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Long-term evolution of cardiomyopathy in dialysis patients

ROBERT N. FOLEY, PATRICK S. PARFREY, GLORIA M. KENT, JOHN D. HARNETT, DAVID C. MURRAY, and PAUL E. BARRE

Divisions of Nephrology and Clinical Epidemiology, Memorial University, and Division of Nephrology, Salvation Army Grace General Hospital, St. John's, Newfoundland; and Royal Victoria Hospital, McGill University, Montreal, Quebec, Canada

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Background. Left ventricular enlargement is very common at the inception of dialysis therapy, and highly predictive of future cardiac morbidity and mortality. It is not known whether cardiac size increases further while on dialysis therapy and whether potentially reversible risk factors for later progression can be identified.

Methods. Baseline and yearly echocardiograms were performed in a prospective inception cohort of 433 dialysis patients. The mean patient follow-up was 41 months; 29 patients had four consecutive echocardiograms at yearly intervals.

Results. The patient subset with four echocardiograms was older (58 vs. 51 years, $P = 0.02$) and had a lower mass ventricular mass index (128 vs. 149 g/m^2, $P = 0.02$) than the parent group. Using repeated measures analysis of variance, applied to those with four echocardiograms, there were progressive increases over time in posterior wall thickness ($P = 0.015$), left ventricular end-diastolic diameter, left ventricular mass index ($P = 0.001$), and cavity volume index ($P = 0.001$). Mass-to-volume ratios did not change. The biggest changes in mass (18 g/m^2 − 14%)and volume index (13 ml/m^2 − 18%) occurred between baseline and year 1, although increases in both were seen after year 1. Hemodialysis versus peritoneal dialysis (41 g/m^2, $P = 0.008$) and anemia (10 g/m^2 per 1 g/dl drop in hemoglobin, $P = 0.02$) were associated with progressive left ventricular enlargement, but only within the first year of dialysis therapy. The left ventricular enlargement seen after year 1 was independent of anemia, blood pressure, serum albumin and mode of dialysis.

Conclusions. Progressive cardiac enlargement, particularly left ventricular dilation with compensatory hypertrophy, continues after starting dialysis therapy. Most of the additional cardiac enlargement seems to occur in the first year of dialysis therapy, suggesting that intervention beyond one year may be relatively ineffective.

Cardiac disease is responsible for about half of all deaths in dialysis patients [1, 2]. Cardiac failure in particular has a very poor prognosis, approximately doubling mortality rates [3, 4]. About three quarters of end-stage renal disease patients starting dialysis therapy have left ventricular hypertrophy, left ventricular dilation or low fractional shortening [5]. This cardiac enlargement appears to progress rapidly as renal function declines [6–8]. In dialysis patients it appears to be strongly predictive of developing clinically-defined ischemic heart disease and cardiac failure for the first time, and is ultimately predictive of higher mortality [9].

Considerably less is known about the long-term natural history of cardiomyopathy in dialysis patients. In particular, it is not known whether cardiac size and function improve or degenerate while on dialysis therapy, and whether reversible risk factors for later progression are similar to those associated with early progression, such as anemia and hypertension [6–8]. In this study, we report the evolution and risk factors of early and late progression in a group of dialysis patients who had four consecutive echocardiograms, at inception of dialysis and at yearly intervals thereafter.

METHODS

Patients

This prospective cohort study of 433 patients 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. Patients were eligible for entry to the study if (*a*) they survived for six months and (*b*) if they had a technically satisfactory echocardiogram within a year of starting renal replacement therapy. Patient recruitment finished in June 1991. The mean patient follow-up was 41 months.

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, hemoglobin and serum albumin levels. A detailed description of the design and definitions used in this study has been published elsewhere [5].

Key words: cardiac morbidity, progressive cardiac enlargement, blood pressure, dialysis mode, albumin, left ventricular dilation.

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Echocardiography

Echocardiography was performed close to inception of dialysis therapy and was scheduled to take part at annual intervals. For this study we selected those 29 patients patients still remaining on dialysis with four consecutive echocardiograms. The echocardiograms were performed at mean time intervals of 2, 18, 30 and 43 months, respectively, following the inception of dialysis therapy. Left ventricular mass index was calculated according to the Penn convention [10]. The formula of Pombo, Troy and Russell was used to calculate cavity volume, which was also indexed to body surface area [11].

Analysis

Repeated measures analysis of variance was used to test whether cardiac dimensions changed overall with time. Bonferroni correction for multiple comparison was applied when when looking at the differences between the first and second, second and third, and third and fourth echocardiograms.

We measured mean monthly hemoglobin levels, predominant mode of dialysis therapy, systolic and diastolic blood pressure and serum albumin levels between the first and second, second and third, and third and fourth echocardiograms. We then used linear regression analysis to test for association between these time-averaged variables, and the difference between the left ventricular mass index from the first and second echocardiogams. Similar analyses were performed looking at the differences between the second and third and between the third and fourth echocardiograms.

RESULTS

Baseline characteristics

The baseline characteristics of the patient subset who subsequently had four consecutive echocardiograms are illustrated in Table 1. This patient subset was older (58 vs. 51 years, $P = 0.02$) and had lower echocardiographic LV mass index than (128 vs. 149 g/m^2, $P = 0.02$) than the parent subset.

Table 1. Baseline characteristics

	Four consecutive echocardiograms		
	No, $N = 404$	Yes, $N = 29$	P
Age *years*	51 (49, 52)	58 (54, 62)	0.02
Diabetic	28%	17%	0.2
Ischemic heart disease	22%	28%	0.4
Cardiac failure	32%	21%	0.2
Hypertension >10 years	36%	21%	0.09
Current smokers	27%	17%	0.3
Baseline echocardiographic classification			
Normal	21%	33%	
Concentric LV hypertrophy	35%	37%	
LV dilation	27%	30%	
Systolic dysfunction	16%	0%	0.5
Left atrial dimension *mm*	39 (38, 39)	37 (35, 40)	0.4
Fractional shortening %	34 (33, 35)	37 (33, 40)	0.07
Left ventricular mass index *g/m^2*	149 (145, 154)	128 (119, 138)	0.02
Left ventricular cavity volume index *ml/m^2*	85 (81, 89)	73 (64, 83)	0.1
Mass/volume ratio *g/ml*	1.9 (1.9, 2.0)	1.8 (1.7, 2.0)	0.5

Interval variables are presented as mean values with 95% confidence intervals in parentheses. LV is left ventricle.

Table 2. Characteristics of the 29 patients with four consecutive echocardiograms while on dialysis therapy, expressed as the mean of each variable (which were measured on a monthly basis)

Variable	Mean (95% Confidence interval)
Systolic blood pressure *mm Hg*	147 (141, 153)
Diastolic blood pressure *mm Hg*	80 (76, 84)
Number of antihypertensives	0.7 (0.6, 0.8)
Proportion due to	
Calcium-channeal blockers	0.34
Beta-blockers	0.32
ACE-inhibitors	0.15
Vasodilators	0.12
Centrally-acting agents	0.05[a]
Mode of dialysis therapy	
Hemodialysis	20/29 (69%)
Peritoneal dialysis	9/29 (31%)
Blood urea *mmol/liter*	28 (26, 30)
Serum creatinine *μmol/liter*	1004 (928, 1080)
Serum albumin *g/dl*	3.8 (3.7, 3.9)
Hemoglobin *g/dl*	8.7 (8.3, 9.1)
Calcium *mmol/liter*	2.4 (2.2, 2.6)
Phosphate *mmol/liter*	1.9 (1.7, 2.1)
Interdialytic weight gain *kg, hemodialysis patients only*	2.3 (1.9, 2.7)

[a] Proportions don't add up to 1 because of rounding error

Characteristics while on dialysis therapy

The treatment characteristics of the 29 patients with four consecutive echocardiograms are shown in Table 2. It is noteworthy that these patients had reasonable blood pressure values, within a relatively narrow range.

Evolution of echocardiographic parameters

Left atrial dimension and fractional shortening remained relatively constant over time (Table 3), and there was a clear tendency for both LV cavity volume and LV mass index to increase over time ($P < 0.001$). Mass/volume ratios remained constant, suggesting that the dominant evolutionary picture was of progressive LV dilation with compensatory LV hypertrophy. Most, but not of all, of the cardiac enlargement took place between the first and second echocardiograms: an increase in LV cavity volume was seen between the second and third studies (5 ml/m^2, $P = 0.055$), while an increase in mass index was seen between the third and fourth studies (9 g/m^2, $P = 0.05$).

Two hundred and seventy-five of the 298 (92%) of the patients still on dialysis had baseline and at least one repeat echocardiogram. When the 29 patients with four echocardiograms were omitted, the mean change in mass index in

Table 3. Evolution of echocardiographic parameters

	Baseline	Change from 1st to 2nd echocardiogram[b]	Change from 2nd to 3rd echocardiogram[b]	Change from 3rd to 4th echocardiogram[b]	*P* for trend[a]
		(95% confidence interval)			
Left atrial dimension	37	0	−1	1	0.6
mm	(35, 40)	(−1, 2)	(−2, 1)	(−1, 2)	
P		0.5	0.3	0.5	
Fractional shortening	37	−1.6	−0.9	0.8	0.4
%	(33, 40)	(−5.8, 2.6)	(−3.0, 1.2)	(−1.1, 2.6)	
P		0.4	0.4	0.4	
LV mass index	128	18	−1	9	0.001
g/m^2	(119, 138)	(8, 28)	(−11, 10)	(0, 20)	
P		0.001	0.8	0.05	
LV cavity volume index	73	13	5	−2	0.001
ml/m^2	(64, 83)	(4, 23)	(0, 10)	(−8, 5)	
P		0.006	0.055	0.6	
Mass/volume ratio	1.83	0.01	−0.03	−0.05	0.5
g/ml	(1.76, 1.91)	(−0.13, 0.16)	(−0.15, 0.10)	(−0.01, 0.01)	
P		0.8	0.7	0.5	

[a] Using repeated measures analysis of variance, this is a *P* for trend from one measure to the next
[b] The *P* values are Bonferroni-corrected for multiple comparisons

Table 4. Serial treatment variables, average of each monthly value measured from one echocardiogram to the next

	From 1st to 2nd echocardiogram	From 2nd to 3rd echocardiogram	From 3rd to 4th echocardiogram
	(95% confidence interval)		
Hemoglobin *g/dl*	8.6	8.2	8.3
	(8.1, 9.2)	(7.7, 8.9)	(7.6, 8.9)
Serum albumin *g/dl*	3.8	3.8	3.8
	(3.7, 3.9)	(3.7, 3.9)	(3.7, 4.0)
Systolic blood pressure *mm Hg*	147	149	150
	(140, 155)	(141, 157)	(143, 158)
Diastolic blood pressure *mm Hg*	81	80	79
	(79, 85)	(76, 84)	(75, 83)
Hemodialysis/ peritoneal dialysis	69%/31%	69%/31%	69%/31%

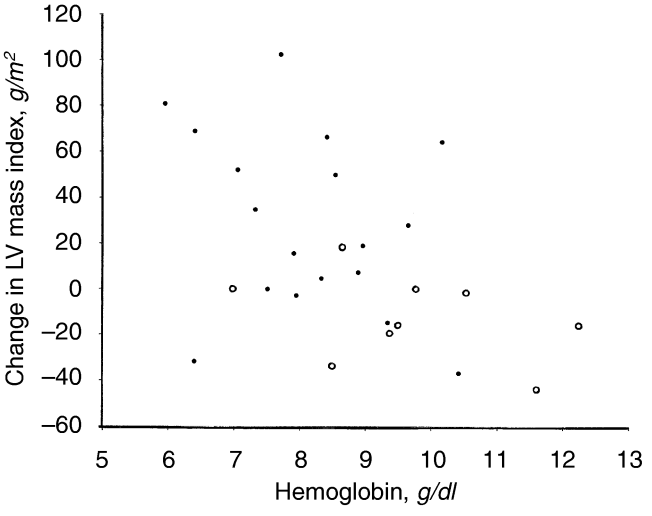

Fig. 1. Scatter-plot of the change in left ventricular mass index from the baseline to the first annual echocardiogram on the y-axis against the mean hemoglobin level during this time interval on the x-axis. Symbols are: (●) hemodialysis subjects; (○ peritoneal dialysis subjects. The correlation co-efficient is 0.46 ($P = 0.02$) for hemoglobin level and 0.50 ($P = 0.008$) for mode of dialysis therapy.

the first year was 2 g/m^2 and the mean change in cavity volume was 1 ml/m^2. Looking at patients with baseline mass index less than 138 g/m^2 and volume index less than 83 ml/m^2 (the upper bounds of the 95% confidence intervals of the subset of 29 patients with 4 echocardiograms), the mean increments were 22 g/m^2 (19%) and 14 ml/m^2 (24%), respectively.

Associations of left ventricular enlargement

The mean hemoglobin, serum albumin and blood pressure values and the predominant mode of dialysis in the interval between each echocardiogram are shown in Table 3. The associations of progressive left ventricular enlargement in each of the time intervals are shown in Table 4. On bivariate analysis, the use of hemodialysis versus peritoneal dialysis (41 g/m^2, $P = 0.008$) and anemia (10 g/m^2 per 1 g/dl drop in hemoglobin, $P = 0.02$) were associated with progressive LV enlargement within the first year of therapy (Fig. 1). Neither variable demonstrated statistical association when both were entered together in a multiple regression model, most likely because of a combination of relatively few observations and a high degree of co-linearity ($r = 0.47$,1.5 g/dl higher in peritoneal dialysis patients, $P = 0.01$) between the mode of dialysis and hemoglobin level (Table 5). The LV enlargement seen after year 1 was independent of anemia, blood pressure, serum albumin and mode of dialysis.

Table 5. Correlation-regression analysis between changes in left ventricular (LV) mass index and serial treatment variables

	Outcome variable, change in LV mass index		
	From 1st to 2nd echocardiogram	From 2nd to 3rd echocardiogram	From 3rd to 4th echocardiogram
Hemoglobin *g/dl*	$r = 0.46$ $\beta = -12$ g/m^2 $P = 0.02$	NS	NS
Serum albumin *g/dl*	NS	NS	NS
Systolic blood pressure *mm Hg*	NS	NS	NS
Diastolic blood pressure *mm Hg*	NS	NS	NS
Hemodialysis vs. peritoneal dialysis	$r = 0.50$ $\beta = 41$ g/m^2 $P = 0.008$	NS	NS

DISCUSSION

The patient subset used in this report clearly is highly self-selected. The major selection factors are probably related to older age, which may have lowered the chance of receiving a renal transplant, lower cardiac mass that appeared to increase longevity on dialysis therapy [5, 9, 12], and compliance. With regard to the latter, the mean interval from inception of dialysis therapy to the fourth echocardiogram was 43.5 months. Ninety-one patients overall remained in the study at this time. Twenty-nine of 91 or 32% represents a 68% chance of having each of three technically successful scheduled echocardiograms after the baseline echocardiogram (which was a study inclusion criterion).

Balanced against the highly-selected composition of the patient population is the increased ability to detect change, because each patient acts as his or her control throughout. We observed very clear increases in left ventricular cavity volume and mass index. The ratio of mass-to-volume, however, remained constant, suggesting that progressive left ventricular dilation with compensatory hypertrophy is the major long-term evolutionary pattern in dialysis patients. Most, but not all, of the left ventricular enlargement took place within the first year. Anemia and the use of hemodialysis as opposed to peritoneal dialysis were asociated with left ventricular enlargment, but only within the first year of dialysis therapy. The left ventricular enlargement seen after one year was numerically smaller, and appeared to take place autonomously of mode of dialysis therapy, blood pressure, serum albumin and hemoglobin levels. Taken together, these data suggest that the therapeutic window for intervention to prevent progressive cardiac enlargement does not remain open much beyond one year.

It is well known that most patients with end-stage renal disease have left ventricular dilation, left ventricular hypertrophy or systolic dysfunction. There is an accumulating literature to suggest these changes in cardiac morphology and function accelerate rapidly as renal function declines in the pre-end-stage renal disease era [6–8]. This study suggests that the process of progressive left ventricular hypertrophy, particularly in response to left ventricular dilation, continues after the institution of dialysis therapy, especially in the first year. Similar findings were in a study of 11 peritoneal dialysis patients by Huting and Alpert [13]. In their study, a follow-up echocardiogram was performed after an interval of 34 months. Left ventricular mass increased from 234 to 299 g ($P < 0.05$); however, mass-to-volume ratios increased from 1.28 to 1.85 g/ml ($P < 0.001$), suggesting that progressive wall thickening was the primary evolutionary pattern [13]. Covic et al described the echocardiographic findings in a cross-sectional study of 30 patients on ten or more years of long-hour (24 hr per week dialysis schedule) hemodialysis [14]. They found left ventricular hypertrophy in 76%. In contrast to our study only 10% had left ventricular dilation, suggesting that wall thickening was the primary pathological process [14].

The major factors associated with progressive LV enlargement in our study were the use of hemodialysis as opposed to peritoneal dialysis and anemia. The creation of fistulae in ESRD patients is known to lead to increased cardiac pre-load, which is usually offset by increased stroke volume [15], and the short-term trade-off for such an adaptative LV dilation is increased wall tension and oxygen demand according to the Law of Laplace. Very large A-V fistulae have been associated with development of cardiac failure that resolved after the fistula was closed [16–18]. London et al have reported that LV dilation is the most characteristic abnormality of normotensive hemodialysis patients without cardiac disease; the degree of LV dilation was related to anemia and the hemodynamic effect of the fistula [19]. There have been few studies comparing the long-term effects of hemodialysis and peritoneal dialysis on cardiac structure and function, although it is possible that the continuous nature of peritoneal dialysis offers theoretical hemodynamic advantages, including avoidance of marked swings in extracellular fluid volume, which may have adverse effects on long-term cardiac function.

Many studies have examined the effect of partial correction of renal anemia using recombinant human erythropoietin. These studies have consistently shown a partial regression of LV dilation and/or LV hypertrophy. This may account for the associations between anemia, cardiac failure and mortality in dialysis patients [20–35].

There was no association between either systolic or diastolic blood pressure and progressive LV hypertrophy in our highly selected subset of patients. It is worth pointing out that average blood pressure levels were probably better than those typically seen in dialysis patients. Similar comments could be made about phosphate and albumin levels, suggesting that this was a relatively healthy and/or more

compliant group of patients. Also, the range of average blood pressures in this subset was narrow, which limits the possibility of showing an association between blood pressure and progressive cardiac enlargement. We have previously shown that hypertension was associated with cardiac enlargement in the overall patient group, a group with both a higher average and a higher variability in blood pressures [5, 9, 36]. Several recent studies also support the notion that hypertension and left ventricular hypertrophy are associated in end-stage renal disease [6, 7, 37].

Our study is limited by small patient numbers and the highly selected nature of its subjects. There was no attempt made at systematic collection of indices of dialysis adequacy, which reflects the treatment practices in use when the study began in the early 1980s. Despite its limitations, our study is likely to be unique for the number of echocardiograms performed in sequence, given that patient "loss" to transplant or death is so rapid. The data presented here strongly suggest that progessive cardiac enlargement, particularly LV dilation with compensatory hypertrophy, continue after starting dialysis therapy. Most of the additional cardiac enlargement occurred in the first year of dialysis therapy. This observation, coupled with the observation that the cardiac enlargement occurring after this time point was independent of the most commonly measured determinants of cardiac work, suggests that intervention beyond one year may be relatively ineffective.

Reprint requests to Robert N. Foley, M.B., Division of Nephrology, Memorial University of Newfoundland, The Health Sciences Centre, St. John's, Newfoundland, Canada, A1B 3V6.
E-mail: rn_foley@hotmail.com

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