Renal disease and the heart

Robin G Woolfson

Cardiovascular disease is responsible for significant morbidity and mortality in renal failure with increased prevalence of hypertension, left ventricular hypertrophy, ischaemic heart disease and valve disease. Optimum blood pressure control is fundamental to the management of these patients but the role of secondary prevention remains poorly defined.

The prevalence of chronic renal failure (CRF) in the general population and the number of new cases of end-stage renal failure (ESRF) requiring dialysis is increasing each year. This is a result of the aging of the population as well as the high levels of renal disease in an enlarging ethnic minority sub-population. The increased susceptibility of Asians and blacks to renal disease reflects an increased prevalence of hypertension and diabetes mellitus as well as other renal diseases (Clark et al, 1993).

Renal disease is associated with increased cardiovascular morbidity and mortality but most epidemiological data come from registries of dialysis patients rather than studies of patients with CRF. Mortality increases with age and for patients commencing dialysis, data from the USA indicate that the 5-year survival is 30% for those aged 45–64 years and only 18% for those aged 65–74 years (de Lemos and Hillis, 1996). Fifty per cent of these deaths are caused by cardiovascular disease (*Figure 1*) which occurs approximately 150 times more commonly than in age-matched controls (Valderrabano et al, 1995; de Lemos and Hillis, 1996).

HYPERTENSION IN RENAL FAILURE

In CRF caused by glomerulonephritis, diabetes mellitus, polycystic kidney disease, reflux nephropathy or renovascular disease, patients tend to be hypertensive, whereas those with chronic tubulo-interstitial disease or chronic outflow tract obstruction are salt losers and often not hypertensive. Hypertension in CRF is multifactorial and is caused by salt and water retention, increased activity of the renin–angiotensin –aldosterone system, increased sympathetic activity, increased local vasoconstriction (e.g. endothelin, leukotrienes, circulating inhibitors of the sodium pump) and reduced local vasodilatation (e.g. reduced nitric oxide; NO).

Why is hypertension harmful?

The prognostic importance of blood pressure is illustrated by a study in which the survival of haemodialysis patients with mean arterial pressure (MAP) <99 mmHg significantly exceeded those with MAP >99 mmHg at 5, 10 and 15 years (Charra et al, 1992). Raised blood pressure leads to changes in left ventricular (LV) mass and compliance which appear early in the course of renal disease. In patients with glomerulonephritis and normal renal function, mean 24-hour, daytime and nocturnal blood pressure were higher than in control patients

Dr Robin G Woolfson is Consultant Nephrologist in the Department of Renal Medicine, Middlesex Hospital, London W1N 8AA

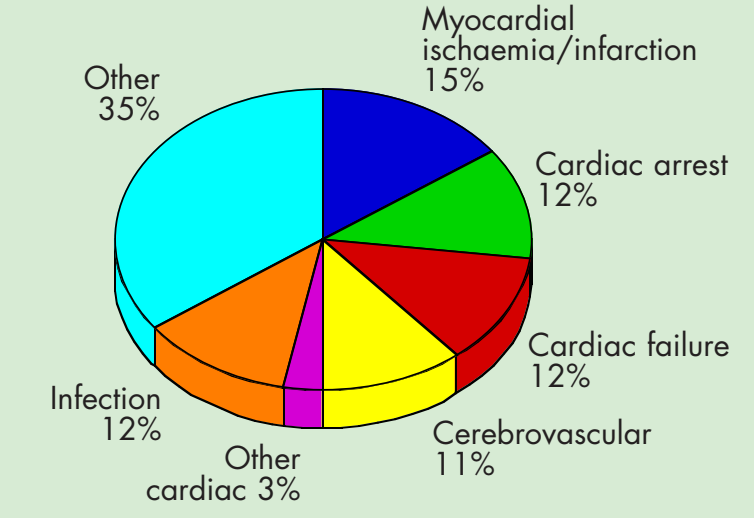

Figure 1. Causes of death in renal replacement therapy patients in 1993 (Valderrabano et al, 1995).

despite equivalent renal function and casual clinic blood pressure measurement of 140/90 mmHg (Stefanski et al, 1996).

Differences in diurnal blood pressure variation presumably underlie the echocardiographic findings of significantly thicker posterior walls and septum and a very much lower ratio of early to late transmitral flow velocity which reflects impaired diastolic relaxation. The loss of nocturnal dip is associated with an adverse cardiovascular outcome and in patients with CRF the percentage decline in nocturnal systolic and diastolic blood pressure correlates inversely with plasma creatinine (Farmer et al, 1997).

In CRF, the importance of blood pressure reduction to preserve renal function is well recognized but the accepted therapeutic goals may not be adequate to minimize cardiovascular risk. The routine use of ambulatory blood pressure monitoring coupled with earlier therapeutic intervention may be the key to further risk reduction.

LEFT VENTRICULAR HYPERTROPHY

LV hypertrophy appears early in the course of CRF and is present in 60–80% of new patients reaching dialysis. There are two morphological patterns: symmetric and eccentric. The symmetric form is closely associated with hypertension, generalized wall thickening and normal cavity dimensions, whereas the eccentric form is accompanied by cavity dilatation. Cardiac myocytes are enlarged with interstitial fibrosis and collagen deposition, reduced numbers of capillaries and widespread myocardial microcalcification. The multifactorial pathogenesis involves uraemia, anaemia, autonomic dysfunction, hyperphosphataemia, iron and aluminium overload, metabolic acidosis, deficiencies of thiamine and carnitine, β2-microglobulin amyloidosis and chronic volume overload caused by arterial venous fistulae, valvular disease and pericardial constriction. A direct cardiotoxic and fibrogenic role has been proposed for parathyroid hormone (PTH).

Reduced ventricular compliance leads to a left shift of the diastolic volume/pressure relation, impaired LV filling and reduced cardiac output (*Figure 2*). Similar changes affect the proximal arterial tree to widen pulse pressure. The combination of low diastolic arterial pressure and increased LV end diastolic pressure reduces diastolic coronary perfusion. These changes lead to poor tolerance of the fluid shifts associated with maintenance haemodialysis and atrial fibrillation, if present.

Anaemia leads to tachycardia, reduced systemic vascular resistance and increased LV volume and is an independent predictor of LV mass index (LVMI). Reversal of anaemia with erythropoietin reduces LVMI, but may compromise outcome, possibly as a result of reduced haemodialysis adequacy because of increased haematocrit or the larger doses of intravenous iron required to maintain the increased haematocrit (Besarab et al, 1998).

LV disease compromises survival in ESRF. In a study of 91 patients, the presence of LVH at the commencement of dialysis increased the risk of mortality by 2.7 (0.9–8.2) (Silberberg et al, 1989). Out of 432 patients who survived more than 6 months of dialysis, initial echocardiographic evidence of LV dilatation, concentric LV hypertrophy or systolic dysfunction was associated with progressively shorter survival (Parfrey et al, 1996) (*Table 1*).

Routine echocardiographic assessment early in the course of CRF may permit interventions to retard or reverse the development of structural LV disease which is associated with an adverse prognosis.

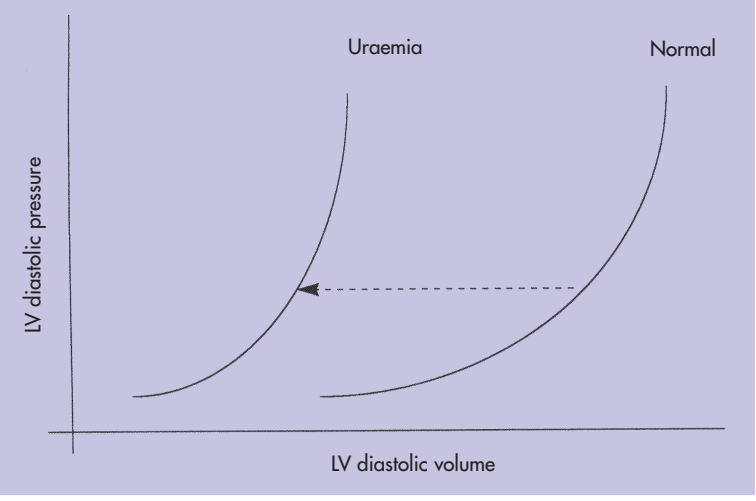

Figure 2. There is left shift of the pressure–volume relationship in uraemia which leads to reduced myocardial compliance. LV = left ventricular.

TABLE 1.
ECHO findings at commencement of dialysis and subsequent survival in 432 end-stage renal failure patients

	ECHO result	Median survival (months)
Systolic dysfunction	16%	38
Concentric LVH	41%	48
LV dilatation	28%	56
Normal ECHO	16%	>66

From Parfrey et al (1996). ECHO = echocardiogram, LV = left ventricular; LVH = left ventricular hypertrophy

ISCHAEMIC HEART DISEASE

Epicardial coronary atheroma affects 24–85% of renal replacement patients, although the relatively low incidence of myocardial infarction (MI) compared with sudden death may be the result of a different time profile of plaque evolution. The multifactorial aetiology of ischaemic heart disease includes hypertension, a high prevalence of diabetes mellitus, smoking, dyslipidaemia, elevated lipoprotein (a), increased oxidative stress, hyperhomocysteinaemia and abnormal endothelial cell function.

Dyslipidaemia

Type IV hyperlipidaemia with raised triglycerides and normal total cholesterol appears early in CRF. The triglyceride/cholesterol ratio is reduced in very low density lipoprotein but increased in intermediate density lipoprotein, low density lipoprotein (LDL) and high density lipoprotein which reflects diminished activity of lipoprotein lipase, lecithin cholesterol acyltransferase and hepatic triglyceride lipase. Disordered lipoprotein metabolism secondary to renal failure, underlying renal disease and drugs leads to reduced levels of apoprotein A and increased levels of apoprotein B and C. The morphology of cholesterol particles is skewed towards increased small dense LDL which is more susceptible to oxidation and more atherogenic. Lipoprotein (a) levels are increased in CRF.

Hyperhomocysteinaemia

Homocysteine is formed by the metabolism of methionine from dietary protein and raised levels are an independent risk factor for ischaemic heart disease, peripheral vascular disease and cerebrovascular disease. Thirty per cent of plasma homocysteine is not protein bound and is filtered by the glomerulus and metabolized by tubular epithelial cells. In CRF, homocysteine levels are elevated because of reduced renal metabolism and low levels of folate, vitamin B_{12} and vitamin B_6, and hyperhomocysteinaemia is associated with vascular disease in ESRF (Bostom and Lathrop, 1997). Although homocysteine levels drop with high-dose folate supplements, as yet there is no evidence of clinical benefit.

Increased oxidative stress

Oxidative stress is increased in renal failure, particularly in patients undergoing haemodialysis. Oxidation of LDL and lipoprotein (a) and formation of advanced glycosylation end-products promote atherogenesis. Acute and chronic vitamin C supplementation improves endothelial function in patients with hypercholesterolaemia, diabetes mellitus and heart failure, but there are no data regarding benefits of antioxidant therapy in patients with CRF.

Abnormal endothelial function

Endothelium-derived NO released in response to luminal flow not only vasodilates underlying vascular smooth muscle but also inhibits its proliferation, regulates endothelial cell permeability and prevents interactions between endothelial cells and circulating neutrophils and platelets. Impaired flow-mediated vasodilatation is seen in atherogenic conditions such as diabetes mellitus and hyperlipidaemia, and is also present in renal failure (*Figure 3*).

Diagnosis of coronary artery disease

The investigation of coronary artery disease has generally been restricted to dialysis patients awaiting transplantation, but these are a diminishing proportion of the patients at risk and an effective non-invasive screening test for the remainder would be very welcome. Although thallium scans may usefully predict subsequent fatal cardiac events in dialysis patients, when compared with coronary angiography, sensitivity and specificity is poor for either the identification of significant coronary stenoses or predicting the future development of unstable angina or MI (Marwick et al, 1990; Vandenberg et al, 1996) (*Table 2*). Recent reports suggest more diagnostic success with dobutamine stress echocardiography but this technique is not routinely available.

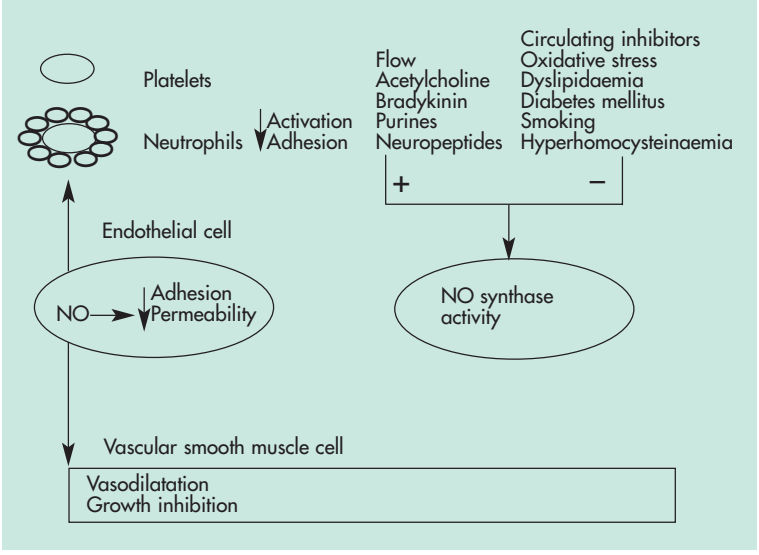

Figure 3. Putative mechanisms and consequences of defects in the endothelium-derived nitric oxide (NO) pathway in uraemia.

Acute MI

The risk of MI can be predicted from the severity of coronary stenoses on angiography as can the incidence of amputation or stroke which reflects the systemic burden of atherosclerosis (Manske et al, 1997). Fifty-three per cent of all MIs occur within 2 years of starting dialysis, and acute infarction in dialysis patients has a 33–47% in-hospital mortality, with 59% of all patients dying within 12 months and 73% within 24 months (Herzog, 1997). There are no data regarding thrombolysis, angioplasty, coronary stenting, β-blockade or angiotensin-converting enzyme inhibition in ESRF patients following acute MI. The optimum timing of haemodialysis following acute MI is not known.

Coronary revascularization

The in-hospital mortality in ESRF patients who undergo coronary artery bypass grafting (CABG) is 0–15%, with mortality at 2 years of 34–49%. Similarly, percutaneous transluminal coronary angioplasty (PTCA) is associated with an in-hospital mortality of 0–9% and 2-year mortality of 47–53%. However, the respective recurrence rates for angina or MI are very different following PTCA or CABG. In one study (Rinehart et al, 1995), recurrent angina, MI or death within 6 months was 3 times more common following PTCA than CABG and in a review of over 12 000 patients, the annual risk of MI was 6% following CABG compared to 40% following PTCA (Collins et al, 1996). Data on coronary stenting in ESRF are keenly awaited.

Management of coronary artery disease

Medical treatment of ischaemic heart disease in ESRF patients should start with control of hypertension, attainment of dry weight and maintenance of haematocrit at 35%. The role of secondary prevention remains unproved.

TABLE 2.
Sensitivity and specificity of cardiac scintigraphy in 47 diabetic end-stage renal failure patients who had previously undergone coronary angiography

		Angiographic stenosis > 50%	> 75%
Stress thallium	Sensitivity	53%	62%
	Specificity	73%	76%
Exercise radionuclide scintigraphy	Sensitivity	44%	50%
	Specificity	63%	67%
Incidence of unstable angina or myocardial infarction (mean follow-up 25±18 months)		Isotope scans	
		Positive	Negative
Stress thallium		2/11	4/22
Exercise radionuclide scintigraphy		2/10	3/20

From Vandenberg et al (1996)

CALCIFIC VALVE DISEASE

Cardiac valve calcification is common in dialysis patients with the aortic valve affected in 28–55%, although only 3–13% have significant aortic stenosis (Raine, 1994). In contrast to non-uraemic patients, the aortic valve tends to be tricuspid rather than bicuspid, although 20% of polycystic kidney disease patients have bicuspid valves. Mitral calcification is slightly less common and mitral stenosis is very rare. Calcified valves are at increased risk of infective endocarditis and deposits may embolise into the coronary circulation. Calcific valve disease is associated with conduction defects which may contribute to the high rate of sudden death in dialysis patients.

Risk factors for aortic stenosis include duration of dialysis, raised calcium phosphate product, raised alkaline phosphatase and raised PTH. Phosphate should be maintained <1.8 mmol/litre with calcium phosphate product <4.5. PTH levels have been implicated in accelerated stenotic disease and parathyroidectomy should be timely. Patients must be examined regularly and serial Doppler echocardiography performed in those with evidence of a pressure gradient, since gradient increases of 10 mmHg per month have been reported. Co-incident myocardial dysfunction can obscure the clinical signs, and in these patients the diagnosis of aortic stenosis must be actively excluded.

The overall mortality of elective valve replacement may be up to 15%. ESRF patients are at increased risk of postoperative haemorrhage, ischaemia, infections and gastrointestinal complications.

RENOVASCULAR DISEASE

The varied clinical presentation of renovascular disease includes hypertension, flash pulmonary oedema, acute renal failure following angiotensin-converting enzyme inhibition or progressive CRF, and demands a high index of suspicion. Stenoses exceeding 50% are present in 42% of patients with peripheral vascular disease (Choudhri et al, 1990), 15% of patients with ischaemic heart disease (Harding et al, 1992) and 30% of elderly patients presenting with congestive cardiac failure (MacDowall et al, 1998). In atherosclerotic disease, CRF is caused primarily by renal atheroemboli from unstable plaques rather than haemodynamic compromise.

The diagnosis of renovascular disease remains problematic. Ultrasound (with Doppler angiography) can be used as a screening test to detect reduced renal size or asymmetry. Captopril renography requires adequate renal function but this investigation may precipitate acute irreversible renal failure in patients with critical atherosclerotic disease. Variations in reported sensitivity and specificity of captopril renography emphasize the importance of standard investigation protocols and the avoidance of hypovolaemia.

Renovascular hypertension secondary to fibromuscular dysplasia, and associated with a positive captopril renogram, can be cured by angioplasty but this is not the case in atherosclerotic disease. Despite early enthusiasm, improvement in renal function occurs in a minority of patients, with no improvement or even deterioration in the remainder, reflecting the underlying pathology. Optimum treatment is not defined but hypertension should be controlled, plaque stabilization and cholesterol-lowering with statin therapy may be helpful (Woolfson and Lachmann, 1998) and anticoagulation with heparin or warfarin is contraindicated. Patients with atherosclerotic renovascular disease who reach dialysis have a poor prognosis (50% mortality at 24 months), which reflects their heavy total ischaemic burden.

CONCLUSIONS

The numbers of patients with CRF and ESRF is increasing progressively and this trend is set to continue. Despite the massive increase in risk of cardiovascular disease in uraemia, little is known about the optimum management of common cardiological problems such as unstable angina, acute MI, heart failure or even the role of secondary prevention. More aggressive blood pressure control coupled with the routine use of ambulatory blood pressure monitoring may prevent the development of LV pathology which appears to be central to the poor outcome of this patient group. HM

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KEY POINTS

- The prevalence of renal failure with its associated cardiovascular risk is increasing.
- Loss of the nocturnal dip in blood pressure can occur early in renal disease and is associated with left ventricular hypertrophy.
- Blood pressure goals required to minimize cardiovascular risk in renal failure patients are not defined.
- Fifty per cent of dialysis patients die from cardiovascular disease, with duration of survival predicted by left ventricular pathology.
- The optimum management of routine cardiological problems, including secondary prevention of coronary artery disease, which occur in dialysis patients is not known.
- Poor control of hyperphosphataemia and secondary hyperparathyroidism contributes to myocardial and valvular heart disease.