Cardiorenal failure: pathophysiology, recognition and treatment

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Clin Med JRCPL 2002;**2**:195–200

In ancient Chinese medicine, the kidney dominates water and is considered a 'yin' organ whereas the heart dominates fire and is a 'yang' organ.

> *When the kidney fails to evaporate fluid which then floods and ascends to depress the function of heart 'yang' there may be clinical manifestations such as oedema, chills and cold limbs, accompanied by palpitations, shortness of breath and stuffiness in the chest, indicating retained water affecting the heart*[1].

This lyrical description of cardiorenal failure predates echocardiography and renal ultrasound by many hundreds of years but, despite these and other advances in diagnosis and treatment, cardiorenal failure remains an under-researched area of nephrology and cardiology. In this review, cardiorenal failure is defined as pulmonary congestion with a serum creatinine of 150 μmol/l or above. This is a somewhat arbitrary definition, but a useful way of distinguishing the 'wet' renal patient from the 'dry'. Five categories of cardiorenal failure may be recognised (Table 1).

Cardiac disease causing renal failure

Pathophysiology

Heart failure in patients with left ventricular (LV) systolic dysfunction is characterised by arterial underfilling. This is sensed by baroreceptors that activate powerful neurohormones, leading to renal vasoconstriction with sodium and water retention (Fig 1)[2]. In the early stages of heart failure, glomerular filtration rate (GFR) is well maintained by preferential constriction of the efferent arteriole under the influence of intrarenal angiotensin II, but in patients with severe heart failure GFR becomes more dependent on afferent arteriolar flow and may therefore fall[2].

Angiotensin-converting enzyme inhibitors

Blockade of the renin angiotensin system, one of the mainstays of therapy for heart failure, may inadvertently make matters worse[3]. Because high levels of intrarenal angiotensin II are required to maintain an adequate glomerular capillary pressure, a fall in GFR with an angiotensin-converting enzyme (ACE) inhibitor is common, reflecting the known effects of ACE inhibitors on renal haemodynamics (Fig 2)[4]. The question then arises of how much renal failure is acceptable. In heart failure, up to 30% increase in serum creatinine can be expected and is not an indication to stop the ACE inhibitor, but a rise in serum creatinine of more than 30% should prompt its temporary withdrawal.

Table 1. Pathophysiology of cardiorenal failure.

- Cardiac disease → renal failure
- Renal disease → cardiac failure
- Bilateral renovascular disease → cardiac and renal failure
- Malignant hypertension → cardiac and renal failure
- Relationship not causal

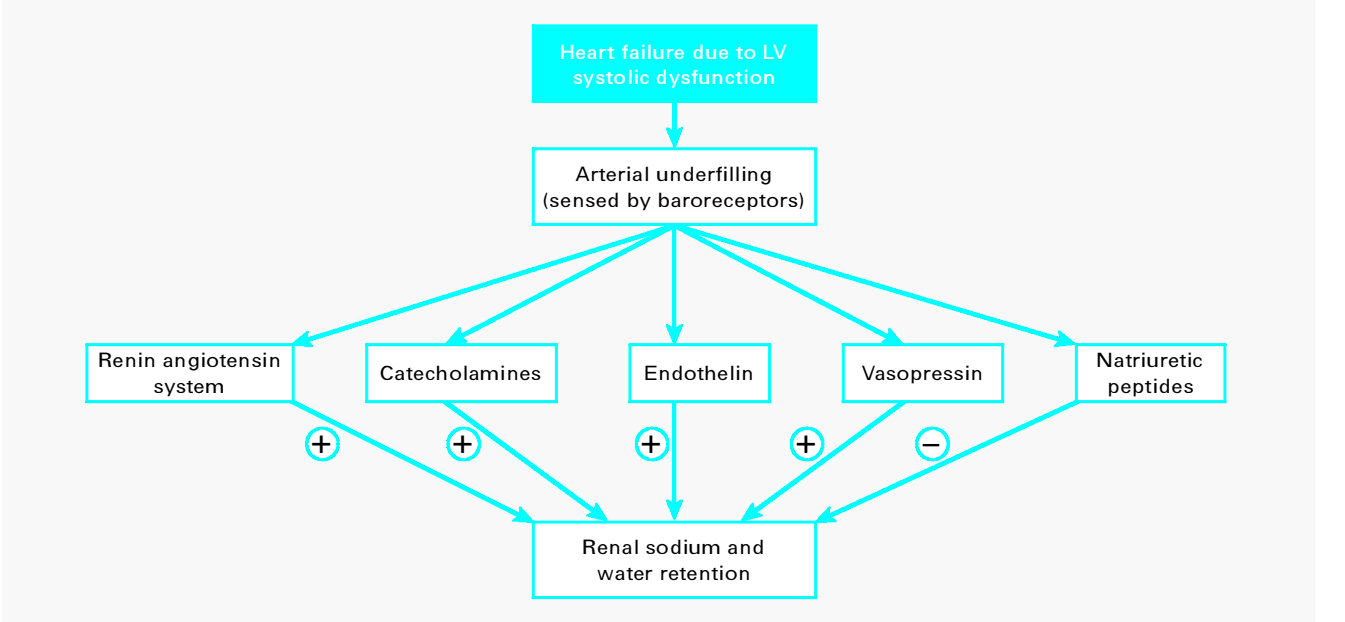

Fig 1. Vasoconstrictor influences that lead to renal sodium and water retention in heart failure. Initially, these correct the arterial underfilling, but ultimately a vicious cycle develops with symptoms and signs of progressive heart failure. Counter-regulatory vasodilator mechanisms such as the natriuretic peptides are largely overwhelmed (LV = left ventricular).

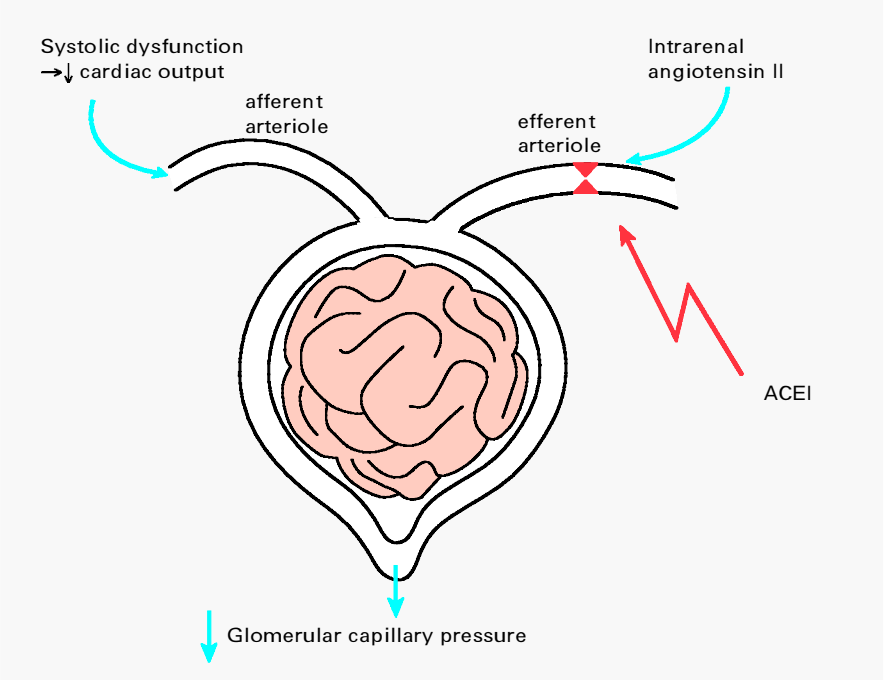

Fig 2. Glomerulus with afferent and efferent arteriole. In the presence of a reduced cardiac output, a high level of intrarenal angiotensin II is required in order to maintain glomerular capillary pressure. If the production of intrarenal angiotensin II is blocked by an angiotensin-converting enzyme inhibitor (ACEI), glomerular capillary pressure falls.

Causes of such a rise include:

- hypotension with mean arterial pressure below 60–65 mmHg
- volume depletion due to excess diuretic therapy or gastroenteritis
- bilateral renovascular (BRV) disease
- co-prescription of a non-steroidal anti-inflammatory drug
- underlying chronic renal failure of any cause[3].

If one or more of these causes can be identified and corrected, it is usually safe to restart ACE inhibitor therapy[3].

Angiotensin receptor blockers

Angiotensin receptor blockers are probably as effective as ACE inhibitors in reducing mortality in heart failure[5]. However, the evidence thus far suggests that patients whose renal function deteriorates on an ACE inhibitor should not be given an angiotensin receptor blocker. The effects on renal function of losartan and captopril were evaluated in the first Evaluation of Losartan in The Elderly (ELITE) study. A persisting increase in creatinine of more than 26.5 μmol/l was recorded in 10.5% of patients in both the losartan and captopril groups. The corresponding figures for any increase in creatinine of more than 26.5 μmol/l were 26.1% and 29.7%, respectively[6].

Hydralazine and nitrates

For those in whom the rise in urea and creatinine is considered unacceptable, withdrawal of ACE inhibitor therapy and replacement by hydralazine and nitrate can be recommended. This drug combination reduces mortality in heart failure. Although the mortality advantage is not as great as with ACE inhibition, patients given a combination of hydralazine 300 mg daily and isosorbide dinitrate 160 mg daily will experience at least as much improvement in exercise performance and LV function with no risk of deterioration in renal function[7].

Diuretic therapy

The principles of diuretic therapy in cardiac failure and renal insufficiency have been summarised by Brater[8]. Loop diuretics are preferred because the diuretic response to thiazides is poor in patients with creatinine clearance below 50 ml/min. In cardiac failure, renal responsiveness to loop diuretics is decreased: responsiveness is not improved by giving larger doses of diuretic, but may be increased by using moderate doses more frequently (eg 40–80 mg bd or tds). In renal insufficiency, the problem is impaired delivery of loop diuretic to the thick ascending limb of the loop of Henle. In this situation, the dose should be increased in order to achieve an effective amount of diuretic at its site of action.

Patients with cardiorenal failure may therefore require frequent administration of large doses of loop diuretics. The maximal natriuretic response to frusemide in severe renal insufficiency (serum creatinine >300 μmol/l, creatinine clearance <20 ml/min) occurs with 160–200 mg intravenously (iv). The maximal oral dose is usually twice the iv dose (ie 320–400 mg). Nothing is gained by using larger doses. If the response to a maximal dose is inadequate, a thiazide should be added. If diuresis remains inadequate, or if treatment is limited by an unacceptable rise in urea or creatinine as a result of intravascular volume depletion, dialysis may be the only option.

Dialysis

A small proportion of patients with severely impaired LV function and renal failure may benefit from – and should be offered – renal replacement therapy (RRT). Patients suitable for this demanding form of treatment will be incapacitated by breathlessness when fluid overloaded and by uraemia when dry. The only absolute contraindications are:

- systolic blood pressure below 100 mmHg
- poor tolerance of dialysis
- the standard contraindications to dialysis (eg dementia, disseminated malignancy and lack of consent).

Successful treatment by intermittent dialysis or haemofiltration may restore the sensitivity of the kidneys to loop

diuretics[9], in which case RRT may be required for only a few weeks. RRT may be repeated at a later date if necessary. For those whose diuretic sensitivity is not restored, peritoneal dialysis has proved successful in the medium to long term, allowing patients to maintain their independence at home with fewer admissions to hospital for periods of up to two years[10].

Renal disease causing cardiac failure

It is often difficult to distinguish between sodium and water retention caused by a diseased heart and that which occurs as a result of diseased kidneys because the clinical manifestations are similar (ie they look the same). Nevertheless, if a patient with advanced renal failure or already on dialysis becomes breathless, the likely explanation is fluid overload due to the failing kidney's inability to respond to a fluid challenge by mounting a diuresis and/or failure by the patient to comply with fluid restriction. A similar problem can arise when a patient with advanced renal failure admitted as an emergency is found to be anaemic and transfused with three or four units of blood before it has been established whether urine is being passed. Mechanical removal of fluid by haemodialysis or haemofiltration is usually associated with a dramatic improvement in symptoms.

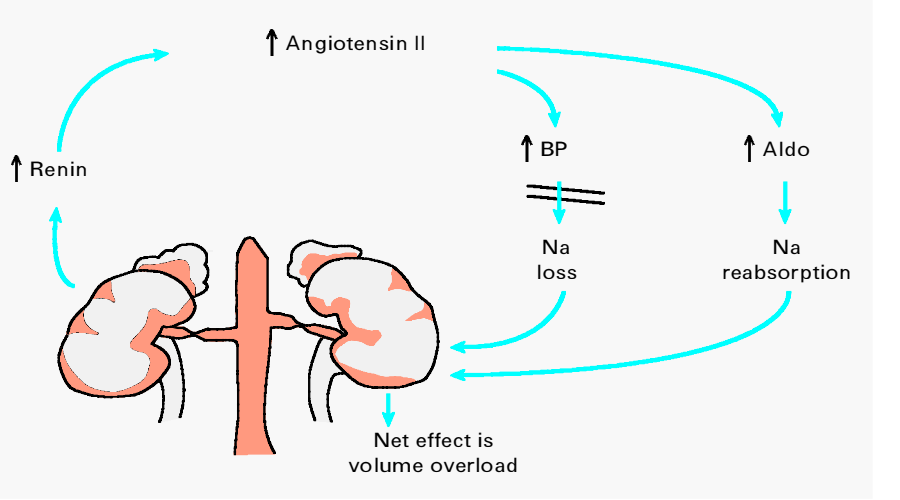

Fig 3. Activation of the renin angiotensin system in bilateral renovascular disease leads to fluid retention. The kidneys fail to sense the high arterial pressure, and so do not mount a pressure natriuresis. This leads to unopposed sodium reabsorption, the net effect of which is volume overload (BP = blood pressure; Na = sodium).

Key Points

- **Cardiorenal failure may be defined as pulmonary congestion with serum creatinine 150 µmol/l or higher**
- **A rise in creatinine of up to 30% with angiotensin-converting enzyme (ACE) inhibition in patients with heart failure is a normal haemodynamic response and is not a reason to stop the ACE inhibitor**
- **Causes of a rise in creatinine of more than 30% with ACE inhibition in patients with heart failure include hypotension, dehydration, bilateral renovascular disease (BRVD), co-prescription of a non-steroidal anti-inflammatory drug and underlying chronic renal failure**
- **BRVD should be suspected in patients presenting with hypertension, heart failure and renal failure, particularly if they have vascular disease at other sites, inequality of renal size on ultrasound and ACE inhibitor-induced worsening of their renal function**
- **Heart failure may be relieved by renal revascularisation in a proportion of patients with BRVD, particularly those with tight bilateral renal artery stenoses, tight unilateral stenosis with a contralateral occlusion, or tight stenosis to a single functioning kidney**

KEY WORDS: CPD, angiotensin-converting enzyme inhibitors; angiotensin receptor blockers, bilateral renovascular disease, cardiac failure, cardiorenal failure, echocardiography, left ventricular systolic dysfunction, pathophysiology, renal failure, treatment

Bilateral renovascular disease causing cardiac and renal failure

The association between pulmonary oedema and bilateral renovascular disease (BRVD) was first described in 1988[11]. Pulmonary oedema occurs when the kidneys, 'protected' by bilateral stenoses, fail to sense the high arterial pressure and so do not mount a pressure natriuresis. The syndrome is therefore characterised by fluid retention rather than by heart failure (Fig 3). Patients with hypertension, heart failure and renal failure are highly likely to have BRVD (Fig 4). This is also likely if there is vascular disease at other sites, inequality of renal size on ultrasound and ACE inhibitor-induced renal failure[3]. The mere demonstration of BRVD in patients with heart failure would not be enough to justify the expense and additional workload created by screening if it were not for the fact that the heart failure in some of these patients may be cured by renal revascularisation. The chance of success is greatest with:

- tight bilateral renal artery stenosis
- tight unilateral stenosis with a contralateral renal occlusion
- tight stenosis to a single functioning kidney[11–13].

Malignant hypertension causing cardiac and renal failure

Both cardiac and renal failure may also be caused by malignant hypertension, though this is fortunately now not common in the UK. The diagnosis of malignant hypertension is clinical, requiring the presence of severe hypertension (diastolic pressure usually, but not always, >130 mmHg), with bilateral retinal haemorrhages and exudates and/or bilateral papilloedema. Malignant hypertension is only rarely asymptomatic. Common clinical manifestations include cardiac and renal failure. Hypertensive encephalopathy, microangiopathic haemolytic anaemia and secondary hyperaldosteronism may also occur. Patients with malignant hypertension are more likely to have an underlying cause for their high blood pressure than are patients with non-malignant hypertension. Renal and renovascular diseases are those most commonly identified, although any cause of raised blood pressure can lead to the malignant phase if the hypertension is sufficiently severe[14].

Relationship not causal

The final explanation for the coexistence of cardiac and renal failure is that a patient has a cardiac condition such as ischaemic heart disease and an unrelated renal one such as diabetic nephropathy or prostatic disease causing obstructive uropathy. In these circumstances, it is possible that cardiac and renal failure may coexist without necessarily being related.

Diagnosis of cardiorenal failure

An algorithm for the assessment and management of patients with cardiorenal failure is suggested in Fig 5. Measurement of blood pressure, renal size by ultrasound, and LV dimensions by echocardiography will usually allow a provisional diagnosis. For example, normal LV function at echocardiography, particularly if associated with LV hypertrophy (LVH), would alert the clinician to the possibility of BRVD, malignant hypertension or intrinsic renal disease. Alternatively, if the echocardiogram shows LV impairment, the pattern of abnormalities will help to identify those patients with a primary cardiac (ischaemic) aetiology and those who have developed these abnormalities secondary to renal disease.

Patients with primarily ischaemic LV impairment will typically have an undilated or dilated ventricle with no associated hypertrophy. There are also likely to be regional wall motion abnormalities, and even regional wall thinning with remodelling. Patients whose primary problem is chronic renal disease usually have a globally dilated left ventricle with associated LVH[15]. LVH is unusual in patients with a globally dilated cardiomyopathy from other causes (eg alcohol, viral), with the exception of hypertrophic cardiomyopathy.

Therapy of cardiorenal disease

Cardiorenal failure presents a major challenge to the nephrologist and the cardiologist. Unlike most forms of oliguria which respond to the infusion of fluid, a different approach is required for patients who present with oliguria and breathlessness and who have clinical and radiological evidence of pulmonary congestion. Infusion of fluid is likely to make matters worse and, in the absence of any other obvious reversible cause or response to iv diuretic, mechanical removal of fluid by haemodialysis or haemofiltration may be the only immediate solution.

For those with lesser degrees of cardiorenal failure, the most appropriate therapy should be determined by the provisional diagnosis (as shown in Fig 5):

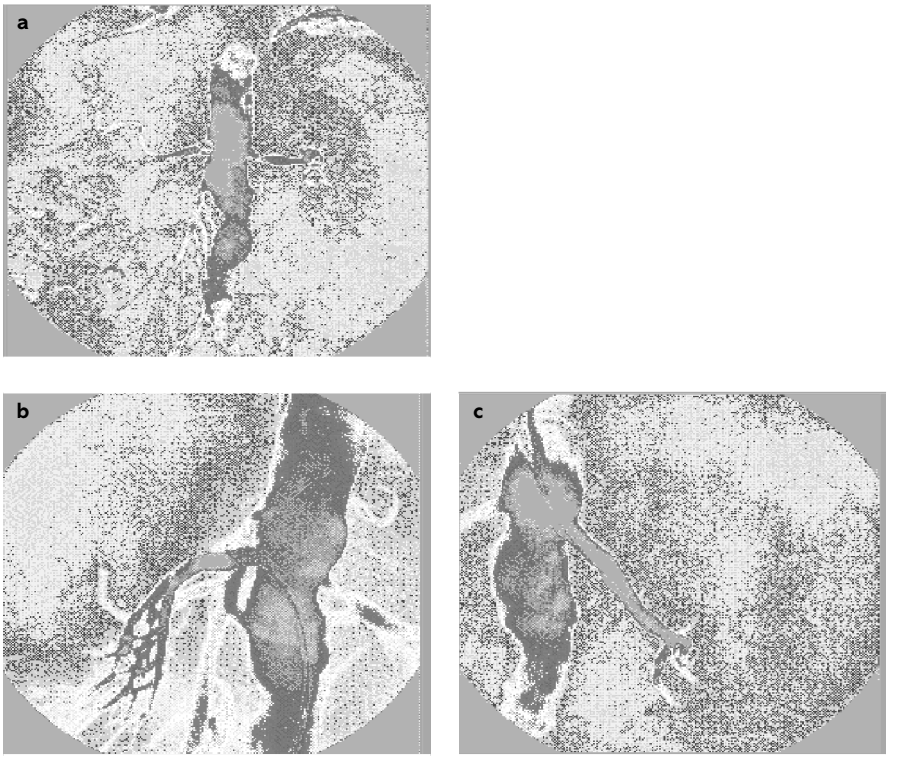

Fig 4. Renal arteriogram showing an atherosclerotic aorta with tight bilateral stenoses in a hypertensive patient who presented with cardiorenal failure and subsequently underwent successful revascularisation: (a) the left renal artery has a tight stenosis approx 1 cm from the origin (the right renal artery is not visible); **(b)** arteriogram showing restoration of flow to the right kidney after placement of a stent; **(c)** successful stenting of the left renal artery. This patient required haemodialysis for three weeks, but recovered renal function after stenting with fall in serum creatinine to 160 μmol/l.

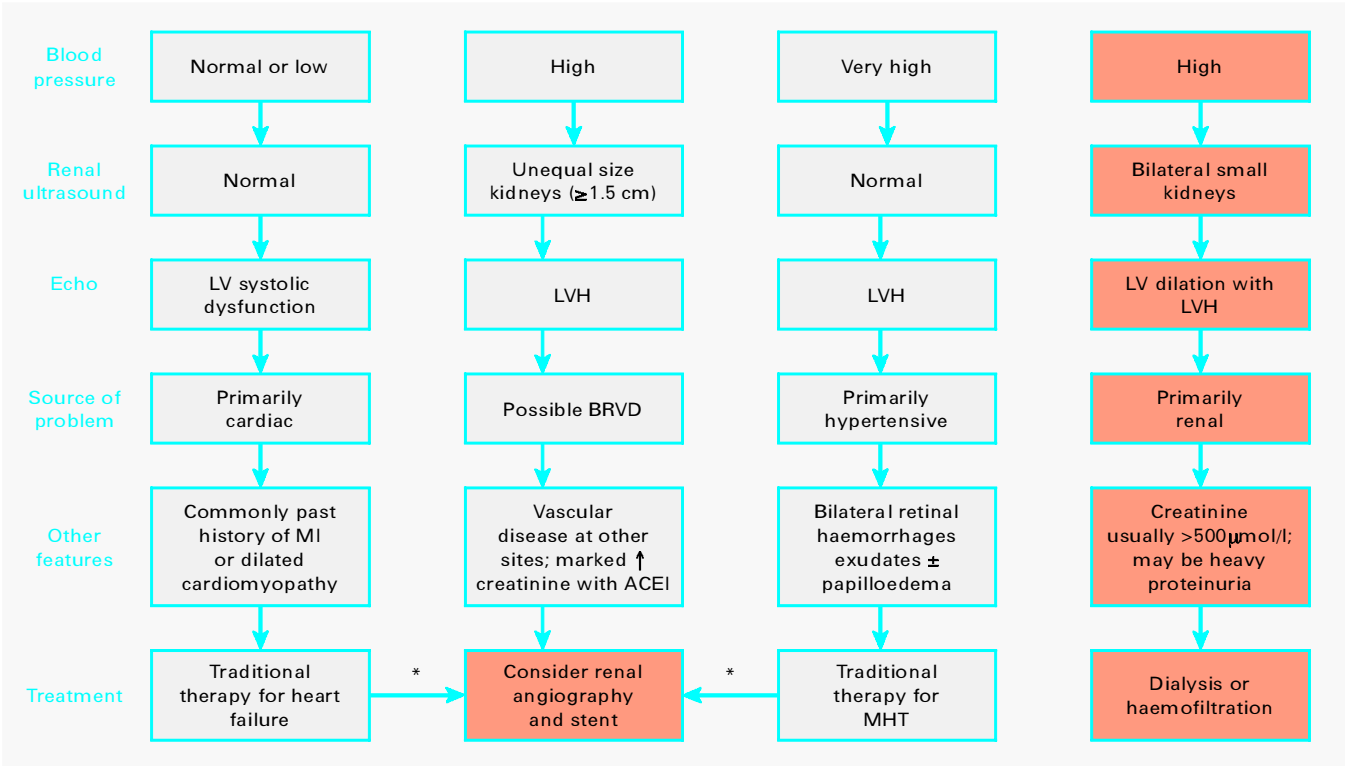

Fig 5. Flow chart showing a diagnostic approach to the evaluation and treatment of cardiorenal failure (pulmonary congestion and serum creatinine greater than 150 µmol/l). *Consider renal angiography if serum creatinine is more than 30% above baseline with an angiotensin-converting enzyme inhibitor (ACEI) at a time when the patient is not hypotensive, volume deplete or taking a non-steroidal anti-inflammatory drug (BRVD = bilateral renovascular disease; LVH = left ventricular hypertrophy; MHT = malignant hypertension; MI = myocardial infarction).

- For many patients with *LV systolic dysfunction*, a high urea and creatinine are an acceptable compromise for the improvement in symptoms and survival achieved with ACE inhibition.
- For those with *BRVD*, the challenge is to identify the subgroup who will benefit from renal revascularisation.
- For patients who present with the *malignant phase of essential hypertension*, tight control of blood pressure offers the best prospect.
- *Dialysis patients with cardiorenal failure* will usually benefit from limiting weight gain between dialysis and re-evaluation of their dry weight.

Acknowledgements

I should like to thank Nicola Johnston for her help with the discussion on echocardiography and Anne Bray for her work on the manuscript.

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Epidemiology of end-stage renal disease

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Clin Med JRCPL 2002;**2**:200–4

Definition

End-stage renal disease (ESRD) is the irreversible deterioration of renal function to an extent that is incompatible with life without renal replacement therapy (RRT), either by dialysis or transplantation. It is the end result of progressive chronic renal failure (CRF) (Table 1). The most valid measure of renal function is the glomerular filtration rate (GFR), but this can be measured only by complex clearance studies (eg inulin). The clearance of the muscle breakdown product creatinine can be used, but at low levels of GFR this overestimates GFR because of tubular secretion of creatinine and extrarenal secretion into the gut. In practice, ESRD is usually taken as a creatinine clearance of below 10 ml/min. Plasma creatinine above 500 μmol/l is a rough guide to ESRD. Several factors influence creatinine production and clearance such as age, sex, weight, ethnic origin and muscle mass.

A lower level of plasma creatinine will be compatible with ESRD in patients with low body weight (eg malnourished or small Indo-Asian women). Simple formulae (eg Cockroft and Gault[1]) use age, sex, weight and plasma creatinine to correct for this and to estimate GFR. These formulae are useful in clinical practice, but most epidemiological studies of CRF/ESRD have relied only on plasma creatinine. In clinical practice, the plot of serial reciprocal measures of plasma creatinine in an individual is a good indication of the rate of decline in GFR.

The epidemiology of ESRD is important as it determines the need for RRT, a complex, costly and lifelong package of care for which demand and provision have grown significantly in the last decade. One year of dialysis costs about £25,000, the first year of transplantation £15,000, with subsequent years over £5,000. It has been estimated that RRT costs consume 1.5–2% of the NHS budget, a figure that is predicted to rise to at least 3%[2].

Sources of information

The incidence of 'diagnosed' CRF in the population has been investigated using raised serum creatinine concentration results from chemical pathology laboratories. This is a specific, though insensitive, marker and is widely used in routine clinical practice. Such population studies of laboratory results are more likely to be representative than nephrology clinic studies where selection factors apply[4], although they exclude a proportion of people with CRF, for example those who are asymptomatic

Table 1. UK Registry definition of end-stage renal disease (ESRD).

A new patient with ESRD is defined as:

- one who is accepted for treatment and transplanted or dialysed for more than 90 days *or*
- one who is diagnosed as ESRD (ie accepted for dialysis in the anticipation that they will need RRT indefinitely), dialysed, and who dies within 90 days *or*
- one who is dialysed initially for ARF but who is subsequently diagnosed as having ESRD
- This excludes patients who were thought to have ESRD and started RRT in the expectation that this would continue indefinitely, but who subsequently recovered within 90 days and were therefore classified in retrospect as having had ARF

ARF = acute renal failure; RRT = renal replacement therapy.