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The kidney
victim or villain in heart failure?

Deteriorating renal function is often a complication of heart failure, and kidney disease itself can lead to cardiomyopathy. The combination of renal failure and heart failure is referred to as the cardiorenal syndrome; management of this syndrome requires the careful adjustment of medications.

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Heart failure is a common cause of hospital admissions in the over 65-year-old population. During admission, patients with heart failure may develop renal failure due to attempts to treat fluid overload. In addition, many patients with heart failure who are hospitalised have renal insufficiency. Unfortunately, the prognosis of these patients is grim. The combination of both kidney and heart failure is now referred to as the cardiorenal syndrome, a situation that poses difficult management decisions for clinicians. It can be tricky to differentiate clinically which organ is the 'victim' and which is the 'villain'. Also, medications targeting renal impairment may interfere independently with cardiac function and vice versa.

How does heart failure impact on renal function?

Simplistically, heart failure is a result of diastolic or systolic dysfunction. Diastolic heart failure is characterised by the inability of the myocardium to relax adequately during diastole and results in symptoms of pulmonary congestion. Systolic heart failure reflects reduced cardiac output.

The left ventricular ejection fraction (LVEF), measured by echocardiography or nuclear testing, is often used to investigate heart failure. A reduction in LVEF, whether diastolic or systolic in origin, may cause renal hypoperfusion (a result of hypovolaemia, neurohormonal-stimulated vasoconstriction or low cardiac output syndrome). Renal hypoperfusion eventually leads to sodium and water retention.

Diastolic dysfunction is found in a substantial proportion of patients with the cardiorenal syndrome. Up to half of all patients with the cardiorenal syndrome have a LVEF of greater than 40%, and many patients have associated hypertension, diabetes or impaired baseline renal function.

Inappropriate activation of the renin–angiotensin system invariably occurs in heart failure, and excessive activation of this system has been implicated in the progression of chronic kidney disease. In addition, patients may have concurrent

IN SUMMARY

- **Increasingly, patients are being diagnosed with both heart and renal failure – the cardiorenal syndrome.**
- **Careful adjustment of cardiovascular medications allows treatment of heart failure without compromising kidney function.**
- **When managing patients with heart failure, be alert for signs of fluid retention and changes in blood pressure and always consider underlying renal disease.**
- **Important laboratory values to determine in patients with heart and renal failure include concentrations of electrolytes, estimated glomerular filtration rate and haemoglobin level.**

intrinsic renal disease secondary to longstanding hypertension, diabetes or atherosclerosis. Usually, more than one causal factor is present. Hence there are a number of pathophysiological changes that, in combination, act synergistically to aggravate both kidney and cardiac failure.

How does renal failure impact on cardiac function?

Cardiovascular disease (CVD) is a major problem in patients with chronic renal failure: almost half of the deaths in patients with end-stage kidney disease are due to cardiac causes. Even a slight decrease in kidney function correlates with a substantial increase in CVD risk and higher mortality, independent of other known risk factors.

Kidney failure can result in left ventricular (LV) dilatation due to volume overload or LV hypertrophy due to high blood pressure. It is rare to find one of these disorders of LV function in isolation. Renal failure is invariably associated with the presence of hypertension. This may be associated with either high or low renin concentrations. In addition, renal failure may lead to salt and water retention.

Anaemia is a common finding complicating both renal and cardiac dysfunction and is discussed later.

There have been several trials exploring the impact of renal dysfunction in patients with heart failure. In fact, kidney failure, as gauged by the estimated glomerular filtration rate (eGFR), is the single most powerful predictor of mortality, exceeding cardiac functional status and LVEF.

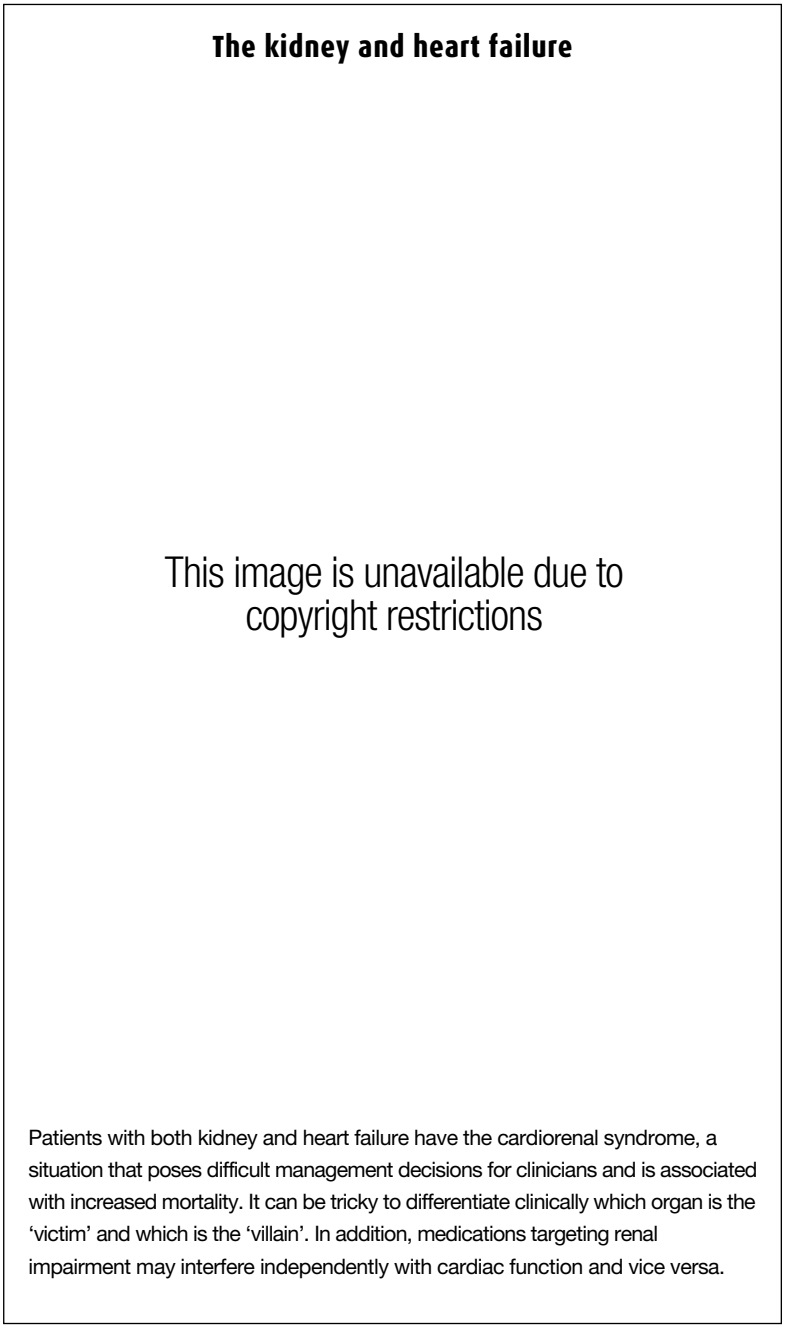
What is the impact of drugs used to treat heart or renal failure?

A significant number of cardiovascular drugs are prescribed by both cardiologists and nephrologists as they have beneficial effects on both the kidney and the heart. For example, ACE inhibitors have both antihypertensive and renoprotective effects. However, other drug classes may be beneficial to one organ but not the other. For example, diuretics prescribed for congestive heart failure are associated with renal hypoperfusion.

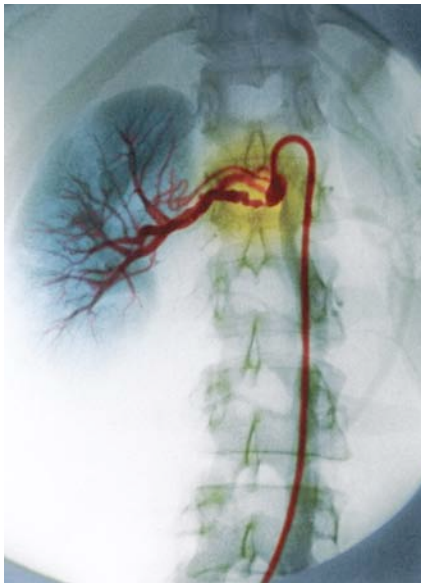
Diuretics

Often patients with heart failure are discharged from hospital on a combination of frusemide, either spironolactone (Aldactone, Spiractin) or eplerenone (Inspra), and possibly a low dose thiazide diuretic. This combination attempts to reduce intravascular volume and the symptoms of congestion or fluid overload. Although frusemide may reduce congestive symptoms, only spironolactone and eplerenone have been shown to produce a mortality benefit in heart failure.

The kidney and heart failure



Patients with both kidney and heart failure have the cardiorenal syndrome, a situation that poses difficult management decisions for clinicians and is associated with increased mortality. It can be tricky to differentiate clinically which organ is the 'victim' and which is the 'villain'. In addition, medications targeting renal impairment may interfere independently with cardiac function and vice versa.



PHOTOLIBRARY

Figure 1. Renal artery stenosis (coloured x-ray). The presence of widespread vascular disease in a patient should increase a clinician's suspicion for significant renal artery stenosis.

It is important to advise patients taking diuretics that they must restrict their total fluid intake to less than 1500 mL/day (see the patient handout on page 23).

ACE inhibitors and angiotensin II receptor blockers

ACE inhibitors are widely prescribed for hypertension and heart failure and as renoprotective drugs in kidney disease. They act on the kidney by reducing glomerular pressure, which may result in a decrease in eGFR. Generally, most nephrologists would tolerate up to a 20 to 25% increase in creatinine level in patients who have started ACE inhibitor (or angiotensin II receptor blocker [ARB]) therapy before investigating for renovascular disease. ACE inhibitors and ARBs can cause a precipitous rise in creatinine in patients with bilateral renal artery stenosis. Stimulation of angiotensin II in patients with renal artery stenosis causes severe glomerular efferent artery constriction in the kidney. Reducing angiotensin II concentrations with either ACE inhibitors or ARBs lowers intraglomerular pressure, causing a dramatic fall in GFR and a resultant rise in serum creatinine concentration. The association between carotid, coronary, peripheral and renal atherosclerotic vascular diseases is high, and the presence of widespread vascular disease should increase a clinician's suspicion for significant renal artery stenosis (Figure 1).

Patients with heart failure often have low blood pressure, and this can limit the dose of ACE inhibitor or ARB that may be prescribed. Reducing the diuretic dose for a short period may allow either the initiation of a low dose ACE inhibitor or an escalation of the current dose. Patients with heart failure who cannot tolerate ACE inhibitors or ARBs because of severe hypotension, significant worsening of renal function or hyperkalaemia have a very high mortality (approximately 50% at six months).

ARBs are a relatively recent addition to the cardiovascular armamentarium. The Candesartan in Heart Failure Assessment of Reduction in Morbidity and Mortality-Added (CHARM-Added) trial showed that candesartan (Atacand) reduced death and hospitalisations when added to ACE inhibitor therapy in patients with chronic heart failure. In addition, the Japanese Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) trial demonstrated a reduction in proteinuria and slower decline in renal function with the combination of losartan (Cozaar) and trandolapril (Gopten, Odrik) than with either medication alone. The Irbesartan in Diabetic Nephropathy Trial (IDNT) and the Irbesartan in Patients with Type II Diabetes Microalbuminuria Study (IRMA-II) confirmed a benefit of irbesartan (Avapro, Karvea) in diabetic nephropathy, both in microalbuminuric and overtly proteinuric patients. In IDNT, irbesartan produced better renal protection than the calcium channel blocker amlodipine (Norvasc) in patients with hypertensive type 1 diabetes, reducing the chance of diabetic nephropathy developing into renal failure. In IRMA-II, higher doses of irbesartan reduced the progression of renal insufficiency. Hence, ARBs may be advantageous for certain patient groups – for example, heart failure patients with diabetes and microalbuminuria.

Increasingly, the combination of an ACE inhibitor and ARB is being prescribed to patients with multiple conditions. However, in those with hypertension, this combination may not be as potent as combining either medication individually with a low dose thiazide diuretic.

Beta blockers

Beta blockers are widely prescribed to patients with heart failure. As well as treating heart failure, they may lower blood pressure but have no other specific renoprotective effects. Although the elimination routes of various beta blockers may differ, dose adjustments for patients with renal impairment are not necessary in practice. Pulse rate and blood pressure are the major dose limiting factors of beta blocker treatment.

Statins

Although not prescribed to treat heart failure, statins are often used in patients with ischaemic cardiomyopathy to slow progressive coronary atherosclerosis. Some observational studies suggest that statins may slow the progression of chronic kidney disease, and randomised placebo controlled trials are currently being undertaken to explore this hypothesis.

Oral hypoglycaemics

Oral hypoglycaemics are not used to treat heart or renal failure *per se*, but they are often coprescribed in patients with these conditions because of the high incidence of diabetes. The dosage of metformin must be lowered as a patient's renal function deteriorates, and extra caution is needed in those with concurrent heart failure because of the risk of developing

continued

Table. Management strategies when pathology results are outside the normal range

Hyponatraemia	
	Advise patients to reduce their fluid intake
	Consider reducing doses of medications that may affect serum sodium levels
	Omit thiazide diuretic
Hypokalaemia	
	Advise patients to increase their intake of foods that are high in potassium
	Advise patients to increase their intake of, or prescribe, potassium supplements
Hyperkalaemia	
	Advise patients to stop taking potassium supplements
	Advise patients to reduce their intake of foods that are high in potassium
	Advise patients to avoid salt substitutes that are potassium chloride, and the fibre supplement, Metamucil, which has a high potassium content
	Ask patients about their use of COX-2 inhibitors and other NSAIDs
Elevated creatinine	
	Review diuretic dose
	Review ACE inhibitor and angiotensin II receptor blocker dose, but aim to continue treatment with these medications if possible
	Consider other causes (obstructive, renovascular or nephritis)
Hyperuricaemia	
	Reduce uric acid levels with allopurinol only if patients develop clinical gout
Anaemia	
	Exclude haematinic deficiency by measuring ferritin/transferrin saturation, vitamin B_{12} levels, folic acid levels

lactic acidosis. No clear guidelines exist for reducing the metformin dose as renal function declines. One suggested approach is to reduce the dose when the eGFR is below 60 mL/min but to cease treatment before the eGFR reaches 30 mL/min.

Thiazolidinediones (pioglitazone [Actos], rosiglitazone [Avandia]) may cause fluid retention. They should not be used in patients with severe heart failure and they should be prescribed with extreme caution to those with moderate heart failure. Patients taking thiazolidinediones should be advised to be vigilant for signs of fluid retention.

Calcium channel blockers

Although not specifically used to treat heart or kidney failure, calcium channel blockers are often coprescribed to manage hypertension. Verapamil (Anpec, Cordilox, Isoptin, Veracaps) should not be used with a beta blocker as heart block may result. This may also occur to a lesser extent with coprescription of diltiazem and a beta blocker, although bradycardia is not infrequent. If possible advise patients to take their own pulse for a few weeks after commencing that combination or after dosage adjustment. The dihydropyridine class of drugs (amlodipine [Norvasc], felodipine [Felodur, Plendil], nifedipine and to a lesser extent lercanidipine [Zanidip]) often cause ankle swelling, especially at maximum dosages. This may be confused with fluid retention from worsening heart or renal failure.

How do you interpret pathology results?

Patients with heart and kidney disease require frequent blood tests to monitor their cardiovascular and renal function. The table summarises the management of patients whose pathology results fall outside the normal range and the box on page 22 provides some tips for rural GPs.

Electrolytes

Electrolyte disturbance is common in patients with heart and/or kidney failure and depends on the drug combinations and doses chosen to treat patients. Sodium concentrations may fall below 130 mmol/L and potassium concentrations may rise or fall. For example, increasing the diuretic dose or adding another diuretic can result in the sodium concentration falling within a week. Electrolytes should be rechecked two weeks after hospital discharge in heart failure patients with renal impairment as the impact of dose changes made in hospital may not be seen for several weeks.

Dietary management of sodium and potassium intake may be required. The patient handout on page 23 includes lists of common foods that are high in sodium and potassium; it may be worth keeping this sheet handy to educate patients.

Renal function

The typical pathology report may show that a patient's urea concentration has increased out of proportion to the creatinine concentration – for example, urea 32 mmol/L, creatinine 175 µmol/L. This reflects renal hypoperfusion. Often higher concentrations of urea and creatinine have to be tolerated to keep the patient euvolaemic, as opposed to having fluid overload and congestive symptoms. Trying to optimise fluid status and achieve the lowest urea and creatinine concentrations possible can be a difficult balance to achieve. There is no specific cut-off when the urea is considered to be too high; urea itself is not a toxin, but rather a marker of other ureamic toxins.

continued

Assessing cardiovascular and renal function: tips for rural GPs

- Frequent blood tests are needed to manage patients with heart and kidney disease.
- Check electrolytes, urea, creatinine and haemoglobin levels one to two weeks after the dosages of diuretic, ACE inhibitors or angiotensin-II receptor blockers have been altered.
- Contact a kidney specialist or cardiologist if a patient's potassium concentration is >6.0mmol/L, urea >20 mmol/L or creatinine >200 µmol/L.
- Keep lists available of foods that have a high sodium and high potassium content to give to patients who need to avoid these electrolytes (see the patient handout on page 23).

Uric acid

Uric acid is an excellent marker of the degree of intravascular depletion. Cardiac patients with renal impairment who are taking high dose diuretics may have uric acid levels as high as 0.7 to 0.8 mmol/L. Uric acid has not been confirmed as a risk factor for progressive renal failure, although this is currently being explored. At present, hyperuricaemia is treated only if patients develop clinical gout.

An acute attack of gout can be treated with colchicine (Colgout, Lengout), or with prednisone (Predsone, Panafcort, Sone) or prednisolone (Predsolone, Panafcortelone, Solone) given in divided doses (10 mg in the morning and 5 mg at night). Once the acute attack has subsided, allopurinol is used to reduce uric acid levels.

The chronic use of COX-2 inhibitors and other NSAIDs for gout is contraindicated in patients with renal impairment. Also, the propensity of these drugs to cause salt and water retention in patients may precipitate or worsen heart failure.

Anaemia

Anaemia is common in patients with heart failure, and early observational studies have demonstrated progressive anaemia as heart failure worsens. Anaemia is also often recognised in patients with chronic kidney disease, in whom relative erythropoietin deficiency is a common causal mechanism. ACE inhibitors and ARBs lower endogenous erythropoietin production.

Patients with heart failure must be screened for iron deficiency. Ferritin is the best marker of iron stores but can be falsely elevated in patients with acute inflammation. Serum iron is not a useful marker.

Warfarin (Coumadin, Marevan) and the platelet inhibitors, aspirin and clopidogrel (Iscover, Plavix), which are often prescribed in combination, increase the risk of gut blood loss.

Small interventional studies with epoetin (Eprex, NeoRecorman), a recombinant human erythropoietin, have shown an improvement in heart failure symptoms and reduced hospitalisation rates; however, larger placebo controlled trials with darbepoetin (Aranesp) are awaited to confirm this. Current government reimbursement for epoetin is limited to patients who have haemoglobin concentrations less than 100 g/L.

Conclusion

As clinicians become better at managing heart and renal failure, increased patient survival will lead to more cardiomyopathy and nephropathy complications. Patients with heart failure and deteriorating renal function need careful adjustment of their medications, often with input from both a cardiologist and a kidney specialist. MT

DECLARATION OF INTEREST: Dr Roger has acted as an adviser to Amgen and F. Hoffmann-La Roche.