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Outcome and risk factors for left ventricular disorders in chronic uraemia

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Abstract

Background. Left ventricular disease occurs frequently in dialysis patients. It may be manifest as concentric LV hypertrophy, LV dilatation with or without LV hypertrophy, or systolic dysfunction. Little is known concerning the clinical outcome and risk factors for these disorders.

Methods. A cohort of 432 end-stage renal disease patients who survived at least 6 months had an echocardiogram on initiation of dialysis therapy. Clinical, laboratory and echocardiographic data was obtained annually during follow-up.

Results. On initiation of ESRD therapy 16% of patients had systolic dysfunction, 41% concentric LV hypertrophy, 28% LV dilatation, and only 16% had normal echocardiograms. Median time to development of heart failure was 19 months in patients with systolic dysfunction, 38 months in concentric LV hypertrophy and 38 months in LV dilatation. The relative risks of heart failure in the three groups were significantly worse than in the normal group, after adjusting for age, diabetes and ischaemic heart disease. Median survival was 38 months in systolic dysfunction, 48 months in concentric hypertrophy, 56 months in LV dilatation, and >66 months in the normal group.

Two hundred and seventy-five patients had a follow-up echocardiogram 17 months after starting dialysis therapy together with serial measurement of potential risk factors prior to the echocardiogram. On follow-up echocardiogram the degree of concentric LV hypertrophy was independently related to hypertension while on dialysis, older age, and anaemia while on dialysis; the degree of LV dilatation was related to ischaemic heart disease, anaemia, hypertension and hypoalbuminemia while on dialysis; the degree of systolic dysfunction was associated with ischaemic heart disease and anaemia during follow-up.

Conclusions. Manifestations of left ventricular disease are frequent and persistent in chronic uraemia, and are associated with high risks of heart failure and death. Potentially reversible risk factors include anaemia, hypertension, hypoalbuminaemia and ischaemic heart disease.

Key words: left ventricular disease; chronic uraemia; heart failure; anaemia; hypertension; hypoalbuminaemia; ischaemic heart disease

Introduction

Cardiac disease is the major cause of mortality in dialysis patients, accounting for about 40% of deaths in most large registries [1,2]. The prevalence of congestive heart failure, myocardial infarction, and angina is high on initiation of ESRD therapy [3,4], as is their incidence during dialysis therapy [5]. Morbidity and mortality from cardiac disease in chronic uraemia usually result from cardiomyopathy and/or ischaemic heart disease [6]. Cardiomyopathy may be manifest as (a) concentric left ventricular (LV) hypertrophy which results from LV pressure overload, (b) LV dilatation which results from LV volume overload, or (c) systolic dysfunction, a reflection of diminished myocardial contractility. On echocardiogram concentric LV hypertrophy is diagnosed by the presence of high LV mass index with normal LV volume and normal LV contractility, LV dilatation by high LV volume with normal contractility, and systolic dysfunction by low fractional shortening of the left ventricle. All these disorders are frequently observed in dialysis patients [7] and together with indices of LV geometry, are independent adverse predictors of mortality [4,7]. The echocardiographic and clinical outcome of left ventricular disease in chronic uraemia have received little attention. Previous studies have been affected by small sample size and weak study design [8,9].

In chronic uraemia there are multiple predisposing factors to left ventricular disease. High blood pressure predisposes to LV hypertrophy [10]. Anaemia, blood volume overload, and arteriovenous fistulae are associ-

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ated with LV dilatation [11]. In addition, diabetes mellitus, ischaemic heart disease, malnutrition and hyperparathyroidism also predispose to cardiomyopathy in non-renal patients [12–16] and occur frequently in chronic uraemia. The uraemic environment itself is probably pathogenic [17]. The relative contribution of these potential adverse cardiac risk factors to the various left ventricular disorders in chronic uraemia is unclear, particularly as no prospective studies, with serial measurement of risk factors, have been undertaken.

From the initiation of end-stage renal disease therapy we have prospectively followed a cohort of 432 end-stage renal disease patients who survived at least 6 months and had an echocardiogram in the first year of therapy [4,7,18]. Serial echocardiograms were performed at annual intervals, together with clinical assessment and collection of laboratory data. In this paper we report on the echocardiographic and clinical outcome of dialysis patients with (a) concentric LVH, (b) LV dilatation, and (c) systolic dysfunction, together with multivariate analyses of the relationships between these conditions and the following risk factors: age, gender, diabetes mellitus, high blood pressure, anaemia, hypoalbuminaemia, weight gains between haemodialysis sessions, and ischaemic heart disease. As the cohort started in 1982, data on adequacy of dialysis, fistula flow rates, and degree of blood volume expansion are not available.

Subjects and methods

Patients

This prospective cohort study was started in the Royal Victoria Hospital Montreal, Quebec in 1982, in the Health Sciences Centre, St John's, Newfoundland in 1984, and in the Grace Hospital, St John's, Newfoundland in 1985. End-stage renal disease patients were eligible for entry to the study if (a) they survived for 6 months and (b) if they had a technically satisfactory echocardiogram within a year of starting renal replacement therapy. Patient recruitment finished in June 1991.

Of 518 patients who survived at least 6 months from the start of ESRD therapy, a cohort of 432 (84% of those eligible) had a echocardiogram performed within 1 year of starting dialysis and consequently entered the study. Eighty-five patients were excluded for the following reasons: failure to obtain a technically adequate echocardiogram within 1 year of starting therapy (71 patients), started therapy elsewhere (7 patients), charts mislaid (5 patients), refusal to participate (2 patients). Two hundred and sixty patients were maintained predominantly on haemodialysis and 171 on peritoneal dialysis. One patient was treated only with renal transplantation.

Patients were treated in university medical centres. The quantity of dialysis delivered was not measured. The mean transfusion rate was 5.2 ± 7.5 transfusions per year. Erythropoietin became available to study patients in 1989; 26% of patients received erythropoietin at some time while on dialysis and 12% received erythropoietin for more than 50% of their time on dialysis. Patients received 1.2 ± 2.1 antihypertensive medications, with calcium-channel blockers (3147 patient months) being the most frequently prescribed, followed by beta blockers (2707 patient months), angiotensin-converting enzyme inhibitors (1546 patient months), vasodilators (1457 patient months), and centrally acting agents (520 patient months). Clinical and echocardiographic details related to the original cohort entered in this study can be obtained from references 4 and 7.

Data collection

At baseline, and at yearly intervals thereafter, a clinical assessment was undertaken to detect the presence of cardiovascular disease. At monthly intervals the data collected included blood pressure, haemoglobin, serum creatinine, albumin, and calcium levels, and interdialytic weight gains. Blood pressure and blood tests were carried out immediately prior to dialysis in haemodialysis patients. Blood pressure was measured in the contralateral arm in patients with patent arteriovenous fistulae or grafts. For each subject, clinical and laboratory values were recorded as baseline values, and the mean of the monthly values while on dialysis, up to the time of the second echocardiogram or the relevant clinical outcome.

Baseline and annual echocardiography were performed using M-mode and 2-dimensional ultrasonography. Baseline echocardiography was performed 3.3 ± 3.9 (SD) months from the time of starting dialysis, and the second echocardiogram was performed 17.6 ± 10.2 months from the time of starting dialysis. Two hundred and ninety-eight patients continued on dialysis after 1 year, the remainder of the cohort having died or received renal transplantation; 275 patients had a second echocardiogram while on dialysis therapy. Complete data from both echocardiograms were available in 245 patients, from which LV mass index, LV volume, and fractional shortening could be calculated. Figure 1 shows the source of patients at various phases of the study. The subset of patients who had at least two serial echocardiograms was very similar to the study population; mean age 51 versus 54 years; proportion males, 63 versus 64%; proportion with diabetes mellitus 27 versus 26%; proportion who had myocardial infarction before starting ESRD therapy, 12 versus 14%; proportion with angina pectoria on starting ESRD therapy, 19 versus 21%; and proportion with heart failure 31 versus 33%.

In 39% of echocardiograms left ventricular mass index was calculated using the regression-corrected American Society of echocardiography cubic formula, and in 61% the formula of Devereux and Reichek, depending on whether

	Patients	
Population	518	Survived at least 6 months in 3 hospitals
	↓	
Original Cohort	432	Echocardiogram performed within first year of starting dialysis
	↓	
	298	Survived >1 year on dialysis and were not transplanted
	↓	
Follow-up Cohort	275	Had at least 2 echocardiograms performed
	↓	
	245	All data available on 2 echocardiograms permitting calculation of LV mass index, LV volume and fractional shortening

Fig. 1. Source of patients at various phases of the study.

the endocardium was included in the measurement of ventricular wall thickness. Both methods give very similar results and are closely correlated with true ventricular mass assessed at autopsy [19]. Similarly, left ventricular cavity dimensions estimated by the Penn convention were regression corrected and presented according to the recommendations of the American Society of Echocardiography [20]. Left ventricular volume was calculated using the formula of Pombo *et al.* [21]. Both left ventricular mass and left ventricular volume were indexed to body surface area, presented in g/m^2 and ml/m^2 respectively.

Definitions

The following definitions were used.

Coronary artery disease. History of myocardial infarction, coronary artery bypass surgery or percutaneous transluminal angioplasty.

Angina pectoris. Precordial chest pain, precipitated by exertion or stress, relieved by rest or nitrates.

Ischaemic heart disease. Coronary artery disease or angina pectoris.

Cardiac failure. An episode of dyspnoea plus two of the following signs: raised jugular venous pressure, bibasilar crackles, pulmonary venous hypertension or interstitial oedema on chest X-ray.

It is possible that excess salt and water could contribute to cardiac failure. However, it should be remembered that the hydrostatic pressure gradient in the pulmonary capillary bed does not favour efflux of fluid, in comparison to the systemic capillary bed, unless there is pre-existing elevation in pulmonary venous pressure.

Cardiovascular death. Death from myocardial infarction, other cardiac cause, vascular causes, or sudden death.

LV hypertrophy by mass index. Mass $>100\ g/m^2$ in females, and mass $>131\ g/m^2$ in males. These values are the upper limits of normality among health participants in the Framingham Heart Study [22].

Left ventricular dilatation. Volume $>90\ ml/m^2$ [21].

Concentric LV hypertrophy. LV hypertrophy with normal LV volume and fractional shortening.

Systolic dysfunction. Fractional shortening $\leqslant 25\%$ on echocardiography.

Normal echocardiogram. Normal LV mass, volume and fractional shortening.

Mode of dialysis therapy. 50% of dialysis time on either haemo or peritoneal dialysis.

Analysis

Patient follow-up started with the first dialysis treatment. The primary morbidity outcome was time to first episode of heart failure. The other major outcome measure was time to death on dialysis therapy. Overall mortality and mortality after 2 years on dialysis were examined. Patients were censored at the time of renal transplantation or at final follow-up. The mean (standard deviation) duration of total follow-up was 41.1 (25.7) months.

Univariate survival analysis was carried out using the product-limit method. All statistical tests are two-tailed, with a P value of less than 0.05 taken to indicate statistical significance. The independent power of different variables to predict early heart failure or death was assessed using Cox's Proportional Hazards models, using the maximum partial likelihood method to direct stepping. Significant differences between groups was obtained using the Mantel test. Stepwise logistic regression was used to identify the independent associations of the different left ventricular disorders, and stepwise linear regression to identify predictors of LV mass index, LV volume and fractional shortening. Multivariate analyses were carried out with BMDP software [23]. Potential predictors of disease on follow-up echocardiogram analysed were age, gender, diabetes, ischaemic heart disease up to second echocardiogram, mean of haemoglobin, blood pressure, serum albumin obtained at monthly intervals from start of ESRD therapy to second echocardiogram. The numbers of patients in each analysis will vary depending on whether all the data is available to characterize the patient from an echocardiographic and a risk factor perspective.

Results

On initiation of end-stage renal disease therapy 41% ($n=168$) had concentric LV hypertrophy, 28% ($n=117$) had LV dilatation, 16% ($n=64$) had systolic dysfunction, and 16% ($n=64$) had normal echocardiogram (Figure 2). At baseline the subset who had serial echocardiograms were very similar to the original cohort, from an echocardiographic perspective: 40% had concentric LV hypertrophy, 28% LV dilatation and 19% had systolic dysfunction.

Concentric LV hypertrophy

Echocardiographic outcome (Table 1). Of 98 patients who had concentric LV hypertrophy on initiation of dialysis and had a follow-up echocardiogram, 59% patients continued to have concentric LVH on second echocardiogram, 21% had LV dilatation, 11% had normalized, and 8% developed systolic dysfunction.

Clinical outcome. The median time to development of heart failure was 38 months in patients with concentric LVH, a substantially worse outcome than in those with normal echocardiogram ($P<0.001$) (Figure 3). The relative risk of developing heart failure, independent of age, gender, diabetes, and ischaemic heart disease, was 3.0 ($P<0.001$).

The median survival was 48 months in patients with concentric LVH, compared to >66 months in those

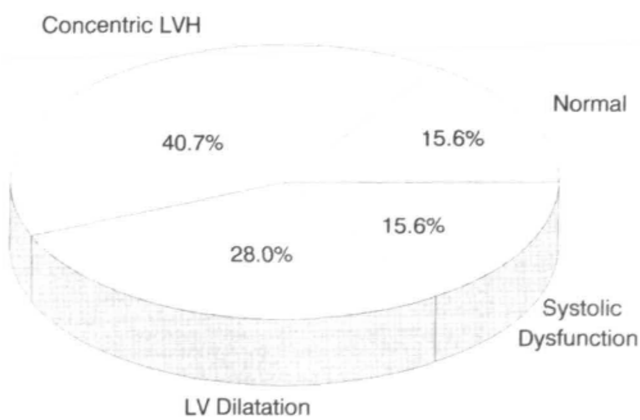

Fig. 2. Prevalence of left ventricular disorders, identified by echocardiography, on starting end-stage renal disease therapy.

Table 1. Echocardiographic diagnoses on initial and second echocardiograms. Each row reveals the echocardiographic outcome for each disorder observed on the initial echocardiogram

		Second Echo: Normal		Concentric LVH		Dilated LV		Systolic dysfunction	
		n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Initial Echo	Normal $n=30$	14	(48)	10	(32)	5	(16)	1	(3)
	Concentric LVH $n=98$	11	(11)	58	(59)	21	(21)	8	(8)
	Dilated LV $n=69$	5	(7)	20	(29)	29	(42)	15	(22)
	Systolic dysfunction $n=47$	2	(4)	11	(23)	9	(19)	25	(53)
	Total $n=245$	32	(13)	99	(40)	64	(26)	49	(20)

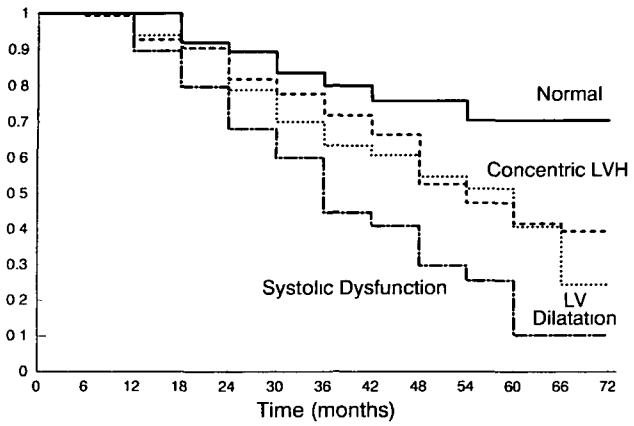

Fig. 3. Time to development of first episode of heart failure, following the initiation of dialysis therapy, in patients with normal echocardiogram, concentric LV hypertrophy, LV dilatation, and systolic dysfunction.

with normal echocardiogram (P=NS) (Figure 4). The proportion of deaths attributed to cardiovascular disease in the concentric LVH group was 63% (37/59), compared to 50% (6/12) in the normal group.

Risk factors. In patients with concentric LVH on follow-up echocardiogram clinical and laboratory data obtained during follow-up were compared to those

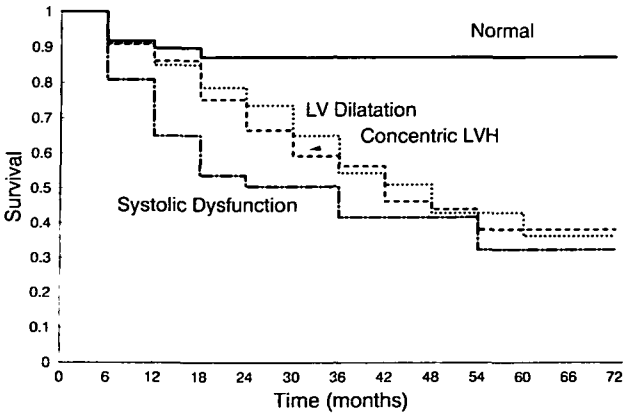

Fig. 4. Survival following the initiation of dialysis therapy of patients with normal echocardiogram, concentric LV hypertrophy, LV dilatation, and systolic dysfunction.

with normal echocardiogram on follow-up (Table 2). In this group independent predictors of the presence of concentric LV hypertrophy (yes/no) were systolic blood pressure and female gender (Table 3). The degree of hypertrophy on second echocardiogram was independently related to higher systolic pressure during dialysis therapy, older age, and lower haemoglobin during follow-up (Table 4). Independent predictors of change in LV mass index from first to second echocardiogram were low haemoglobin level during follow-up (higher by 7 gm/m^2 for each 10 g/l decrement in haemoglobin distribution curve, P=0.008) and diabetes mellitus (higher by 14.6 gm/m^2 if diabetes present, P=0.008).

Left ventricular dilatation

Echocardiographic outcome (Table 1). Of 69 patients who had LV dilatation at baseline and had a follow-up echocardiogram 42% continued to have dilatation, 29% had concentric hypertrophy, 7% normalized, and 22% developed systolic dysfunction.

Clinical outcome. The median time to development of heart failure in patients with LV dilatation was 38 months, significantly worse than those with normal echocardiogram (P=0.002) (Figure 3). The relative risk for development of heart failure, independent of age, gender, diabetes, and ischaemic heart disease was 2.74 (P=0.002).

The median time to death was 56 months, which was not significantly worse than those with normal echocardiogram (Figure 4). However, late mortality (after 2 years on ESRD therapy) was worse and approached statistical significance in those with LV dilatation, independent of age, gender, diabetes and ischaemic heart disease (relative risk=2.3, P=0.07). The proportion of deaths attributed to cardiovascular disease was 47% (14/34).

Risk factor. Sixty-five patients who had LV dilatation on follow-up were compared to 35 patients with normal echocardiogram on follow-up (Table 2). Independent and significant predictors of the presence of LV dilatation (yes/no) were anaemia and ischaemic heart disease (Table 4). Independent predictors of LV volume (ml/m^2), using multiple linear regression, were ischaemic heart disease, lower haemoglobin level during follow-up, together with higher diastolic blood

Table 2. Clinical, biochemical and echocardiographic characteristics of dialysis patients grouped according to echocardiographic diagnosis on follow-up echocardiogram

	Normal	Concentric LVH	LV Dilatation	Systolic dysfunction
	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)
Age (years)	51 ± 16	55 ± 15	54 ± 15	56 ± 14
Systolic blood pressure (mmHg)	140 ± 21	149 ± 18*	147 ± 17	138 ± 18
Diastolic blood pressure (mmHg)	79 ± 13	83 ± 9	82 ± 9	78 ± 10
Serum creatinine (μmol/l)	834 ± 243	941 ± 289*	894 ± 299	883 ± 318
Haemoglobin (g/l)	93 ± 17	89 ± 17	84 ± 18*	90 ± 16
Serum albumin (g/l)	38 ± 6	37 ± 4	37 ± 5	38 ± 8
Serum calcium (mmol/l)	2.29 ± 0.18	2.34 ± 0.17	2.33 ± 0.18	2.3 ± 0.18
LV mass index (g/m^2)	101 ± 20	158 ± 31	192 ± 54***	187 ± 61***
LV volume (ml/m^2)	57 ± 16	66 ± 14**	118 ± 28	123 ± 58***
Fractional shortening (%)	37 ± 6	36 ± 6	33 ± 4**	19 ± 5.3
Male	25/35 71%	59/102 58%	41/65 63%	40/57 70%
Diabetes mellitus	9/35 26%	29/102 28%	11/65 17%	22/57 39%
Ischaemic heart disease up to second echo	5/35 14%	33/102 32%*	21/65 32%*	27/57 47%**

Normal echocardiogram ($n=35$), concentric LV hypertrophy ($n=102$), LV dilatation ($n=65$), and systolic dysfunction ($n=57$). Blood pressure and biochemical data are the means of serial data from initiation of dialysis to time of second echocardiogram. Echocardiographic data are derived from the follow-up echocardiogram

*when compared to normal group $P<0.05\geqslant0.01$; **when compared to normal group $P<0.01\geqslant0.001$; ***when compared to normal group $P<0.001$.

Table 3. Significant predictors of (A) the presence of concentric LV hypertrophy and (B) LV mass index on follow-up echocardiography in patients with concentric LV hypertrophy ($n=102$) or normal echocardiogram ($n=35$)

	Outcome	Associations	Odds ratio (Logistic regression)	*P*
A	Concentric LV hypertrophy present on 2nd echo	1. Each increment of 1 mmHg in mean systolic blood pressure	1.03	0.02
		2. Female	2.6	0.03
			Beta coefficient (Multilinear regression)	*P*
B	LV mass index (g/m^2)	1. Each increment of 1 mmHg in mean systolic blood pressure	0.92	0.002
		2. Each increment of 1 year of age	0.57	0.005
		3. Each decrement of 1 g/l in mean hemoglobin	0.52	0.005

In model A multiple logistic regression was used and in B multilinear regression. In both models covariates included age, gender, diabetes mellitus, mean of haemoglobin, systolic blood pressure, serum albumin levels obtained at monthly intervals from start of end-stage renal disease therapy to second echocardiogram.

pressure, and lower serum albumin levels during dialysis therapy (Table 4).

Systolic dysfunction

Echocardiographic outcome (Table 1). Of 47 patients who had systolic dysfunction at baseline and had a follow-up echocardiogram, 53% continued to have systolic dysfunction. The latter patients differed from the group whose contractility normalized by having significantly lower fractional shortening at baseline (18.5 ± 4.6 versus 21.0 ± 3.8) and significantly lower blood pressure during follow-up (136 ± 19 versus 149 ± 20 mmHg). Of 49 patients who had systolic dysfunction on follow-up, all but one had echocardiographic disease at baseline.

Clinical outcome. The median time to development of heart failure in patients with systolic dysfunction was 19 months (Figure 3). The odds ratio for development of heart failure, independent of age, gender, diabetes, and ischaemic heart disease was 3.66 ($P<0.001$).

The median time to death in patients with systolic dysfunction was 38 months ($P<0.001$) (Figure 4). The odds ratio for mortality, compared to those with normal echocardiograms, independent of age, gender, diabetes, and ischaemic heart disease was 1:88. The proportion of deaths attributed to cardiovascular disease was 67% (20/30).

Table 4. Significant predictors of (A) the presence of LV dilatation and (B) LV volume on follow-up echocardiography in dialysis patients with LV dilatation and normal echocardiogram

	Outcome	Associations	Odds ratio (Logistic regression)	*P*
A	LV dilatation present on 2nd echo	1. Ischaemic heart disease	5.1	0.008
		2. Each decrement of 1 g/l in mean haemoglobin	1.04	0.02
		3. Each increment of 1 mmHg in mean diastolic blood pressure	1.04	0.06
			Beta coefficient (Multilinear regression)	*P*
B	LV volume (ml/m^2)	1. Ischaemic heart disease	24.1	0.009
		2. Each decrement of 1 g/l in mean haemoglobin	0.45	0.004
		3. Each increment of 1 mmHg in mean diastolic blood pressure	0.8	0.04
		4. Each decrement of 1 g/l in mean serum albumin level	0.85	0.04

In model A multiple logistic regression was used and in B multilinear regression. In both models covariates included age, gender, diabetes mellitus, mean of haemoglobin, systolic blood pressure, and serum albumin levels obtained at monthly intervals from start of end-stage renal disease therapy to second echocardiogram.

Risk factors (Table 5). The 57 patients who had systolic dysfunction on second echocardiogram were compared to 35 patients with normal echocardiogram (Table 2). The one independent predictor of the presence of systolic dysfunction (yes/no) was ischaemic heart disease (Table 5). The predictors of fractional shortening (%) using multiple linear regression were ischaemic heart disease and lower haemoglobin level during follow-up.

Modality of dialysis therapy

Addition of mode of therapy (haemo versus peritoneal dialysis) had no impact on the results of the multivariate analyses. Haemodialysis patients were analysed separately and weight gains between dialyses were included in the multivariate models. Large weight gains between dialyses were not predictive of any of the echocardiographic abnormalities.

Discussion

Left ventricular disease is a frequent occurrence in end stage renal disease, being present in 84% of dialysis patients on initiation of dialysis and in 86% during follow-up 1–2 years later. This may manifest itself as concentric LV hypertrophy, LV dilatation, or systolic dysfunction, all of which occur frequently in chronic uraemia. Differentiation of concentric LV hypertrophy from LV dilatation is probably important as their aetiology is different, the former resulting from LV

Table 5. Significant predictors of (A) the presence of systolic dysfunction and (B) fractional shortening on follow-up echocardiography in dialysis patients with systolic dysfunction and normal echocardiogram

	Outcome	Associations	Odds ratio (Logistic regression)	*P*
A	Systolic dysfunction present on 2nd echo (Yes/No)	1. Ischaemic heart disease	5.2	0.001
			Beta coefficient (Multilinear regression)	*P*
B	Fractional shortening	1. Ischaemic heart disease	6.4	0.02
		2. Each decrement of 1 g/l in mean haemoglobin distribution curve	0.18	0.02

In model A multiple logistic regression was used and in B multilinear regression. In both models covariates included age, gender, diabetes mellitus, mean of haemoglobin, systolic blood pressure, serum albumin levels obtained at monthly intervals from start of end-stage renal disease therapy to second echocardiogram.

pressure overload and the latter from LV volume overload. Furthermore LV geometry has a major impact on clinical outcome: the ratio of LV mass to volume is of prognostic importance in both conditions, but in diametrically opposite directions [7]. In concentric LV hypertrophy the degree of LV hypertrophy predicts adverse outcome, whereas in LV dilatation this is not the case: the degree of LV dilatation predicts adverse outcome [7].

In chronic uraemia normalization of LV mass, volume or contractility may occasionally occur, but more frequently persistence of the abnormality is observed. Concentric hypertrophy or LV dilatation is usually present prior to the development of systolic dysfunction. The evolution of concentric hypertrophy into LV dilatation, or *vice versa*, may be partly related to when the echocardiogram is performed in relation to haemodialysis. When echocardiograms are performed pre- and post-haemodialysis LV mass index may vary by 25 g/m^2 because of reduction in LV end-diastolic diameter [24]. It may also be related to relative importance of various risk factors present at the time the echocardiogram was performed.

Compared to patients with normal echocardiograms the clinical outcomes of patients with left ventricular disorders are adverse. The median survival for dialysis patients with systolic dysfunction was 38 months, for concentric LV hypertrophy 48 months and LV dilatation 56 months. Time to onset of heart failure was 19 months in the former group and 38 months in both latter groups. It is likely that each underlying cardiomyopathy is prognostically important, as both the adverse cardiac morbidity and mortality outcomes are independent of age, gender, diabetes mellitus, and ischaemic heart disease.

Multiple potential risk factors for left ventricular disease exist in chronic uraemia. The prospective design of this study permits an evaluation of the relative importance of several risk factors, particularly as a substantial amount of data was collected while patients were on dialysis prior to their second echocardiogram. It was not possible to determine the importance of inadequate dialysis, volume overload, or fistula flow rates.

Patients with normal echocardiogram at baseline who went on to develop left ventricular disease, would have been the optimal cohort to study. Comparison of patients with and without progressive concentric LV hypertrophy or LV dilatation would also have provided greater insight. Unfortunately there were small numbers of patients in the various subgroups. However, the analyses presented in this paper of associations between potentially reversible risk factors and various LV disorders do permit hypothesis generation.

Age

In the current study older age was associated with concentric hypertrophy and in another study with systolic dysfunction [25]. In the normal population the effects of ageing include increase in myocyte size, increased rate of degenerative change, and loss of myocytes [26].

Diabetes mellitus

In the current study diabetes was associated with increasing LV mass index in the subset with concentric LV hypertrophy when compared to those with normal echocardiogram. Diabetes has been identified as a predictor of LV hypertrophy in chronic renal failure [25]. In the Framingham study increased LV mass attributable to diabetes was observed in females without renal disease [12]. Echocardiographic LV hypertrophy is probably more frequently found in hypertensive diabetic patients than in hypertensive non-diabetic patients [27]. A comparison of the pathological spectrum of hypertensive, diabetic, and hypertensive–diabetic heart disease shows that the latter had a significantly higher heart weight and a higher total fibrosis score than either of the other two groups [28].

Hypertension

In chronic uraemia the correlation between LV mass and blood pressure, obtained in cross sectional studies, was often weak or absent [11,25]. The current prospective study identifies hypertension as a predictor of both concentric LV hypertrophy and LV dilatation. In a prospective study of dialysis patients older age and systolic hypertension were associated with the development of LV hypertrophy [10]. Furthermore control of blood pressure in a small group of hypertensive patients induced regression of LV hypertrophy [29].

Anaemia

The current observations suggest that anaemia may predispose to not only concentric LV hypertrophy and to LV dilatation, but also to systolic dysfunction. The improvement of LV mass and volume following partial correction of anaemia with erythropoietin demonstrates that both increased LV mass and volume can be partly attributed to anaemia [30–33].

Hypoalbuminaemia

Low serum albumin levels in chronic uraemia exert an adverse impact on survival [34,35], are associated with the subsequent development of *de novo* heart failure [18], and in this report are associated with LV dilatation.

Ischemic heart disease

The role of coronary artery disease is difficult to determine in dialysis patients, because of the importance of non-atherosclerotic disease in the causation of ischaemic syndromes [36,37]. Obviously it was not possible to perform coronary arteriograms in all patients in this study, and as in the Framingham study, a clinical definition was used to define ischaemic heart disease. Ischaemic disease is an important cause of

systolic dysfunction of nonrenal patients [14]. In the current study ischaemic disease was a significant predictor of LV dilatation and of systolic dysfunction.

Aetiology of cardiomyopathy in chronic uraemia (Figure 5)

The following hypothesis is proposed. LV pressure overload leads to concentric LV hypertrophy, which in dialysis patients is induced by high blood pressure, exacerbated by older age, diabetes and anaemia. LV volume overload leads to LV dilatation, which is accompanied by compensatory LV hypertrophy to maintain normal wall tension. Anaemia is one cause of LV dilatation, but it is highly likely that salt and water overload and arteriovenous fistulae also induce LV dilatation [11]. Initially the hypertrophic response in chronic uraemia is adaptive to pressure or volume overload, but becomes maladaptive as overload persists, contributing to an unnatural growth response in the hypertrophied heart [38]. Premature cell death occurs as result of the continuing overload [38], the cell death being exacerbated by ischaemic heart disease, anaemia, and malnutrition. It is also possible that hyperparathyroidism predisposes to LV dilatation, as it may cause cell death [39] and inadequate hypertrophy [40]. Thus, it is likely that cell death in the presence of either concentric LV hypertrophy or LV dilatation would be catastrophic, predisposing to further LV dilatation, and eventually in some patients, systolic dysfunction.

This interpretation is supported by the adverse clinical outcomes of the left ventricular disorders that occur in chronic uraemia, with the worst outcome in those with systolic dysfunction. In patients with LV dilatation the worst outcome occurred in those with high LV volumes (>120 ml/m^2) and low LV mass to volume ratios (<1.8) [7]. In patients with concentric LV hypertrophy adverse prognosis is not associated with LV volume, but with high LV mass, and the higher the mass to volume ratio the higher the subsequent mortality [7].

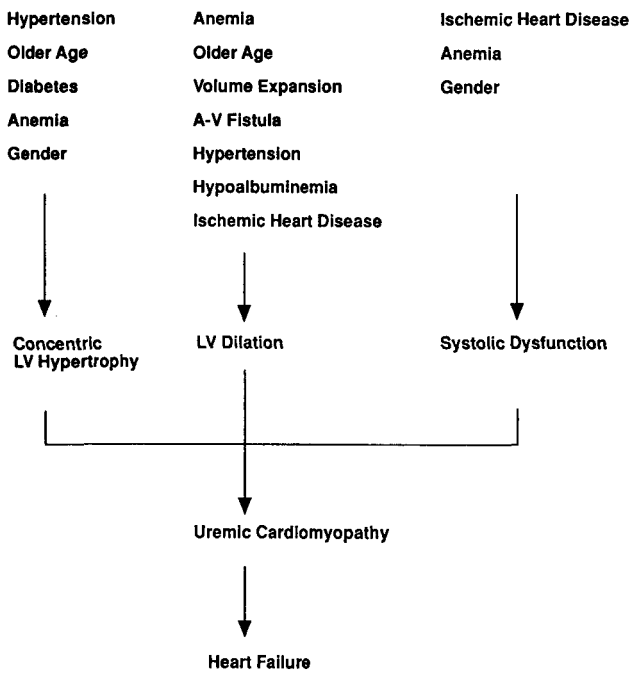

Fig. 5. Potential risk factors for the development of LV disorders in chronic uraemia.

Conclusions

In chronic uraemia left ventricular disease manifests itself as concentric LV hypertrophy, LV dilatation or systolic dysfunction, all of which occur frequently and are persistent in dialysis patients. These manifestations have adverse clinical outcomes, with the worst prognosis in those with systolic dysfunction. Risk factors for concentric LV hypertrophy may include older age, diabetes mellitus, hypertension and anaemia, for LV dilatation anaemia, hypertension, ischaemic heart disease and hypoalbuminaemia, and for systolic dysfunction ischaemic heart disease and anaemia.

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References

1. *USRDS 1994 Annual Report*. National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 1994
2. *Canadian Organ Replacement Register, 1992 Annual Report*. Canadian Institute for Health Information, Don Mills, Ontario. March 1994
3. Foley RN, Parfrey PS, Hefferton D *et al.* Advance prediction of early death in patients starting maintenance dialysis. *Am J Kidney Dis* 1994; 23: 836–845
4. Foley RN, Parfrey PS, Harnett JD *et al.* Clinical and echocardiographic disease in end-stage renal disease: prevalence, associations and risk factors. *Kidney Int* 1995; 47: 186–192
5. Churchill DN, Taylor DW, Cook RJ *et al.* Canadian Hemodialysis Morbidity Study. *Am J Kidney Dis* 1992; 19: 214–234
6. Parfrey PS, Harnett JD. Cardiomyopathy. In: Massry SG, Glassock RJ ed. *Textbook of Nephrology*. 3rd edn. Williams and Wilkins, Baltimore, 1995; 1342–1353
7. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol* 1995; 5: 2024–2031
8. Parfrey PS, Harnett JD, Griffiths SM *et al.* The clinical course of left ventricular hypertrophy in dialysis patients. *Nephron* 1990; 55: 114–120
9. Parfrey PS, Griffiths SM, Harnett JD *et al.* Outcome of congestive heart failure, dilated cardiomyopathy, hypertrophic hyperkinetic disease and ischemic heart disease in dialysis patients. *Am J Nephrol* 1990; 10: 213–221
10. Harnett JD, Kent GM, Barre PE, Taylor R, Parfrey PS. Risk factors for the development of left ventricular hypertrophy in a prospectively followed cohort of dialysis patients. *J Am Soc Nephrol* 1994; 4: 1486–1490
11. London GM, Fabiani F, Marchais SK *et al.* Uremic cardiomyopathy: an inadequate left ventricular hypertrophy. *Kidney Int* 1987; 31: 973–980
12. Galdeisi M, Anderson KM, Wilson PWF *et al.* Echocardiographic evidence for a distinct diabetic cardiomyopa-

thy (The Framingham Heart Study). *Am J Cardiol* 1991; 68: 85–89
13. Shapiro LM, Howatt AP, Calter MM. Left ventricular function in diabetes mellitus I. Methodology and prevalence and spectrum of abnormalities. *Br Heart J* 1981; 45: 122–128
14. Saxon LA, Stevenson WG, Middlekauff HR *et al.* Predicting death from progressive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1993; 72: 62–65
15. Keys A, Henschel A, Taylor HL. The size and function of the human heart at rest in semi-starvation and in subsequent rehabilitation. *Am J Physiol* 1947; 150: 153–169
16. Stefenelli T, Mayr H, Bergler-Klein J, Globits S, Woloszezuk W, Niederle B. Primary hyperparathyroidism: incidence of cardiac abnormalities and partial reversibility after successful parathyroidectomy. *Am J Med* 1993; 95: 197–202
17. Weisenee D, Low-Friedrich I, Richle M, Bereiter-Hahn J, Schoeppe W. In vitro approach to 'uremic cardiomyopathy'. *Nephron* 1993; 65: 392–400
18. Harnett JD, Foley RN, Kent GM, Murray DC, Barre PE, Parfrey PS. Congestive heart failure in dialysis patients. Prevalence, incidence, prognosis and risk factors. *Kidney Int* 1995; 47: 884–890
19. Devereux RB, Alonso DR, Lutas EM *et al.* Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; 57: 450–458
20. Sahn DJ, Demaria A, Kisslo J, Weyman A. Recommendations regarding qualification in M-mode echocardiography. Results of a survey of echocardiographic measurements. *Circulation* 1978; 58: 1072–1082
21. Pombo JF, Troy BL, Russell RO Jr. Left ventricular volumes and ejection fractions by echocardiography. *Circulation* 1971; 43: 480–490
22. Levy D, Savage DD, Garrison RJ, Anderson KM, Kannel WB, Castelli WP. Echocardiographic criteria for left ventricular hypertrophy: the Framingham Study. *Am J Cardiol* 1987; 59: 956–960
23. Dixon WJ, Brown MB, Engelman L *et al.* ETS: *Statistical Software Manual.* Berkeley, University of California Press, 1985
24. Harnett JD, Murphy B, Collingwood P *et al.* The reliability and validity of echocardiographic measurement of left ventricular mass in hemodialysis patients. *Nephron* 1993; 65: 212–214
25. Greaves SC, Gamble GD, Collins JF *et al.* Determinants of left ventricular hypertrophy and systolic dysfunction in chronic renal failure. *Am J Kidney Dis* 1994; 24: 768–776
26. Wei JY. Age and the cardiovascular system. *N Engl J Med* 1992; 327: 1735–1739
27. Grossmann E, Shemesh J, Shamiss A *et al.* Left ventricular mass in diabetes-hypertension. *Arch Intern Med* 1992; 152: 1001–1004
28. van Hoeven KH, Factor SM. A comparison of the pathological spectrum of hypertensive, diabetic and hypertensive-diabetic heart disease. *Circulation* 1990; 82: 848–855
29. Cannella G, Paoletti E, Delfino R, Peloso G, Malinari S, Traverso GB. Regression of left ventricular hypertrophy in hypertensive dialyzed uremic patients on long-term antihypertensive therapy. *Kidney Int* 1993; 44: 881–886
30. London GM, Zins B, Pannier B *et al.* Vascular changes in hemodialysis patients in response to recombinant human erythropoietin. *Kidney Int* 1989; 36: 878–882
31. Silberberg JS, Racine N, Barre PE *et al.* Regression of left ventricular hypertrophy in dialysis patients following correction of anemia with recombinant human erythropoietin. *Can J Cardiol* 1990; 6: 1–4
32. Fellner SK, Lang RM, Neumann A *et al.* Cardiovascular consequences of the correction of the anemia of renal failure with erythropoietin. *Kidney Int* 1993; 44: 1309–1315
33. Wizemann V, Schafer R, Kramer W. Follow-up of changes induced by anemia compensation in normotensive hemodialysis patients with left ventricular hypertrophy. *Nephron* 1993; 64: 202–206
34. Owen SR, Lew NL, Yan Liu SM, Lowrie EG, Lazarus JM. The urea reduction ratio and serum albumin concentrations as predictor of mortality in patients undergoing hemodialysis. *N Engl J Med* 1993; 329: 1001–1006
35. Iseki K, Kawazoe N, Fukiyama K. Serum albumin is a strong predictor of death in chronic dialysis patients. *Kidney Int* 1993; 44: 115–119
36. Roig E, Bertiu A, Castaner A *et al.* Disabling angina pectoris with normal coronary arteries in patients undergoing long-term hemodialysis. *Am J Med* 1981; 71: 431–434
37. Rostand SG, Kirk KA, Rutsky EA. Dialysis-associated ischemic heart disease: insights from coronary angiography. *Kidney Int* 1984; 25: 653–659
38. Katz AM. The cardiomyopathy of overload: an unnatural growth response in the hypertrophied heart. *Ann Intern Med* 1994; 121: 262–371
39. Bogin E, Massry SG, Harary I. Effect of parathyroid hormone on rat heart cells. *J Clin Invest Med* 1981; 67: 1215–1227
40. London GM, de Vernejoul M-C, Fabiani F *et al.* Secondary hyperparathyroidism and cardiac hypertrophy in hemodialysis patients. *Kidney Int* 1987; 32: 900–907

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