Comorbidities in chronic heart failure

Increased risk requiring increased vigilance

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Chronic heart failure is complex and may be associated with many other major conditions, such as hypertension, atrial fibrillation, ischaemic heart disease and type 2 diabetes. Treating these comorbidities judiciously can achieve the three major goals of improving survival, improving symptoms and reducing hospitalisations. Patients with chronic heart failure require regular monitoring of their cardiac situation because they are at an increased risk of deterioration if their general health or comorbidities worsen.

Key points

- **Heart failure is a common, increasingly complex condition, with a high morbidity and mortality. It is associated with a high rate of hospitalisations and readmissions making it a very expensive condition.**
- **Heart failure leads to a poor quality of life due to dyspnoea and fatigue, and current therapy has made only some progress into treating these factors.**
- **As most people with heart failure are elderly there is a high incidence of comorbidities, which have a major influence on the patients' heart failure symptoms and readmission rate.**
- **Treating the comorbidities judiciously can have a favourable impact on symptoms, hospitalisation rates and ultimately survival in these complex and unwell patients.**

It is estimated that 440,000 Australians have chronic heart failure (CHF), or approximately 4% of the population aged over 45 years, and there are an additional 40,000 new cases of CHF diagnosed each year in Australia.[1,2] The total annual cost of treating CHF in Australia is estimated to be about $1 billion and accounts for 1 to 2% of the annual health budget.[3,4] This will rise as the population ages and more people live longer with CHF. In 2009 to 2010, CHF was the primary diagnosis for 45,000 hospital admissions in Australia, was the secondary diagnosis for another 60,000 admissions and led to nearly 800,000 visits to GPs.[2-4] CHF is therefore common and costly and is associated with a high mortality and morbidity.

The typical patient with CHF is elderly and has multiple medical conditions that may complicate management or may be as a consequence of treatment. The median age of patients with CHF who are managed at the heart failure clinic at Concord Hospital, Sydney, is 78 years. These patients have an average of four major comorbidities. They receive an average of seven different medications and often have contraindications to many treatments used to treat CHF. Treating these comorbidities judiciously can achieve the three major goals of improving survival, improving symptoms and reducing hospitalisations.

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This article discusses the major conditions that may coexist in patients with CHF and describes some treatment options that may positively impact on long-term outcomes.

Conditions that coexist with CHF

Hypertension

Hypertension is perhaps the most common comorbidity in patients with CHF. It may be one of the main contributory factors to the CHF and tight control of blood pressure using appropriate agents may improve left ventricular function as well as symptoms. A simple guide is to aim for a systolic blood pressure of approximately 105 to 110 mmHg and a pulse rate of about 55 to 60 beats per minute.

Angiotensin converting enzyme (ACE) inhibitors (or angiotensin receptor blockers [ARBs] in patients who are truly intolerant of ACE inhibitors) are first-line therapy, followed by beta blockers, aldosterone antagonists, nitrates and hydralazine. If blood pressure remains above target, then specialist advice should be sought. Calcium channel blockers should be avoided because centrally-acting agents are negatively inotropic and peripherally-acting agents exacerbate ankle oedema. Prazosin has been found to have a neutral effect on survival and moxonidine is contraindicated in patients with CHF. Secondary causes of hypertension should be investigated if blood pressure is difficult to control.

Postural hypotension

Many patients with CHF, particularly the elderly, will experience sudden drops in blood pressure on standing. The key is to avoid intravascular volume depletion by attempting to reduce blood pressure using ACE inhibitors (or ARBs), beta blockers, aldosterone antagonists or vasodilators and minimising the dosage of diuretic. Some patients may be able to be completely weaned off diuretics, but this is not usually the case if they have more than mild to moderate valvular regurgitation on echocardiography. Taking once-daily ACE inhibitors (e.g. ramipril, perindopril, lisinopril) or once-daily beta blockers (e.g. bisoprolol, nebivolol, metoprolol succinate) at night may reduce postural hypotension and may also impact on the increased cardiovascular mortality that occurs between 3 am and 8 am.[5-7]

Ischaemic heart disease

Approximately 60% of CHF in Australia is caused by ischaemic heart disease, which is due to either prior myocardial infarction or ongoing myocardial ischaemia. It is crucial to investigate patients with CHF for ischaemia because if identified and treated this can make a dramatic difference to ventricular function and prognosis. Clues include Q waves (particularly in patients with diabetes who may have silent ischaemia/infarction), left bundle branch block or ST/T wave changes on an ECG; however, the resting ECG may be completely normal.

Functional testing with stress ECG or echocardiography, myocardial perfusion imaging or CT coronary angiography may be used to investigate coronary artery status but coronary angiography is the gold-standard investigation and may also allow for percutaneous coronary intervention if it is clinically indicated. Patients with left ventricular dysfunction who undergo coronary artery bypass grafting (CABG) have a higher perioperative mortality than those with normal left ventricular function; however, patients with left ventricular dysfunction and myocardial ischaemia have an improved long-term survival if they undergo surgical revascularisation with CABG compared with medical therapy.[8] Improving myocardial perfusion improves ventricular function, symptoms of ischaemia, exercise capacity and survival.

Atrial fibrillation

Atrial fibrillation (AF) may occur as a consequence of elevated left atrial pressure in patients with CHF. Alternatively, if patients have AF with a rapid ventricular rate, they may develop rate-related cardiomyopathy. Regardless of this, it is important to avoid tachycardia because it may exacerbate symptoms by increasing the risk of myocardial ischaemia, reducing left ventricular filling times and reducing the levels of myocardial energy-dependent substrates such as adenosine triphosphate and intracellular calcium.

No studies have shown a benefit of rhythm control strategies compared with rate control in patients with AF, but anticoagulation is crucial to avoid thromboembolic complications. Nonvitamin K oral anticoagulants may be preferable if there are no contraindications. Beta blockers are first-line therapy to control ventricular rate in patients with AF and CHF, but digoxin may be added if rate control is inadequate. Digoxin should not be used alone for rate control and some registry data suggest adverse outcomes with the use of digoxin, but this has not been studied in prospective randomised trials.

Amiodarone may be used for attempted pharmacological cardioversion or maintenance of sinus rhythm after cardioversion but use of this agent may be limited by its side effects. Use of centrally-acting calcium channel blockers should be avoided. Flecainide is contraindicated for treating AF in patients with a reduced ejection fraction because of increased mortality. In patients who are highly symptomatic from palpitations or in whom rate control is difficult, consideration could be given towards electrical cardioversion or pulmonary vein isolation.

1. Causes of worsening renal function in chronic heart failure

- Older age
- Aggressive diuresis
- Renal hypoperfusion
- Diabetes
- Renovascular disease
- Renal calculi
- Urosepsis
- Concomitant unrelated renal disease

2. Tips to avoid worsening of renal function in chronic heart failure

- Avoid high-dose diuretics
- Avoid NSAIDs
- Use aldosterone antagonists (e.g. spironolactone or eplerenone) judiciously by avoiding or taking less frequently (e.g. one to three times per week)
- Monitor renal function regularly (particularly during exacerbations or intercurrent infections)
- Maintain tight glycaemic control in patients with diabetes as this may slow progression of their renal disease
- Angiotensin converting enzyme inhibitors/angiotensin receptor blockers may slow progression of renal impairment

Renal impairment

There is a strong relation between worsening renal function and adverse outcome in patients with CHF (Boxes 1 and 2). Low levels of serum sodium, potassium and magnesium are also predictors of increased mortality in patients with heart failure. This may be the effect of using high-dose diuretics to treat patients who are fluid overloaded or because patients with more advanced CHF have higher levels of renin, angiotensin II and aldosterone, which may also lead to these electrolyte disturbances. Low potassium and magnesium levels may also cause proarrhythmia and should be treated appropriately.

Thiazide diuretics become less effective as renal function deteriorates, although their use in patients with CHF should have a limited place when used in combination with loop diuretics (e.g. frusemide) and aldosterone antagonists in those who are resistant to loop diuretics alone. Doses of medications that are renally excreted (e.g. digoxin) should be reduced and, in some cases, they should be avoided. Patients undergoing renal replacement therapy such as peritoneal dialysis, haemodialysis or renal transplantation pose additional complexities and care from multiple specialists is often required.

Lung disease

Chronic obstructive pulmonary disease or asthma may coexist with CHF and make the initial diagnosis difficult. Beta blockers can be tolerated by about 85% of patients with chronic obstructive pulmonary disease and some with mild or stable asthma. The patient should be trialled on a cardioselective beta blocker used for heart failure, such as bisoprolol or nebivolol, and if well tolerated it should be continued. However, if the patient develops a severe bronchoconstrictor response the beta blocker should be stopped, and if a mild or moderate wheeze develops, respiratory function testing should be performed. If the forced expiratory flow in one second (FEV_1) increases by more than 17% from before to after using nebulised bronchodilators, then the patient has true reversible airways disease and the beta blocker should be discontinued. If the FEV_1 increases by less than 17%, then the patient may tolerate beta blockers, although the addition of an inhaled corticosteroid (e.g. fluticasone or budesonide) and/or a long-acting inhaled muscarinic antagonist (e.g. tiotropium) may be worth considering (Flowchart).

Type 2 diabetes

Approximately one-third of patients with CHF have type 2 diabetes. This may accelerate coronary artery disease (including silent myocardial ischaemia), renal impairment and peripheral vascular disease. Silent myocardial ischaemia should be looked for and treated if present. Patients with CHF and type 2 diabetes have a higher mortality than those without type 2 diabetes. Metformin is first-line therapy. The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) study showed that in patients with coronary artery disease, type 2 diabetes and CHF, use of empagliflozin (a sodium glucose cotransporter-2 inhibitor) leads to reductions of 35% in hospitalisation for CHF, 38% in cardiovascular death, and 32% in all-cause mortality.[9] Recent CHF guidelines now recommend empagliflozin in patients with CHF and concomitant type 2 diabetes.[10]

Peripheral vascular disease

Patients with CHF may have coexistent peripheral vascular disease (PVD). Risk factors for PVD include diabetes and smoking. The degree of tissue hypoxia is exacerbated by poor peripheral perfusion secondary to CHF. PVD may mask symptoms of CHF because claudication may occur before any symptoms of dyspnoea or fatigue. Symptoms of myocardial ischaemia may also be masked and ischaemic heart disease should be looked for as atherosclerosis usually affects the entire vascular system.

Surgical revascularisation may pose a higher risk in patients with CHF and often percutaneous approaches are preferred as they have lower procedural mortality. Aortic cross clamping for aortic aneurysm repair may dramatically increase afterload, which is not well tolerated by a failing heart. Nitrates may temporarily improve peripheral ischaemic symptoms through vasodilatation and perhexiline may give similar benefits.

Anaemia

There is a direct correlation between haemoglobin level and survival in patients with CHF. Anaemia is usually multifactorial, but the most common aetiologies include iron deficiency, renal impairment, chronic low-grade blood loss, myelodysplasia and vitamin B_{12} or folic acid deficiency. Despite the association between anaemia and mortality in CHF, correcting the anaemia with darbepoetin did not improve survival in a large multicentre trial.[11] Anaemia should be considered for correction once the haemoglobin level falls below 100 g/L. Polycythaemia should be avoided (haemoglobin level above 160 g/L)

as this may be associated with increased blood volume, increased blood viscosity and possibly thromboembolic complications.

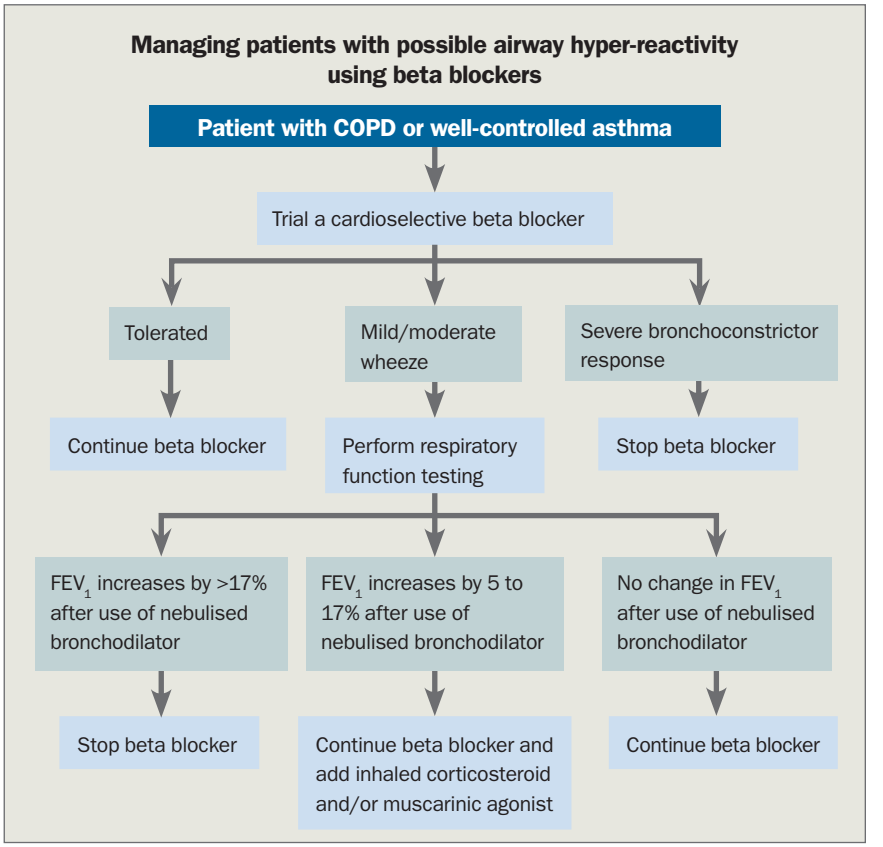
Iron deficiency

There is a strong relation between the ferritin level and survival in patients with CHF and this is independent of the haemoglobin level. Iron is important in many metabolic processes including oxidative phosphorylation and mitochondrial function and is crucial to all muscle function, particularly cardiac muscle. Iron deficiency should be looked for in all patients with CHF and treated. In CHF, iron deficiency is defined as a serum ferritin level of less than 100 µg/L, or below 300 µg/L if the transferrin saturation is less than 20%. It is also important to remember to investigate why the patient is iron deficient and to look for occult blood loss, which is often gastrointestinal in origin.

The FAIR Heart Failure Study showed that in patients with CHF and iron deficiency who are treated with intravenous ferric carboxymaltose there is a significant improvement in symptoms, exercise capacity and left ventricular function within one month and this persisted beyond six months.[12] Recent research suggests that the symptomatic improvement may occur within days.[13] Intravenous ferric carboxymaltose is administered in an outpatient setting over 15 minutes. There are no data to support the benefit of oral iron as it is poorly absorbed in patients with CHF. Patients with chronic illness, such as CHF, also have high levels of hepcidin, which inhibits uptake of iron after absorption.

Sleep apnoea

Patients with CHF are often overweight and have concomitant obstructive sleep apnoea. These patients should be treated with continuous positive airway pressure therapy or mandibular advancement splints, as appropriate, because these can reduce the risk of myocardial ischaemia, secondary pulmonary hypertension and nocturnal ventricular arrhythmia. Unfortunately, treatment of central sleep apnoea with autoset positive airway pressure ventilation has been shown to increase mortality in people with CHF and is now contraindicated.[14] Central sleep apnoea is associated with more severe grades of CHF and may respond to more aggressive treatment for CHF.



Gout

Gout may occur as a consequence of diuretic therapy or in association with renal disease in patients with CHF. Exacerbations should be treated with colchicine. NSAIDs and corticosteroids should be avoided because of fluid retention and other side effects. There is a significant association between the serum uric acid level and increasing mortality in patients with CHF. This may be due to increased catabolism as patients with CHF become more unwell or the increased dose of diuretics that result in higher uric acid levels. Regardless of this, uric acid itself is negatively inotropic and in patients with cardiac cachexia (>6% reduction in dry weight over a 12-month period), there is a theory that a xanthine oxidase inhibitor, such as allopurinol, may improve outcomes, although this has yet to be proven in large trials.

Arthritis

As CHF affects predominantly the elderly, there is a high incidence of arthritic concomitant conditions. It is important to avoid NSAIDs in these elderly patients as they cause fluid retention, worsen renal function, increase blood pressure and may precipitate a decompensation of CHF. Paracetamol, codeine or similar analgesia, glucosamine, intra-articular injection of corticosteroids/local anaesthetics and joint replacement may need to be considered.

Thyroid disease

Hyperthyroidism in patients with CHF may cause high output hyperdynamic decompensation and thyroid function should be checked in all patients who are newly diagnosed with CHF. Hypothyroidism can mimic CHF and patients with CHF who become hypothyroid can become debilitated and retain fluid.

Amiodarone is often used in patients with CHF to treat atrial and ventricular arrhythmias. Because of its high iodine

concentration, many patients with CHF treated with amiodarone will develop either hypothyroidism (Wolff–Chaikoff effect) or hyperthyroidism (Jod-Basedow effect). The incidence is over 10% and increases with chronicity of usage.[15] Patients treated with amiodarone should have thyroid function testing performed approximately every three months and abnormalities should be treated promptly.

Depression

Patients with CHF have a poor quality of life and depression may be a direct consequence of their illness or may coexist. Treatment of the CHF itself may greatly improve depressive symptoms. Patients with CHF and depression have a higher mortality than those without depression. Studies using various antidepressant medications to try to improve symptoms of depression in patients with CHF have largely been disappointing but they have shown that slow selective serotonin reuptake inhibitors are safe to be given to patients with CHF.[16]

There are theoretical reasons to avoid drugs that increase sympathetic tone such as slow serotonin and noradrenaline reuptake inhibitors.

Nonadherence and poor understanding of therapy

Unfortunately, nonadherence with medications, fluid restriction and salt restriction are the most common causes of rehospitalisation in patients with CHF. Nurse-led programs have had a major impact on these avoidable causes of readmission; however, the 30-day readmission rate for patients with CHF in Australia is 24 to 28%.[2-4]

Educating the patient in hospital, follow up within one week at home with the patient and carers, weekly phone calls for at least one month, instruction on fluid restriction, daily weights and prescription of an action plan on what to do if symptoms occur have been shown to be of major benefit and most states and territories in Australia have implemented such programs. Blister packs, instructional booklets and DVDs in multiple languages, home help for domestic assistance and district nursing to supervise medication administration have all been shown to be useful in avoiding rehospitalisation.

Conclusion

CHF is complex and associated with many other medical, surgical and psychosocial conditions. CHF may negatively impact on these conditions, which may also adversely affect the severity of the underlying CHF. Optimising the CHF status is crucial because the heart may be the innocent bystander when other illnesses intervene causing cardiac decompensation in a previously stable patient. Patients with CHF require regular monitoring of their cardiac situation because they are at increased risk of deterioration if their general health or comorbidities worsen. Their CHF may be only a part of their overall health but it is the pivotal point for reducing hospitalisations and improving long-term survival. **CT**

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