Serial Change in Echocardiographic Parameters and Cardiac Failure in End-Stage Renal Disease

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Abstract. Echocardiographic abnormalities are the rule in patients starting dialysis therapy and are associated with the development of cardiac failure and death. It is unknown, however, whether regression of these abnormalities is associated with an improvement in prognosis. As part of a prospective cohort study with mean follow-up of 41 mo, 227 patients had echocardiography at inception and after 1 yr of dialysis therapy. Improvements in left ventricular (LV) mass index, volume index, and fractional shortening were seen in 48, 48, and 46%, respectively. Ninety patients had developed cardiac failure by 1 yr of dialysis therapy. Twenty-six percent of the remaining 137 patients subsequently developed new-onset cardiac failure.

The mean changes in LV mass index were 17 g/m^2 in those who subsequently developed cardiac failure compared with 0 g/m^2 among those who did not ($P = 0.05$). The corresponding values were -8 *versus* 0% for fractional shortening ($P < 0.0001$). The associations between serial change in both LV mass index and fractional shortening and subsequent cardiac failure persisted after adjusting for baseline age, diabetes, ischemic heart disease, and the corresponding baseline echocardiographic parameter. Regression of LV abnormalities is associated with an improved cardiac outcome in dialysis patients. Serial echocardiography adds prognostic information to one performed at baseline.

Abnormalities of left ventricular (LV) size, shape, or function are present in between 70 and 80% of dialysis patients (1–4). Echocardiographic LV hypertrophy in dialysis patients is independently associated with higher subsequent mortality rates, as is the case in the general population, in patients with essential hypertension, and in patients with coronary artery disease (1,2). In dialysis patients, high cavity volume and low contractility are also associated with higher mortality (1). The known, or strongly suspected, causes of these echocardiographic abnormalities in dialysis patients are highly diverse and may include age, coronary artery disease, gender, hypertension, anemia, the uremic internal milieu, hyperparathyroidism, large interdialytic fluid gains, and the presence of arteriovenous fistulae and grafts (1,3,5–21). The mechanisms by which these abnormalities subsequently lead to early demise are not clearly understood.

Echocardiography is easily performed, noninvasive, safe, reproducible, and accurate (22). As such, is it is a very attractive surrogate marker in the evaluation of different therapeutic agents. The validity of a surrogate marker, like echocardiography, is heightened if it can be shown that regression of these abnormalities over time improves prognosis and/or progression worsens prognosis. It has been shown that regression of elec-

trocardiographic LV hypertrophy improves prognosis in the general population (23), and recently it has been shown that regression of echocardiographic LV hypertrophy improves prognosis in subjects with essential hypertension (24).

The purpose of this study was to determine the prognostic impact of serial changes in echocardiographic parameters in dialysis patients.

Materials and Methods

This prospective cohort study began in 1982 and involved three university-affiliated nephrology centers in eastern Canada. The eligibility criteria for the study were survival for 6 mo following the inception of dialysis therapy and availability of a technically satisfactory echocardiogram within 1 yr of starting dialysis therapy. The study involved 432 dialysis patients. Mean follow-up was 41 mo.

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 BP, hemoglobin and serum albumin levels, and interdialytic weight gain in hemodialysis patients. At yearly intervals, all changes related to renal replacement therapy, admissions to hospital, and autopsy notes were recorded.

Peritoneal dialysis consisted of 8 L of dialysate for the vast majority of patients in the study. We did not routinely record hemodialysis time, membrane type, dialysate and blood flow rates, or urea reduction ratios at all centers. Hemodialysis times were recorded systematically from 1986 onward in one center. In the first week of January of each year, the median total hemodialysis times were as follows: 1986, 12.0 h; 1987, 12.0 h; 1988, 10.5 h; 1989, 10.5 h; 1990, 9.5 h; 1991, 9.0 h. Dialysis prescription was similar in the other two centers.

Baseline and annual echocardiography were performed using M-mode and two-dimensional ultrasonography. The protocol recommended that echocardiography be performed with the patient at dry weight, within 24 h after dialysis therapy in hemodialysis patients. LV mass index was calculated according to the Penn convention (25). LV cavity volume was calculated by the formula of Pombo *et al.* (26). The initial echocardiogram was performed at a median of 0 mo after the start of ESRD therapy. Two hundred ninety-eight patients were alive and still on dialysis at 1 yr after starting dialysis therapy. Two hundred seventy-five of these (92%) had a repeat echocardiogram, at a median interval of 13 mo after the initial study. This patient subset was almost identical to the parent group of 433 patients, with no statistically or clinically significant differences in terms of baseline clinical and echocardiographic parameters (27). Of these 275 patients, all the data points (posterior wall thickness, septal thickness, end-diastolic diameter, and body surface area at baseline and first follow-up study) to calculate LV dimensions were available in 250. Of these, 23 had finished dialysis treatment before 1 yr. Thus, the final substrate for this study consisted of 227 patients.

Definitions

Ischemic heart disease: Previous history of myocardial infarction, coronary artery bypass surgery or percutaneous transluminal angioplasty, coronary artery disease, or angina pectoris.

Cardiac failure: Dyspnea, plus two of the following: raised jugular venous pressure, bibasalar crackles, pulmonary venous hypertension or interstitial edema on chest x-ray, requiring hospitalization or extra ultrafiltration.

The outcome events studied were the first ever episodes of cardiac failure, ischemic heart disease, and death occurring after 1 yr on dialysis therapy. Patients with a history of any of these events before 1 yr of dialysis therapy were excluded from outcome analysis. Thus, a patient with an episode of ischemic heart disease, but without ever developing cardiac failure before 1 yr of dialysis therapy, would be excluded from the ischemic heart disease analysis but included in the analysis of cardiac failure and death. Transplantation was a censoring event, so that the time of transplantation was considered the final follow-up on dialysis therapy and events occurring after this were analyzed as not having occurred.

Changes in echocardiographic LV mass index (indexed to surface area), cavity volume index, and fractional shortening between the baseline and first annual echocardiogram were tested for association with outcome events occurring after 1 yr.

Statistical Analyses

Normally distributed continuous variables were compared using ANOVA. Categorical variables were compared using χ^2 analysis. All statistical tests are two-tailed with a *P* value <0.05 to indicate statistical significance. The proportional hazards model was used to adjust the serial changes in echocardiographic parameters and time to outcome events for baseline age, diabetes mellitus, ischemic heart disease, and the corresponding echocardiographic parameter measured at baseline.

Results

Patient and Treatment Characteristics

The characteristics of patients with serial echocardiograms are shown in Table 1. Virtually all patients were Caucasian. At baseline the mean LV mass index, cavity volume index, and fractional shortening were 161 g/m², 88 ml/m², and 34%, respectively.

Table 1. Patient characteristics $(n = 227)^a$

Age (yr)	55 (53 to 57)
Male/female (%)	62/38
Diabetes mellitus (%)	28
Hypertension >10 yr (%)	23
Ischemic heart disease (%)	25
Cardiac failure (%)	33
Mode of dialysis at 3 mo	54% HD/46% PD
LV mass index (g/m²)	161 (157 to 169)
LV cavity volume index (ml/m²)	88 (82 to 93)
LV fractional shortening (%)	34 (32 to 35)
SBP[b] (mmHg)	145 (143 to 148)
DBP[b] (mmHg)	81 (79 to 82)
Hemoglobin[b] (g/dl)	8.9 (8.6 to 9.1)
Serum albumin[b] (g/dl)	3.7 (3.7 to 3.8)

[a] Continuous variables are expressed as means with 95% confidence intervals for the means in parentheses. HD, hemodialysis; PD, peritoneal dialysis; LV, left ventricular; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[b] Average of monthly values measured between baseline and follow-up echocardiogram.

Outcomes

Between inception and 1 yr of dialysis therapy, LV mass index decreased in 48%, volume index decreased in 48%, and fractional shortening increased in 46%.

Seventy-six of the 227 patients had a history of cardiac failure at inception of dialysis therapy, while an additional 14 patients developed cardiac failure in the first year of dialysis therapy. Thirty-six of the remaining 137 (26%) patients developed new-onset cardiac failure after 1 yr. In this group, LV mass index had increased on average by 17 g/m², compared with a mean change of 0 g/m² in those remaining free of cardiac failure after 1 yr (P = 0.05) (Table 2). The association between the change in LV cavity volume and the subsequent development of cardiac failure was not statistically significant. Fractional shortening fell by 8% in those destined to develop cardiac failure, compared with 0% in those without cardiac failure (P < 0.0001). Using similar analytic strategies, there was no association between serial echocardiographic changes and ischemic heart disease and death. The associations between changes in LV mass index, fractional shortening, and cardiac failure were virtually identical when patients with normal mass index, cavity volume, and fractional shortening were excluded from analysis. Figure 1 shows the times to development of cardiac failure in patients with and without regression of LV hypertrophy and systolic dysfunction.

Multivariate Analysis

The proportional hazards model was used to adjust event-free times for age, diabetes, ischemic heart disease, as well as the corresponding baseline echocardiographic parameter (Table 3). Cardiac failure after 1 yr was associated with baseline LV mass index, as well as the change in mass between baseline and 1 yr. Baseline cavity volume was also associated with

Table 2. Associations between changes in echocardiographic parameters between baseline and 12 mo and new-onset cardiac failure after 12 mo[a]

Parameter	Cardiac Failure		P Value
	No (n = 101)	Yes (n = 36)	
Change in LV mass index (g/m^2)	0 (−10 to 9)	17 (1 to 33)	0.05
Change in LV cavity volume index (ml/m^2)	4 (3 to 10)	5 (5 to 14)	No association
Change in fractional shortening (%)	0 (−1 to 2)	−8 (−11 to −4)	<0.0001

[a] Continuous variables are expressed as means with 95% confidence intervals of the means in parentheses.
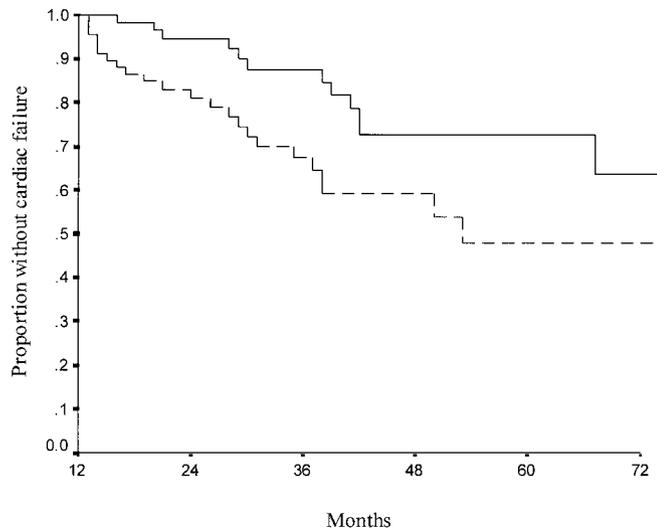

Figure 1. Kaplan–Meier curve showing the time to first onset of cardiac failure in patients whose left ventricular (LV) mass index stayed the same or decreased (——) and those whose LV mass increased (– –). $P = 0.03$ by the log-rank test.

subsequent cardiac failure; the temporal change in cavity volume, however, was not associated with cardiac failure. A fall in fractional shortening was strongly associated with cardiac failure and carried more prognostic weight than the corresponding baseline measurement (Figure 2). The associations between temporal change in mass index and fractional shortening and time to new-onset cardiac failure were unchanged in the following proportional hazards models:

- including baseline mass index, cavity volume index, fractional shortening, as well as changes in these variables;
- excluding patients with normal mass index, cavity volume, and fractional shortening;
- including hemoglobin and BP levels measured between baseline and follow-up echocardiograms.

Neither ischemic heart disease nor death was associated with change in echocardiographic parameters; baseline values, however, strongly predicted these events.

Discussion

In this study, we found that a lowering of cardiac size and an increase in fractional shortening over a 1-yr period after inception of dialysis therapy were both associated with a reduced

subsequent likelihood of cardiac failure. These associations were independent of baseline age, diabetes mellitus, ischemic heart disease, and baseline echocardiographic parameters. However, neither ischemic heart disease nor death was associated with serial changes in echocardiographic parameters.

It is difficult to be certain whether dialysis patients with pulmonary edema truly have cardiac failure or a generalized increase in extracellular fluid volume. We were aware of this when designing the study. Although considerable clinical effort was made to determine that pulmonary edema was occurring at dry weight, quantitative determination of volume status was not routinely performed. It would probably have been difficult to routinely apply investigations such as central venous pressure measurement, bioimpedance, or inferior vena caval ultrasound in all cases of acute pulmonary edema. This legitimate concern can also be applied to the echocardiographic studies. However, our definition of cardiac failure appeared to result in the selection of a group with a very poor prognosis: mortality was 5.18 times higher in patients who developed new-onset cardiac failure compared to those who remained free of cardiac failure ($P < 0.0001$). It is noteworthy that changes in the LV parameter most typically associated with acute volume overload, cavity volume, were not subsequently associated with cardiac failure.

There is considerable evidence, accumulated over several years, that cardiac failure in dialysis patients is associated with very poor survival (28–30). We and others have shown that echocardiographic abnormalities at inception of dialysis therapy are associated with shorter survival in dialysis patients, as seems to be the case in general, hypertensive, coronary artery disease and renal transplant populations (1,2,31–34). In addition, previous analysis of this study cohort has strongly suggested that the association between LV abnormalities and death is through the intermediate stage of cardiac failure (35). It was particularly noteworthy that a lag phase of approximately 2 yr was required before baseline echocardiographic abnormalities were translated into increased mortality risk (1,35). A time lag between abnormalities of LV size and outcome has also been observed in subjects with essential hypertension (32). It is tempting, therefore, to speculate that the lack of association between serial echocardiographic changes and mortality in this study may be a lag phase effect.

Serial change in LV parameters was not associated with the subsequent occurrence of ischemic heart disease events. However, the echocardiographic classification at baseline and first

Table 3. Cox regression analysis: associations between baseline echocardiographic parameters, changes in echocardiographic parameters between baseline and 12 mo, and cardiac failure after 12 mo

Parameter	Hazards Ratio (95% confidence interval)	*P* Value
Change in LV mass index[a] (per 20 g/m²)		
baseline	1.3 (1.1 to 1.4)	0.001
difference	1.3 (1.1 to 1.5)	0.0006
Change in LV cavity volume index[b] (per 20 ml/m²)		
baseline	1.3 (1.1 to 1.6)	0.01
difference	1.2 (0.9 to 1.4)	No association
Change in LV fractional shortening[c] (per 5%)		
baseline	0.9 (0.7 to 1.2)	No association
difference	0.7 (0.6 to 0.8)	0.0001

[a] The model covariates were age, diabetes mellitus, ischemic heart disease, and LV mass index at baseline and the change in LV mass index from baseline to 1 yr.

[b] The model covariates were age, diabetes mellitus, ischemic heart disease, and LV cavity volume index at baseline and the change in LV volume index from baseline to 1 yr.

[c] The model covariates were age, diabetes mellitus, ischemic heart disease, and LV fractional shortening at baseline and the change in LV fractional shortening from baseline to 1 yr.
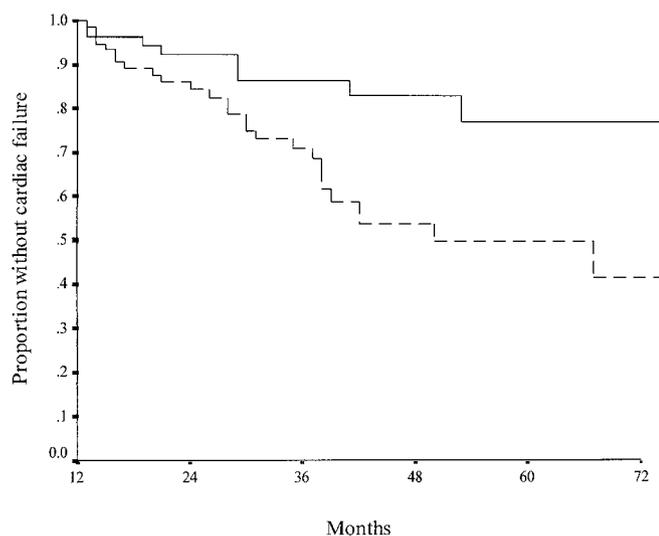
Figure 2. Kaplan–Meier curve showing the time to first onset of cardiac failure in patients whose percentage fractional shortening stayed the same or decreased (—-) and those whose percentage fractional shortening increased (———). *P* = 0.004 by the log-rank test.

year were both associated with this outcome. It is conceivable that occlusive vascular disease and LV abnormalities share risk factors, especially in the predialysis phase. In this study, LV echocardiographic parameters were highly correlated at baseline and 1 yr. It is possible that echocardiographic abnormalities at baseline may be associated with subsequent coronary artery disease via shared risk factors, without being directly involved in each other's pathogenesis.

Many potentially reversible risk factors have been associated with echocardiographic abnormalities in chronic renal disease (1,3,5–21). Anemia and hypertension, however, appear to be the risk factors most consistently associated with this progression, both in observational studies and in controlled clinical trials. Both risk factors are associated with cardiac outcomes in

end-stage renal disease. In previous reports from this study, anemia and hypertension were associated with cardiac failure, a pre-lethal occurrence that predated two-thirds of all dialysis patient deaths. In addition, both anemia and hypertension were associated with progression of echocardiographic abnormalities in the first year of dialysis therapy (6,20). In the current report, the prognostic impact of serial echocardiographic change was independent of, and dominant over, both risk factors. Taken together, these observations suggest that risk factors like anemia and hypertension may exert their adverse impact through the following maladaptive cascade: risk factor, progression of LV echocardiographic abnormalities, cardiac failure, death.

In conclusion, regression of LV abnormalities is associated with improved cardiac outcome in dialysis patients. Serial echocardiography adds prognostic information beyond that provided by a single baseline study. Echocardiographic outcomes appear to be very useful surrogate markers for intervention trials in dialysis patients.

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