sparing diuretics (such as spironolactone or amiloride), electrolyte supplements or ACE inhibitors.

Spironolactone

Spironolactone is an aldosterone antagonist, and as such is another agent to use in the inhibition of the renin-angiotensin-aldosterone system. In the RALES study of patients with severe heart failure, the addition of spironolactone 25 mg daily to conventional therapy resulted in significant reductions in mortality and hospitalisation over 2 years.¹³ The place of spironolactone in treating less severe heart failure is unclear, although it is useful as a potassium-sparing diuretic when an ACE inhibitor does not maintain the serum potassium in the high normal range. Dose reduction is not specifically required in the elderly, but if clinically significant increases in serum creatinine or potassium levels develop, the dose should be reduced to 12.5 mg daily.

Adverse Effects

Troublesome gynaecomastia occurred in 8-9% of patients in the RALES study.¹³ Other potential problems are hyperkalaemia, particularly in the majority of patients who should also be receiving an ACE inhibitor. Regular monitoring of serum potassium is mandatory.

Digoxin

Digoxin has been used for many years for its potential positive inotropic effect. It also has some parasympathomimetic activity, reducing heart rate in patients with atrial fibrillation and in sinus rhythm and thus allowing improved ventricular filling. This may be one mechanism for its effectiveness in relieving symptoms of heart failure. It reduces hospital admissions in heart failure patients in sinus rhythm being treated with ACE inhibitors, but does not appear to reduce mortality.¹⁴ Withdrawal of digoxin from stable patients on ACE inhibitors results in worsening heart failure.¹⁵

Adverse Effects

Digoxin toxicity is infrequent but occurs more readily in the elderly with reduced lean body mass and renal impairment. Routine monitoring of digoxin levels is not

necessary, but a high index of suspicion should be maintained. Levels should be checked in the case of intercurrent illness, or if visual disturbances, nausea, or new arrhythmias occur.

β -blocking agents

β -blockers inhibit the effects of sympathetic nervous system activation, which is an important mediator of the tachycardia, vasoconstriction and sodium retention of heart failure. Metoprolol,¹⁶ bisoprolol¹⁷ and carvedilol¹⁸ have been shown to reduce clinical disease progression, hospitalisation and mortality in patients with mild to moderate heart failure (left ventricular ejection fraction less than 35-45%; New York Heart Association class II-III). Early results suggest a benefit from carvedilol in patients with severe heart failure also.¹⁹ Carvedilol is a non-selective β -blocker and also acts as a vasodilator through its α_1 -blocking properties. The clinical relevance of these properties, in contrast to the selective β_1 -blockers metoprolol and bisoprolol, has not yet been fully evaluated.

Carvedilol is currently the only β -blocker approved for use in systolic heart failure in Australia. It is indicated in all patients with mild to moderate heart failure without contraindications to β -blockade, such as definite bronchoconstriction, sick sinus syndrome, or second and third degree atrioventricular block.

Adverse Effects

Hypotension and bradycardia are predictable side effects which can be minimised by starting at very low doses, such as 3.125 mg twice daily. The dose should be gradually titrated upwards at intervals of 2 to 4 weeks to the maximum tolerated dose or 25 mg twice daily. Heart failure symptoms may deteriorate initially, particularly in patients with fluid retention at the onset of therapy. Diuretic dosage should be optimised before starting carvedilol. Despite these precautions, some patients will feel worse for the first few weeks of therapy before they notice any symptom improvement, and it is important to emphasise the long-term benefits of reduction in disease progression and mortality to ensure continued compliance. The elderly may be particularly at risk of bradyarrhythmias because of underlying degenerative conduction system disease exacerbated by β -blockade.

Vasodilators

Vasodilators reduce left ventricular preload and afterload and hence reduce pulmonary venous congestion, which is one of the causes of dyspnoea in heart failure patients. Such drugs are therefore helpful in symptom relief but have not been consistently shown to confer any prognostic advantage. The exception is the combination of hydralazine and isosorbide dinitrate, which was used in the placebo-controlled Veterans Affairs Vasodilator-Heart Failure Trial (V-HeFT I) of 642 male patients with mild to moderate chronic congestive heart failure.²⁰ After a mean follow-up period of 2.3 years, mortality was reduced by 25% in patients on the vasodilator combination, compared to those on placebo or on prazosin. However, in the V-HeFT II study in which heart failure patients were randomised to the nitrate/hydralazine combination or to enalapril, a mortality advantage was seen only in the enalapril group.²¹ Vasodilators may be helpful in patients unable to tolerate ACE inhibitors but are not recommended as first line therapy.

Adverse Effects

High doses of isosorbide dinitrate (160 mg per day) and hydralazine (300 mg per day) were used in the V-HeFT studies, which may not be well tolerated by all patients in clinical practice. Furthermore, dosing is required three or four times daily, which may result in reduced compliance. Common side effects include headache, which often resolves within the first few days of therapy, and hypotension.

Anticoagulation

Patients with severely depressed left ventricular contractility appear to be at increased risk of thromboembolism, presumably secondary to blood stasis and intraventricular thrombus formation. There are as yet no published randomised controlled studies of anticoagulation to prevent stroke or peripheral embolisation in heart failure, and the available non-randomised data are conflicting.^{22,23} The results of the WASH (Warfarin/Aspirin Study in Heart failure) study are awaited.²⁴ Nonetheless, anticoagulation is often recommended²⁵ and can generally be undertaken safely in the elderly.²⁶ The combination of atrial fibrillation, left atrial enlargement and moderate to severe left ventricular dysfunction on echocardiography was associated with an annual rate of thromboembolism approaching 20% in the first Stroke Prevention in Atrial Fibrillation Study.²⁷ Patients in this group should be anticoagulated to an International Normalised Ratio of 2.0-3.0, in the absence of compelling contraindications such as active bleeding, previous intracranial haemorrhage, frequent falls or non-compliance.

DIASTOLIC LEFT VENTRICULAR DYSFUNCTION

In the elderly, this is frequently a result of hypertensive left ventricular hypertrophy, although hypertrophic cardiomyopathy is sometimes diagnosed for the first time in old age. Diastolic dysfunction is one of the earliest manifestations of myocardial ischaemia but is often overshadowed by coexisting systolic dysfunction. It accounts for up to 50% of all cases of heart failure in patients aged over 65 years.²⁸

Diastolic dysfunction comprises either impaired active relaxation or reduced compliance ('increased stiffness') of the myocardium. Left ventricular stroke volume is reduced unless filling pressure and the time available for ventricular filling are maintained. Therefore the principles of management are to address the underlying cause (usually ischaemia or hypertension), to avoid hypovolaemia and to reduce heart rate. Diuretics should be avoided unless there is frank pulmonary oedema. β -blocking agents such as atenolol are useful to reduce heart rate and have the added advantage of treating underlying ischaemia and hypertension. If these agents are poorly tolerated or contraindicated, the non-dihydropyridine calcium antagonists verapamil and diltiazem can be used to achieve heart rate reduction, provided there is no systolic dysfunction in which case these agents may precipitate pulmonary oedema.

In patients with left ventricular hypertrophy, the combination of tachycardia, hypercontractility and relative volume depletion may contribute to dynamic left ventricular outflow tract obstruction. This may be evident on a resting echocardiogram or inducible on a stress echo, using either exercise or dobutamine as the stres-

or. In such cases, the negative inotropic and negative chronotropic effects of β -blockers and calcium antagonists in combination are useful. Relatively high doses may be necessary to abolish exercise-induced outflow tract obstruction and dyspnoea.

VALVE DISEASE

When valve disease is the primary cause of heart failure, consideration should be given to the suitability of the patient for surgical intervention, which will be dictated by many factors including advanced age, frailty and comorbidities. The technical feasibility of an operation (either repair or replacement) will be affected by the nature of the lesion and the potential need for concomitant procedures, such as multiple valve surgery or coronary artery bypass grafting. Discussion of these issues is beyond the scope of this article.

Drug therapy for valve disease is most appropriate for regurgitant lesions which result in left ventricular volume overload, raised left atrial pressure and pulmonary venous congestion. Diuretics, ACE inhibitors and vasodilators can be used in the same way as for systolic left ventricular failure.

Aortic stenosis is frequently complicated by angina, which is caused by the increased oxygen demand and wall stress of the hypertrophied myocardium, sometimes in the presence of coexisting coronary artery stenoses. Conventional antianginal therapy with nitrates and calcium antagonists reduce systemic blood pressure. In patients unable to increase cardiac output due to fixed outflow tract obstruction, such agents may induce presyncope or cardiovascular collapse and should be used with caution, if at all.

Perhexiline is sometimes useful in reducing myocardial oxygen demand and relieving angina in aortic stenosis, and is generally well tolerated. Rapid loading with this drug may result in nausea and dizziness, which can be minimised by using low doses initially (50 to 100 mg daily). Careful monitoring of drug levels is required to ensure levels are kept between 150 and 600 $\mu\text{g/L}$, to maintain therapeutic efficacy. Levels greater than 1000 $\mu\text{g/L}$ are associated with the potential for side effects, particularly peripheral neuropathy and hepatotoxicity.²⁹

RIGHT VENTRICULAR FAILURE

Right ventricular failure is frequently associated with left ventricular failure, either because of involvement in the underlying disease process (such as ischaemia or cardiomyopathy) or secondary to pulmonary hypertension. Isolated right ventricular dysfunction is less common but may occur in the setting of pulmonary hypertension (pressure overload), atrial septal defect (volume overload) or right ventricular infarction.

Drug treatment is directed at relieving the symptoms of hepatic and peripheral venous congestion using diuretics and ACE inhibitors without inducing symptomatic hypovolaemia. Tricuspid regurgitation secondary to right ventricular dilatation may cause persistent elevation of the jugular venous pressure. Aggressive attempts to lower this may result in severe reduction in right ventricular stroke volume and hence hypotension and fatigue.

The underlying cause of right ventricular failure may require specific treatment, such as anticoagulation for pulmonary embolism, or atrial septal defect closure.

CONCLUSION

Accurate diagnosis of the cause of heart failure is essential to ensure appropriate management. The various treatment strategies used in younger populations are applicable to older patients. They are generally well tolerated provided they are used cautiously, with small starting doses and with appropriate clinical and biochemical monitoring. The goals of treatment (symptom relief or mortality reduction) need to be carefully evaluated, especially if adverse effects preclude the use of multiple agents. In systolic heart failure, diuretics should be used initially in combination with an ACE inhibitor to achieve resolution of symptoms, followed by careful initiation of a β -blocker once fluid balance is optimised. Spironolactone should be added in patients with severe heart failure. Digoxin may be added if symptoms persist, particularly in patients with persistent tachycardia and those with contraindications to β -blockade. Angiotensin II antagonists and vasodilators should be reserved for patients intolerant of ACE inhibitors. Selected patients may benefit symptomatically and prognostically from surgical intervention where indicated.

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