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Uraemic Cardiomyopathy: an Overload Cardiomyopathy

C. Rigatto, P. S. Parfrey

Despite myriad technological improvements, survival on dialysis remains worse than that for many cancer patients. The leading cause of death is cardiovascular, and disorders of LV structure and function (commonly termed uraemic cardiomyopathy) appear to be the most important arbiters of patient life span. Although some of the cardiac risk factors in renal patients are shared with the general population, others are unique to the uraemic state. Prospective cohort studies have shown that chronic anaemia and hypertension are independently linked to LV morphology and survival, but the role of many other uraemia-related cardiovascular risk factors remains unclear. Rigorous, prospective cohort studies are required to unravel the influences of homocysteine, oxidative stress, chronic inflammation and secondary hyperparathyroidism on cardiac outcomes in end stage renal disease. Since many of these risk factors begin well before the patients start dialysis and appear to be modified following renal transplantation, quality studies in both the chronic renal failure and the renal transplant populations are needed. *J Clin Basic Cardiol* 2001; 4: 93–95.

Key words: renal failure, LVH, anaemia, hypertension

The survival of patients on dialysis is severely foreshortened compared with individuals in the general population. Among males over 65 years of age, five-year survival on dialysis is only 20 %, lower than for colon and prostate cancer. Among females in the same age group, survival on dialysis is worse than for breast and colon cancer. The leading cause of death among dialysis patients is cardiac disease, which accounts for 49 % of all mortality, a proportion greater than that in the general population [1].

Cardiac disease in dialysis patients is due to disorders of perfusion (ischaemic disease) or to disorders of structure and function (collectively termed “uraemic cardiomyopathy”). These two processes are closely interrelated. Ischaemia can cause myocyte death, resulting in structural and functional changes due to ventricular remodeling and loss of contractility. Conversely, cardiomyopathy can exacerbate perfusion abnormalities because of changes in systemic haemodynamics (eg, blood pressure, aortic and arterial impedance, wall stress, and LV end-diastolic pressure) and in the microcirculation of the heart [2, 3].

Symptomatic ischaemic heart disease is present in 35 % of patients beginning dialysis. 31 % of patients starting dialysis have a history of congestive heart failure (CHF), while 22 % have a history of ischaemic heart disease (IHD) [4]. Although both IHD and CHF predict adverse outcome, the impact of ischaemic heart disease on mortality is weaker and is not independent of CHF, suggesting that left ventricular (LV) structure and function are the key determinants of survival [5]. In this paradigm, the impact of IHD is mediated through changes in LV function (Table 1), highlighting the importance of cardiomyopathy in dialysis patients.

Table 1. Impact of CHF on survival in dialysis

Variable	Relative risk of death	p
Age per year	1.03	<0.001
Diabetes	2.00	<0.001
CHF	1.93	<0.001
IHD	–	NS

Risk Factors for Uraemic Cardiomyopathy

Potential risk factors for cardiomyopathy in uraemic individuals are summarized in Table 2. Many are identical to those for coronary artery disease and may well exert their adverse impact via ischaemia.

Traditional risk factors such as hypertension, diabetes and LV hypertrophy are more frequent in the chronic renal failure population and account for a portion of the increased cardiovascular risk. In addition, several haemodynamic and metabolic derangements characteristic of dialysis patients may play a role in the genesis of cardiac hypertrophy and dysfunction. Anaemia is present in the majority of patients despite treatment with erythropoietin, and constitutes a chronic flow overload state. Arteriovenous fistulae are commonly created for vascular access in haemodialysis patients and contribute to the flow overload. Homocysteine levels are elevated in the majority of dialysis patients and may be an independent risk factor for cardiac disease [6]. Secondary hyperparathyroidism is an expected complication of renal failure; parathyroid hormone excess is potentially cardiotoxic [7, 8]. Hypoalbuminaemia has been linked to mortality and to *de novo* development of heart failure and ischaemic heart disease in a large cohort study [9]. Although the underlying mechanism remains unclear, low albumin may be a marker for malnutri-

Table 2. Cardiac risk factors in uraemia

Category	Risk factor
Traditional	Smoking Hypertension Dyslipidaemia Diabetes LV hypertrophy
Uraemic Haemodynamic	Anaemia AV fistula Volume overload
Metabolic	Hypoalbuminaemia Hyperhomocysteinaemia Oxidative stress Chronic inflammation 2° Hyperparathyroidism

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tion, vitamin deficiency, thrombotic tendencies, inadequate dialysis, or chronic inflammation.

The relative importance of traditional vs uraemic risk factors remains controversial. In the majority of cases, studies implicating a particular risk factor have been either small, retrospective, or have not been adjusted for the presence of other risk factors. These methodological shortcomings have frequently led to conflicting results. A case in point is the ongoing controversy about whether hypertension is an adverse cardiac risk factor in dialysis patients. Cross-sectional and prospective studies in prevalent dialysis patients have shown an inverse association between mortality and blood pressure, with hypertension predicting longer survival [10]. As will be discussed below, most patients in these studies had significant LV abnormalities at baseline. Since LV dysfunction is strongly associated with both low blood pressure and mortality, it is likely that the results of these studies were confounded by reverse-causality, leading to the observation of a non-causal association between blood pressure and death. Only studies which adequately account for the prevalence of baseline cardiac disease at the start of dialysis and which prospectively follow the progression of LV structural changes over time can determine the role of cardiac risk factors in an unbiased manner.

Cardiac Structure

The prevalence of risk factors for and consequences of cardiac structural abnormalities have been studied in a large cohort of patients starting dialysis in Canada [4]. Extensive baseline and yearly follow-up data were collected. Serial echocardiograms were obtained annually over a median follow-up period of 48 months. Concentric LV hypertrophy (LVH), eccentric LVH (LV dilatation, LVD) or systolic dysfunction were present in 84 % of patients and conferred a three-fold increase in risk for the subsequent development of heart failure (Table 3). This effect was independent of age, gender, diabetes and IHD. The associations between risk factors and cardiac structure are summarized in Figure 1. The risk factors shown were derived from multivariate analysis and are

Table 3. Cardiac structural abnormalities at initiation of dialysis

Findings on Echo	Prevalence	Adjusted RR of CHF	p
Concentric LVH	41 %	3.0	<0.001
LV dilatation	28 %	2.7	0.002
Systolic dysfunction	16 %	3.6	<0.001
Normal	16 %	—	—

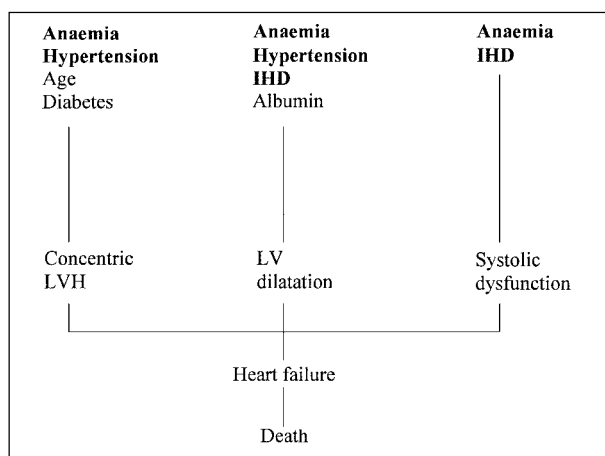


Figure 1. Factors associated with the presence of cardiomyopathy in dialysis patients

independent of each other and of other determinants of cardiac disease. Anaemia, hypertension, and IHD appear to be the key independent predictors of cardiac structural abnormalities, which in turn predict CHF and death. These results have recently been corroborated in two distinct settings. In a prospective cohort study of patients with early chronic renal failure, Levin et al. have shown that anaemia and hypertension independently predict increasing LV mass [11]. Similarly, Parfrey et al. [12] and Rigatto et al. [13] have shown that improvement in hypertension following renal transplantation is associated with partial regression of LVH.

Based on the data summarized above, a pathophysiological model for the development of cardiomyopathy in uraemia can be proposed (Figure 2). In this model, the principal abnormalities are LV pressure overload, determined largely by blood pressure and arterial impedance, and LV flow overload, determined principally by anaemia, salt and water overload and AV fistula creation. Although initially adaptive, in the presence of chronic and uncontrolled pressure and flow overload (ie, persistent anaemia and hypertension), the hypertrophy becomes maladaptive, resulting in myocyte loss, systolic dysfunction, CHF and death. Ischaemia exacerbates these changes by promoting myocyte loss, as may many of the characteristic metabolic derangements of uraemia, depicted here in a modulatory role. It is worth emphasizing that this scheme is provisional, based on the best evidence from large prospective studies.

Future Research Directions

Research into heart disease in patients with renal failure is still in its infancy, and much remains to be done. The role of risk factors such as homocysteine, oxidative stress, chronic inflammation, and secondary hyperparathyroidism urgently needs to be investigated in large, prospective and methodologically rigorous studies.

Most of the literature on cardiac disease in renal failure concerns dialysis patients. It has now become clear that most

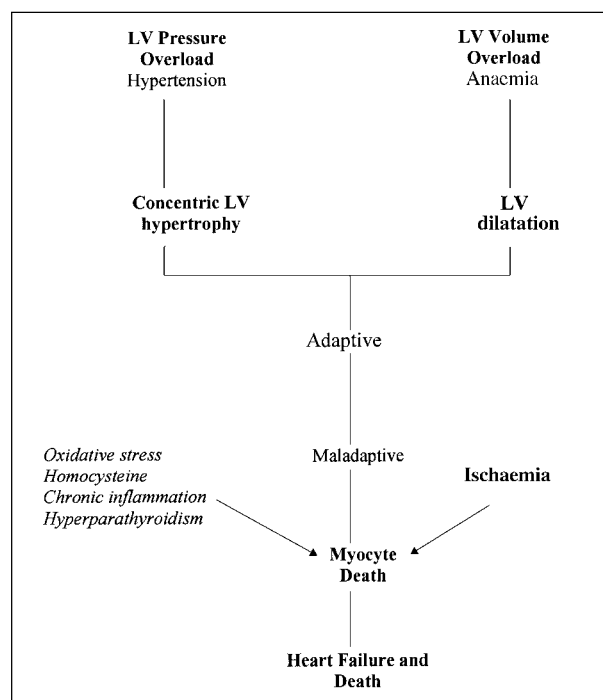


Figure 2. Pathogenesis of uraemic cardiomyopathy

of the risk factors associated with cardiomyopathy begin well before the start of dialysis and worsen as renal function worsens (eg, hypertension, anaemia). Studies of cardiac disease in chronic renal failure (CRF) remain few, however. From a methodological viewpoint, renal cohorts assembled during mild to moderate chronic renal failure (CRF) permit risk factors to be measured before onset of cardiac disease. Such cohorts are less susceptible to confounding by reverse causality, a recognized problem afflicting many cross-sectional and prospective studies in dialysis patients [10]. Because of this, studies of cardiac risk in pre-dialysis patients can more reliably establish causal relationships. A recent cohort study in this population has demonstrated the importance of anaemia and hypertension as independent risk factors for LV growth in the pre-dialysis period [11]. Further studies must be done in this population to clarify the role of other risk factors.

Renal transplantation is a phase of renal disease which has a unique cardiac risk profile and is associated with partial regression of LVH. The link between this altered risk profile and subsequent cardiac events has not been definitively studied. Our group is presently compiling a large, detailed database of 1100 renal transplant patients followed prospectively over a median period of 9 years. We hope this study will lead to a deeper understanding of the causes of cardiovascular disease in this unique population.

Conclusion

Cardiomyopathy is frequent among patients beginning dialysis and is a strong independent predictor of CHF and death. The key reversible risk factors for cardiomyopathy appear to be chronic anaemia and hypertension, and these disturbances are prime targets for intervention. Future research must clarify the role of other metabolic and haemodynamic derangements in the development of uraemic cardiomyopathy.

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