Recent advances in the management of chronic heart failure

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BACKGROUND The management of chronic heart failure (CHF) has undergone a revolution in the past decade, highlighted by dramatic turnarounds in opinion, renewed focus on 'traditional' therapies and the emergence of novel diagnostic and treatment options.
OBJECTIVE Based on review of the current evidence, this article aims to provide an update of the issues pertaining to the diagnosis and treatment of CHF.
DISCUSSION Underlying this revolution on the management of CHF have been novel insights into the pathophysiology of CHF. Promising findings from recent clinical trials will also be examined in this article.

With the shift in the focus of medical treatment of cardiac failure for symptom relief to long term restoration in ventricular function, early and accurate diagnosis assumes greater importance.

Diagnosis

Echocardiography or other objective testing is required for the assessment of ventricular function and may also identify potential contributors to dysfunction. Furthermore, the distinction between systolic and diastolic dysfunction, or detection of their co-existence, has relevance to treatment.

Cardiac catheterisation is less commonly indicated. Coronary angiography should be considered in patients with suspected ventricular dysfunction due to ischaemia, for whom coronary revascularisation is an option. Haemodynamic measurements may have a role in refractory chronic heart failure (CHF) and recurrent diastolic dysfunction, and myocardial biopsy is helpful in cases of uncertain aetiology.

Limitations of many investigations in CHF include relative expense, invasiveness in the case of catheterisation and poor access in some communities, especially those that are remote.

The recent recognition of blood based biochemical markers of ventricular dysfunction raises the potential for their measurement to be used as a screening tool in identifying which patients require more definitive testing.

Brain natriuretic peptide (BNP) is released predominantly from the left ventricle in response to increased intraventricular pressure. An elevated blood level of BNP is highly sensitive and moderately specific to systolic ventricular dysfunction and to a lesser extent, diastolic dysfunction.[1-3] Brain natriuretic peptide is also a useful marker of prognosis in patients with established heart disease[4-6] and limited data suggest it may be useful for the guidance of heart failure therapy.[7]

Serum BNP levels can be measured via a rapid 'stix' test on blood drawn from a finger prick, or by the precursor of BNP, N-terminal pro-BNP (NTproBNP) which can be assayed in the laboratory. There are theoretical advantages to the latter test in terms of specificity for cardiac synthesis.

Pharmacological therapy

In recent times, the medical treatment of CHF has undergone a paradigm shift from short term haemodynamic re-adjustment to long term restoration of myocardial structure and function. This has been motivated by recognition of the importance of neurohormonal systems in the pathophysiology of CHF, and in par-

ticular, chronic activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, leading ultimately to pathological ventricular remodelling.

The majority of current evidence for drugs used to treat CHF has been drawn from studies of systolic dysfunction. In contrast, the specific drug treatment of diastolic dysfunction cannot yet be guided by robust trial data, although these will be forthcoming. Pharmacological therapy will therefore be considered separately for each of the types of ventricular dysfunction.

Systolic ventricular dysfunction

Optimal drug therapy for the patient with systolic heart failure should include an angiotensin converting enzyme (ACE) inhibitor and a beta blocker.

There is unequivocal evidence for decreased mortality and morbidity risk conferred by ACE inhibitors in patients with left ventricular systolic dysfunction, across the range of symptom severity.[8–10] Even patients without symptoms should be considered for therapy.[11] The crucial action of ACE inhibitors, rather than short term effects on afterload, is impairment of the progression of ventricular remodelling and hypertrophy via inhibition of tissue RAAS. Angiotensin converting enzyme inhibitors should be commenced at low doses and limited evidence supports up-titration to maximally tolerated doses.[12]

When added to background ACE inhibitor therapy, beta blockers are also associated with significant survival benefit.[13–17] These agents block adrenergic activity within the chronically failing heart, now known to be a key mediator of myocardial remodelling.[18,19] Benefits may also arise from the reduction or prevention of myocardial ischaemia and arrhythmia. Two beta blockers are now available in Australia for the indication of heart failure: carvedilol, a beta and alpha-1 antagonist, and bisoprolol, a beta-1 selective antagonist. Carvedilol is effective across the severity range in CHF,[13,16] while the evidence for bisoprolol is mainly in mild to moderate CHF.[16] Given the potential for worsening of heart failure symptoms, hypotension and bradycardia, initiation of beta blockers requires care. Therapy should commence at low doses when CHF is stable, with subsequent careful up-titration and regular monitoring for adverse effects.

The addition of spironolactone to background ACE inhibition and beta blockade will confer further survival benefit in patients with New York Heart Association (NYHA) Class III and IV symptoms.[20] The mechanism of action of this agent is inhibition of aldosterone. Aldosterone not only exacerbates sodium and water retention, but also remodelling in CHF. Potassium levels should be monitored with the combination of ACE inhibitors and spironolactone.

Diuretics are important for achieving and maintaining euvolaemia, but offer no survival benefit by themselves.

The indications for digoxin in CHF are relief of severe symptoms in sinus rhythm[21] and control of ventricular rate in atrial fibrillation (AF).

The role of angiotensin 2 receptor blockers (ARBs) for the treatment of CHF remains controversial. Current data suggest no real superiority of ARBs to ACE inhibitors other than improved tolerance.[22,23] The addition of an ARB to patients receiving background ACE inhibition may reduce risk of morbid events such as hospitalisation, but there is no effect on mortality and no benefit is observed among patients taking beta blockers as well. In fact, the combination of all three agents (ACE inhibitors, ARBs and beta blockers) may be associated with increased mortality.[24] Taken together, current evidence supports the use of ARBs as alternatives to ACE inhibitors in patients who are intolerant to ACE inhibitors, and perhaps as adjunctive treatment to ACE inhibitors among those unable to receive beta blockers.

Anticoagulation or antiplatelet therapy for patients with CHF is generally indicated for atrial fibrillation, severe ventricular dilatation and proven thromboembolic disease.

Diastolic ventricular dysfunction

Diastolic ventricular dysfunction may occur in up to 40% of patients with CHF.[25] It is observed more commonly in the elderly (especially women) and in patients with hypertension and coronary heart disease.[26–29] However, it is important to note, relevant to treatment, that it often co-exists with systolic dysfunction.

In the absence of trial data for specific therapeutic strategies, the cornerstone of management remains attention to the underlying cause(s) of diastolic dysfunction. In particular, control of hypertension and adequate management of coronary heart disease are crucial. Beta blockers and centrally acting, nondihydropyridine calcium channel antagonists (verapamil and diltiazem) may be considered for improvement in ventricular filling. However, there is no strong supportive evidence for this.

As with systolic dysfunction, remodelling contributes to ongoing diastolic dysfunction. However, it is unclear if the benefits of inhibiting the RAAS and sympathetic nervous system, observed in studies of systolic heart failure, can be extrapolated to patients with diastolic heart failure. The use of ACE inhibitors and beta blockers to target ventricular remodelling may be considered and is further indicated in the presence of comorbid conditions such as diabetes mellitus (for ACE inhibitors), arrhythmias (for beta blockers), hypertension and coronary heart disease (for both).

Digoxin and diuretics should be used with caution in patients with diastolic dysfunction as these agents may reduce ventricular filling. Verapamil and diltiazem are absolutely contraindicated if there is co-existent systolic heart failure.

Currently, trials are underway[30,31] or are being planned, to examine specific effects of various pharmacological agents in patients with diastolic dysfunction.

Novel agents

Expanding knowledge about the pathophysiological mechanisms underlying CHF continues to elucidate potential new targets for therapy. Many new agents for the treatment of CHF have recently been, or are currently being, studied in randomised clinical trials.

To date, drugs that have not demonstrated significant improvements in major clinical outcomes, over and above standard therapy for CHF (ACE inhibitors and beta blockers) include:

- the endothelin antagonist bosentan
- the vasopeptidase inhibitor omapatrilat,[32] and
- etanercept, an inhibitor of tumor necrosis factor-alpha.

The efficacy of the selective aldosterone receptor antagonist eplerenone, remains under trial.[33]

Lack of benefits with the above novel agents was observed despite each having sound mechanistic basis to support its use. It is unclear if this situation reflects inadequate study design or that ACE inhibitors and beta blockers provide maximal benefit that can be achieved with pharmacotherapy in CHF. Further trials of newer agents are required to provide the answer.

Ancillary therapies

Multidisciplinary care

There is now firm evidence to suggest benefits of multidisciplinary strategies in the management of patients with CHF.[34–37] Interventions of proven benefit include home visits, nurse practitioners to deal with clinical problems early and patient self management. Paramedical care is also important, especially exercise rehabilitation, attention to nutrition and psychological support. In light of this recent evidence, a number of specialised heart failure clinics have been established around the country whose roles include the advocacy of multidisciplinary care.

The benefits of telephone support for patients with CHF, especially those in remote areas, is about to be trialled in a nationwide study sponsored by the National Health and Medical Research Council of Australia.

Sleep apnoea

The roles of obstructive and central sleep apnoea (with Cheynes-Stokes respiration) in CHF have recently come to light.[38,39] Both these conditions may exacerbate ventricular dysfunction, making their exclusion a necessary part of the work-up in all patients with CHF.

Management requires the involvement of specialised respiratory units. Overnight oximetry may be used to help in the diagnosis, but the definitive investigation is polysomnography. In obstructive sleep apnoea, weight reduction and continuous positive airway pressure (CPAP) ventilation are effective treatments and may improve cardiac function.[40] Central sleep apnoea can also be caused by CHF, due to sympathetic over activity and pulmonary congestion, thereby creating the potential for a vicious cycle. Optimisation of medical treatment of CHF is the key to management. If persistent, nasal oxygen may be considered.[41]

Metabolic supplementation

A number of metabolic and nutritional supplements have been proposed for the treatment of CHF. These are based on putative metabolic deficiencies including from within the failing myocardium.[42]

The best characterised of these is co-enzyme Q10 (ubiquinone), which is a necessary cofactor in mitochondrial energy production. While some studies have shown that co-enzyme Q10 supplementation may lead to improvements in objective measures of ventricular function and exercise tolerance,[43,44] others have reported conflicting results.[45,46] More conclusive evidence is required from major mortality and morbidity trials.

Novel therapies

Biventricular pacing involves pacing of both ventricles to improve the coordination between their contractions. Coordination can be disordered in CHF, contributing to ventricular functional disturbance. Patients carefully selected on the basis of symptoms and an abnormal electrocardiogram (widened QRS complex, indicative of ventricular dyssynchrony) have been shown to benefit from biventricular pacing in terms of symptoms, functional status and reductions in hospitalisation.[47–49] The current evidence is promising, but long term data are needed to determine if this therapy has any impact on survival.

Stem cell therapy for CHF remains in the research arena but has been attracting growing interest.[50,51] The main strategy involves autologous transplantation of bone marrow derived stem cells that can be directed toward the heart, where they differentiate into angioblasts. Subsequent new vessel formation may reduce ischaemia and improve ventricular function. Another approach relies on transfer to the heart of immature skeletal muscle cells that differentiate into functional cardiac myocytes.

Conclusion

The past decade has witnessed significant developments in the management of CHF. In terms of diagnosis, BNP represents a promising convenient blood based test, but echocardiography remains the cornerstone investigation. The pharmacological treatment of systolic ventricular dysfunction is well supported by evidence and should constitute ACE inhibition and beta blockade and spironolactone where indicated. Diuretics should be used to achieve euvolaemia; digoxin provides symptomatic relief in severe heart failure and/or rate control in AF, and ARBs should only be used when there is intolerance to ACE inhibitors. In contrast, little evidence exists for treatment of diastolic ventricular dysfunction, and hence the mainstay is control of aetiological factors. Beta blockers or centrally acting calcium channel antagonists may be used to increase ventricular filling and beta blockers and/or ACE inhibitors may be used to target pathological ventricular remodel-

ing, but these therapies are not mandated by trial evidence. Ancillary CHF therapies of importance include multidisciplinary care and management of sleep apnoea. Novel strategies for which the evidence of efficacy remain to be proven include eplernone, supplementation with co-enzyme Q10, biventricular pacing and stem cell therapy.

SUMMARY OF IMPORTANT POINTS

- Measurement of brain natriuretic peptide (BNP), or its N-terminal precursor, represents a promising new diagnostic test for CHF.
- Optimal therapy for patients with ventricular systolic dysfunction includes an ACE inhibitor and a beta blocker, with the addition of spironolactone in severe cases.
- Currently, there is no strong evidence for therapeutic strategies beyond ACE inhibition and beta blockade, with or without spironolactone, nor for ventricular diastolic dysfunction.

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