Prognostic Value of Echocardiographic Indicators of Left Ventricular Systolic Function in Asymptomatic Dialysis Patients

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Abstract. Patients with end-stage renal disease (ESRD) are at high risk for heart failure, but the prevalence and the prognostic value of asymptomatic systolic dysfunction in these patients are unknown. In this prospective cohort study, the authors have therefore assessed by echocardiography the prevalence and the prognostic value of systolic function as estimated by ejection fraction (EF), fractional shortening at endocardial level (endoFS), and at midwall (mwFS), in a cohort of 254 asymptomatic dialysis patients. Systolic dysfunction had a prevalence rate of 26% by endoFS and of 48% by mwFS. During the follow-up period, 125 patients had one or more fatal and nonfatal CV events. On multivariate COX regression analysis, the three LV systolic function indicators were independently associated with incident fatal and nonfatal CV events, and there were no differences in the predictive power of these indicators ($P > 0.30$). The prediction power of LV function indicators was largely independent of traditional and novel risk factors in ESRD such as C-reactive protein and asymmetric dimethyl arginine (ADMA). ADMA was significantly related with LV function indicators as well as with mortality and incident CV events, but these links were much reduced (P = NS) in models including LV function indicators. Of note, the risk of CV events was minimal in patients with normal LV mass and function, intermediate in patients with either LVH or systolic dysfunction, and maximal in patients displaying both alterations. The study of myocardial contractility by echocardiography provides prognostic information independently of LV mass and other risk factors in ESRD. Risk stratification by simple systolic function parameters may prove useful in secondary prevention strategies in these patients.

Cardiac disease is the major cause of death in patients with end-stage renal disease (ESRD). The detection of echocardiographic abnormalities associated with subclinical cardiac disease is considered to be an important step for the characterization of individuals at risk for heart failure in the general population (1). Although the problem is now felt to be of paramount importance, there are very few studies examining the prognostic power of echocardiographic abnormalities in ESRD. Landmark observations by Parfrey and Foley (2–5) in the 1990s showed that alterations of left ventricular (LV) mass and function are exceedingly frequent in patients with ESRD, and the prediction value of LVH in the dialysis population is now firmly established (3,5–7). In contrast, the prognostic power of systolic function in ESRD has been scarcely studied. The issue is important because systolic function was a marker of shorter survival in a series of patients studied on the eve of renal transplantation (8) and because associations between changes in fractional shortening and subsequent cardiac failure (9) or between systolic function and survival were reported in a population with a high prevalence of heart failure (4). Yet the prevalence of systolic dysfunction in asymptomatic dialysis patients is still unknown, and it is undefined whether such an alteration predicts cardiovascular (CV) complications in these patients.

Systolic function by echocardiography may be estimated by methods based on measurements made at endocardial level (*i.e.*, by standard fractional shortening [endoFS] or by ejection fraction [EF], which is the index used in the large majority of studies) (10). Since these methods may overestimate systolic function in patients with concentric hypertrophy or remodeling of the left ventricle, a new, geometry-independent index of myocardial contractile efficiency, midwall fractional shortening (mwFS), has been proposed as a measure of systolic function.

This prospective cohort study was conceived to assess the prevalence and the independent prognostic value of systolic

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function in a large cohort of asymptomatic dialysis patients. Another major goal of the study was the comparison of the prognostic value of the above-mentioned methods of measurement of LV function in the same cohort.

Materials and Methods

Protocol

The protocol conformed to the ethical guidelines of our institutions, and informed consent was obtained from each participant. All studies were performed during a nondialysis day, midweek, between 8 a.m. and 1 p.m.

Study Cohort

Two hundred and fifty-four patients with ESRD (144 men and 110 women) who had been on regular dialysis treatment (RDT; 203 on hemodialysis [HD] and 51 on chronic ambulatory peritoneal dialysis [CAPD]) for at least 6 mo, with left ventricular ejection fraction (EF) $>$ 35% and without a history of heart failure (defined on the basis of criteria outlined by Parfrey [4]), were eligible for the study. These patients represented about 70% of the whole dialysis population of four dialysis units. The remaining 30% of patients were excluded because of the presence of circulatory congestion or major infections (20%) or because they were hospitalized for intercurrent illnesses or for logistic reasons/unwillingness to participate in the study (10%). The prevalence of diabetes mellitus in this cohort was 15% (37 of 254 patients). One hundred twenty-two patients had had one or more cardiovascular (CV) events. In particular, 63 patients had had one CV event (myocardial infarction in 8 cases, anginal episodes in 29 cases, peripheral artery diseases in 11 cases, arrhythmia in 10 cases, transient ischemic attacks in 4 cases, and stroke in 1 case) and the remaining 59 patients had had two or more CV complications. All HD patients were virtually anuric (24-h urine volume $<$ 200 ml/d), whereas a minority ($n = 6$) of CAPD patients had a 24-h diuresis $>$ 500 ml/d. HD patients were being treated thrice weekly with standard bicarbonate dialysis (38 mmol/L Na, 35 mmol/L HCO_3, 1.5 mmol/L K, 1.25 mmol/L Ca, 0.75 mmol/L Mg) and cuprophan or semi-synthetic membranes (dialysis filters surface area: 1.1 to 1.7 m^2). Dry weight was established for each patient on a trial-and-error basis and was defined as the weight below which the patient suffered frequent hypotensive episodes during the latter part of the dialysis session and experienced malaise, cramps, and dizziness after dialysis.

The average urea Kt/V in these patients was 1.22 $\pm$ 0.27. Patients on CAPD were all on a 4-exchange/d schedule with standard dialysis bags. The average weekly Kt/V in these patients was 1.67 $\pm$ 0.31. One hundred seven patients were habitual smokers (22 $\pm$ 17 cigarettes/d). One hundred thirty-five patients were on treatment with erythropoietin. One hundred eleven patients were being treated with antihypertensive drugs (78 on monotherapy with ACE inhibitors, AT-1 antagonists, calcium channel blockers, alpha- and beta-blockers, and the remaining 33 on double or triple therapy with various combinations of these drugs).

Follow-up Study

Patients were followed up for 41 $\pm$ 22 mo after the initial assessment. During the follow-up, CV events (myocardial infarction, documented angina, heart failure, transient ischemic attacks or stroke, peripheral artery disease, venous thrombosis, artery thrombosis, new onset of ECG-documented arrhythmia) and causes of death were accurately recorded. Each death was reviewed and assigned an underlying cause by a panel of five physicians. As a part of the review process, all available medical information about each death was collected. This information always included study and hospitalization records. In the case of an out-of-hospital death family members were interviewed by telephone to better ascertain the circumstances surrounding death.

Laboratory Measurements

Fasting blood sampling was obtained between 8.00 and 12.00 a.m. Serum lipids, albumin, hemoglobin, calcium and phosphate, C-reactive protein (CRP), and homocysteine were measured by standard methods in the routine clinical laboratory. Plasma asymmetric dimethyl arginine (ADMA) was measured as previously reported (11).

BP Measurements

In hemodialysis patients predialysis and postdialysis BP were calculated as the average value of all recordings (12 measurements [*i.e.*, 3/wk]) taken during the month preceding the study. The mean value of predialysis and postdialysis BP was then obtained for each patient and considered for global statistical assessment. In CAPD patients, the BP values were obtained by averaging home blood pressure measurements (10 to 20 measurements/mo).

Echocardiography

These studies were performed within 2 h after blood sampling during a midweek nondialysis day in HD patients and at empty abdomen in CAPD patients. All echocardiographic measurements were carried out according to the recommendations of the American Society of Echocardiography by an observer unaware of biochemical results. Left ventricular mass (LVM) was calculated according to the Devereux formula and indexed to height$^{2.7}$ (LVMI) (12). Left ventricular hypertrophy (LVH) was defined by a LVMI $>$ 47 g/$m^{2.7}$ in women or $>$ 50 g/$m^{2.7}$ in men. EF was calculated by the Teicholz method (13). Fractional shortening at endocardial levels was calculated by the formula: endoFS = (LVEDD $-$ LVESD)/LVEDD $\times$ 100, where LVEDD and LVESD represent the diameter of the LV at end diastole and end systole, respectively). Fractional shortening at midwall (mwFS) was calculated according to the method of Shimizu *et al.* (14) as described in full detail by De Simone *et al.* (15). To have an estimation of end systolic stress, circumferential end-systolic stress was calculated (16). Ejection Fraction $<$ 50%, endoFS $<$ 28%, and mwFS $<$ 14% (17) were considered indicative of LV systolic dysfunction.

Statistical Analyses

Data are reported as mean $\pm$ SD, median and interquartile range, or as percent frequency, and comparisons between groups were made by *t* test, Mann-Whitney test, or χ^2 test, as appropriate. Relationships between paired parameters were analyzed by Pearson product moment correlation coefficient.

The performance of LV systolic function (estimated on the basis of EF, endoFS, and mwFS) in the prediction of survival and CV events (fatal and nonfatal) was tested by the multivariate Cox regression method. To construct multivariate Cox models, we preliminarily identified a set of variables that significantly differed ($P < 0.05$) in patients who died and in those who survived and in those with and without incident CV events ("basic model," Table 1). Tested covariates included traditional risk factors (age, male gender, smoking, diabetes, cholesterol, previous CV events, arterial pressure, and antihypertensive treatment), hemoglobin, albumin, calcium and phosphate, CRP, homocysteine, and ADMA. To assess the prognostic value of the three indicators of systolic function, we compared three

Table 1. Demographic, anthropometric, biochemical, and hemodynamic characteristics in survivors and nonsurvivors and in patients with and without incident CV events[a]

	Survivors (n = 123)	Nonsurvivors (n = 131)	P	Without CV Events (n = 129)	With CV Events (n = 125)	P
Age (yr)	52.7 ± 15.0	67.4 ± 12.0	<0.001[b]	55.2 ± 16.8	65.5 ± 11.9	<0.001[b]
Males n (%)	59 (48%)	85 (65%)	0.007[b]	69 (53%)	75 (60%)	0.29
Duration of RDT (mo)	39 (15–92)	44 (19–101)	0.53	38 (15–103)	45 (19–90)	0.43
Patients with previous CV events n (%)	36 (29%)	86 (66%)	<0.001[b]	43 (33%)	79 (61%)	<0.001[b]
Diabetic patients n (%)	7 (5%)	30 (23%)	<0.001[b]	10 (8%)	27 (22%)	0.002[b]
Smokers n (%)	40 (33%)	67 (51%)	0.003[b]	41 (32%)	66 (53%)	0.001[b]
On antihypertensive teraphy n (%)	55 (45%)	56 (43%)	0.75	44 (34%)	67 (54%)	0.002[b]
Hemoglobin (g/L)	107 ± 18	105 ± 20	0.44	108 ± 19	104 ± 19	0.11
Albumin (g/L)	41.7 ± 5.3	38.7 ± 5.4	<0.001[b]	41.0 ± 5.4	39.3 ± 5.8	0.02[b]
C-reactive protein (mg/L)	4.0 (3.4–11.6)	11.6 (4.1–22.4)	<0.001[b]	4.7 (3.4–14.5)	8.3 (3.5–19.4)	0.01[b]
Cholesterol (mmol/L)	5.39 ± 4.43	5.29 ± 1.36	0.57	5.31 ± 1.45	5.37 ± 1.36	0.74
Phosphate (mmol/L)	2.01 ± 0.46	1.92 ± 0.45	0.12	1.95 ± 0.47	1.98 ± 0.44	0.63
Calcium (mmol/L)	2.29 ± 0.25	2.24 ± 0.28	0.18	2.27 ± 0.28	2.26 ± 0.25	0.56
Homocysteine (μmol/L)	26.8 (19.2–42.3)	27.0 (21.0–39.1)	0.96	24.9 (18.2–38.4)	28.7 (21.9–43.4)	0.09
ADMA (μmol/L)	2.65 (1.46–3.93)	3.34 (2.14–4.79)	0.002[b]	2.68 (1.52–4.09)	3.24 (2.13–4.71)	0.03[b]
Systolic BP (mmHg)	131.6 ± 20.7	134.8 ± 24.1	0.27	129.8 ± 20.5	136.8 ± 24.0	0.01
Diastolic BP (mmHg)	76.4 ± 11.6	73.6 ± 12.9	0.06	76.0 ± 11.6	73.9 ± 13.0	0.19
Heart rate (beats/min)	80.9 ± 10.4	80.2 ± 13.5	0.64	80.5 ± 10.7	80.6 ± 13.4	0.94

[a] ata are expressed as mean ± SD, median interquartile range), or percent frequency, and comparisons between groups were made by t test, Mann-Whitney test, or χ^2 test, as appropriate.

[b] Significant.

separate Cox models. These models included the variables of the basic model (see above) and EF, endoFS, and mwFS, respectively. End systolic circumferential stress (*i.e.*, an indicator of the afterload of the left ventricle) and the treatment modality (HD/CAPD) were always introduced into these Cox models. To compare the statistical strength of the three models, we used the −2 log likelihood (−2 Log L) test. This test compares different Cox models fitted to the same set of survival data; the smaller the −2 Log L value, the better the agreement between the model and the observed data (18). The difference between the −2 Log L of the models, which are being compared, gives a statistical estimate as to which of them provides a better fit to the data. A 3.841 difference in −2 Log L coincides with a significance level of 0.05 in a χ^2 distribution, with 1 degree of freedom and indicates a better prediction of risk estimate provided by the method leading to the lowest −2 log L value. By this strategy, we constructed models of adequate statistical power (at least 10 events for each variable in models). Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated with the use of the estimated regression coefficients and their standard errors in the Cox regression analysis. The study of the interaction between LVH and systolic dysfunction in predicting incident cardiovascular outcomes was made by constructing multivariate Cox models, including all variables of the basic model mentioned above and listed in Table 3. All calculations were made using a standard statistical package (SPSS for Windows Version 9.0.1, Chicago IL).

Results

Seventy-seven percent (196 of 254 patients) displayed LVH at echocardiography. As expected, ejection fraction and its monodimensional equivalent (fractional shortening at endocardial level) identified a lower number of patients with LV chamber dysfunction (22% and 26%, respectively) when compared with the corresponding midwall measurement (48%). EF ($r = -0.48$), endoFS ($r = -0.46$), and mwFS ($r = -0.55$) were inversely related to LVMI (all $P < 0.001$). Of note, at comparable mwFS, both EF (Figure 1A) and endoFS (Figure 1B) were consistently higher ($P < 0.001$) in patients with concentric remodeling or concentric LVH than in patients with eccentric LVH or normal LV mass and geometry. This phenomenon indicates that systolic function by EF or endoFS is systematically overestimated in the presence of concentric remodeling or concentric LVH.

Systolic Function and Survival

During the follow-up period (41 ± 22 mo), 131 patients died, 77 of them of CV causes. The independent relationship between indicators of systolic function and all-cause mortality was tested in separate Cox models. These models included the systolic function indicators, circumferential stress, and treatment modality as well as variables that significantly differed in patients who died and in those who survived (Table 1). In these multivariate analyses, EF ($P = 0.09$), endoFS ($P = 0.08$), and mwFS ($P = 0.08$) just failed to predict all-cause mortality, and no differences emerged in the predictive power for survival of these indicators (−2 Log likelihood test among models, $P > 0.70$).

Systolic Function and Cardiovascular Outcomes

During the follow-up period, 125 patients had one or more fatal and nonfatal CV events. Patients with incident CV events were older, with a higher prevalence of individuals with background CV complications, diabetic patients, smokers, and antihypertensive drugs users. Serum CRP, plasma ADMA, and systolic BP were higher and serum albumin lower in patients with incident CV events than in those without such events (Table 1). As shown in Table 2, patients who died and those with incident CV events displayed higher LVMI and depressed EF, endoFS, and mwFS in comparison with those who survived and with those who did not develop incident events. On multivariate Cox regression analysis, the three LV systolic function indicators independently predicted fatal and nonfatal CV events (Table 3) in statistical models including circumferential stress and treatment modality as well as all covariates that significantly differed in the two groups (Table 1); again, there were no differences in the predictive power of these indicators (−2 Log likelihood test among models, $P > 0.30$). Introducing LVMI into these models did not affect the hazard ratios of these estimators (Figure 2). Furthermore, in these models, both ADMA and CRP failed to be independently associated with the outcome. ADMA was significantly related with LV function indicators (r ranging from −0.19 to −0.38, $P \leq 0.003$) as well as with mortality and incident CV events (Table 1), but its prediction

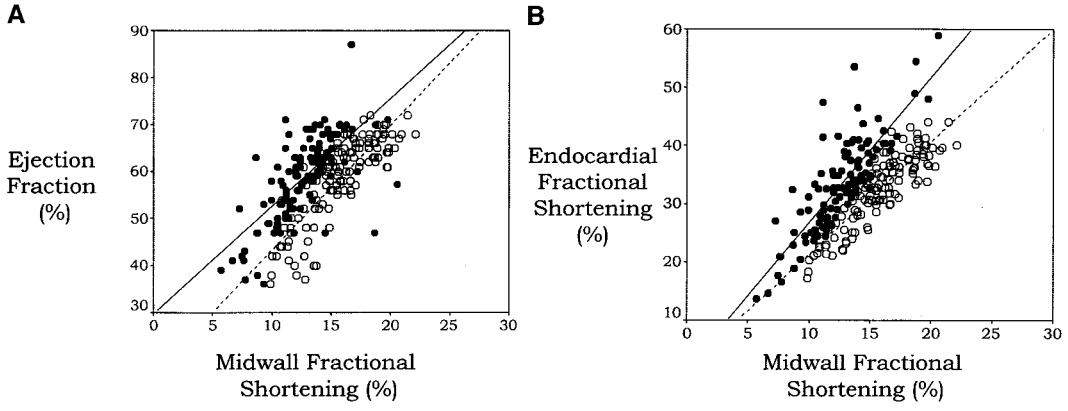

Figure 1. Relationship between midwall fractional shortening with ejection fraction (A) and endocardial fractional shortening (B). ●, patients with concentric remodelling or concentric LVH; ○, patients with eccentric LVH or normal LV geometry.

Table 2. Echocardiographic data in survivors and nonsurvivors and in patients with and without incident CV events[a]

	Survivors (n = 123)	Nonsurvivors (n = 131)	P	Without CV Events (n = 129)	With Incident CV Events (n = 125)	P
Left ventricular end diastolic diameter (cm)	4.94 ± 0.59	5.17 ± 0.73	0.006	4.98 ± 0.67	5.13 ± 0.67	0.07
Interventricular septum thickness (cm)	1.13 ± 0.22	1.25 ± 0.18	<0.001	1.15 ± 0.21	1.25 ± 0.19	<0.001
Posterior wall thickness (cm)	1.06 ± 0.20	1.18 ± 0.18	<0.001	1.08 ± 0.21	1.17 ± 0.17	<0.001
Relative wall thickness	0.44 ± 0.11	0.47 ± 0.11	0.03	0.45 ± 0.12	0.46 ± 0.10	0.23
LVMI (g/height$^{2.7}$)	55.6 ± 16.3	71.6 ± 19.8	<0.001	58.0 ± 17.9	69.9 ± 20.0	<0.001
Circumferential end systolic stress (kdynes/cm^2)	139.4 ± 40.7	155.2 ± 55.0	0.01	140.4 ± 48.1	155.0 ± 49.2	0.02
Ejection fraction (%)	61.6 ± 8.2	54.8 ± 10.1	<0.001	60.9 ± 9.0	55.2 ± 9.7	<0.001
Endocardial fractional shortening (%)	35.2 ± 6.7	30.1 ± 7.3	<0.001	34.6 ± 6.7	30.4 ± 7.7	<0.001
Midwall fractional shortening (%)	15.5 ± 3.1	13.1 ± 3.0	<0.001	15.2 ± 3.2	13.2 ± 3.1	<0.001

[a] Data are expressed as mean ± SD. The comparisons between groups were made by t test.

power for these complications was much reduced (P = NS) in models including LV function indicators (Table 3). Of note, LVH and systolic dysfunction however estimated interacted in predicting incident CV events (Figure 3) because the risk of such events was minimal in patients with normal LV mass and function (reference group), intermediate in patients with either LVH or systolic dysfunction, and maximal in patients displaying both alterations (P for trend ≤ 0.02).

Discussion

This study shows that LV systolic dysfunction is frequent in asymptomatic dialysis patients and that, independently of LV mass and other risk factors, it carries prognostic value for incident CV complications. Furthermore, our data show that the presence of systolic dysfunction interacts with LVH in the prediction of incident CV events in these patients.

Cardiomyopathy and Systolic Dysfunction in ESRD

Although the precise mechanism responsible for cardiomyocyte dysfunction in ESRD is still incompletely understood, studies by Raine *et al.* (19) in the early 1990s showed that cardiac energetics and myocardial calcium utilization are impaired in the uremic heart. Other studies indicate that uremia affects the very composition of cardiac myofibrils because the proportion of V1 isomyosin is increased, and the response of this isomer to regulatory signals is set at a higher level in the rat (20). Furthermore, it has been recently documented that renal failure leads to alterations in cardiac gene expression, which in turn alters calcium cycling and contractile function (21).

Independently of the mechanism(s) responsible for cardiac dysfunction, the identification of asymptomatic individuals with left ventricular dysfunction is important and formally recommended by current guidelines (22). Asymptomatic systolic dysfunction represents a preclinical phase of congestive heart failure. Such an alteration has a 3% to 6% prevalence in the general population, and it is currently recommended that screening for this condition should be part of preventive strategy of chronic heart failure (10,23). Patients with ESRD represent a population at high risk for heart failure (2,4). Indeed it has been shown that more than one third of patients starting dialysis treatment (4) display clinical evidence of heart failure and that myocardiopathy progresses after starting dialysis (5). Systolic function in dialysis patients has been scarcely investigated. In a recent study in patients without coronary heart disease, systolic LV apex-base function has been reported to be unaltered (23). Other studies in unselected pediatric (24) and adult (4,25,26) ESRD patients showed that systolic function is depressed. Until now, only one study has tested the prognostic power of systolic function in the dialysis population (4), but this study included a substantial proportion of patients with overt heart failure. If the echocardiographic study of systolic function has to be applied in clinical practice for risk stratification in ESRD, it is important to focus the attention in asymptomatic patients because it is well demonstrated that the presence of overt heart failure *per se* is an ominous prognostic factor in the general (27) and dialysis populations (2). How-

Table 3. COX regression analysis of ejection fraction, endocardial fractional shortening, and midwall fractional shortening for incident fatal and non fatal CV events[a]

	Units	Hazard ratio (95% CI)	*P*
Ejection fraction–based model[b]			
age	1 yr	1.03 (1.02–1.05)	<0.001
ejection fraction	1% decrease	1.04 (1.02–1.07)	0.001
previous CV events	yes/no	1.82 (1.23–2.71)	0.003
smoking	yes/no	1.45 (0.98–2.14)	0.06
antihypertensive treatment	yes/no	1.41 (0.90–2.21)	0.13
circumferential end systolic stress	1 kdynes/cm^2	1.00 (0.99–1.01)	0.17
treatment modality	CAPD/HD	1.49 (0.83–2.70)	0.18
ADMA	1 μmol/L	1.06 (0.96–1.16)	0.25
systolic pressure	1 mmHg	1.01 (0.99–1.02)	0.31
diabetes	yes/no	0.84 (0.51–1.38)	0.49
albumin	1 g/L	1.01 (0.97–1.06)	0.59
CRP	10 mg/L	1.01 (0.92–1.10)	0.90
	Units	Hazard ratio (95% CI)	*P*
Endocardial fractional shortening–based model[c]			
age	1 yr	1.03 (1.02–1.05)	<0.001
endocardial fractional shortening	1% decrease	1.06 (1.02–1.10)	0.002
previous CV events	yes/no	1.86 (1.25–2.77)	0.002
smoking	yes/no	1.43 (0.97–2.11)	0.07
treatment modality	CAPD/HD	1.64 (0.90–2.98)	0.11
antihypertensive treatment	yes/no	1.40 (0.89–2.19)	0.14
circumferential end systolic stress	1 kdynes/cm^2	1.00 (0.99–1.01)	0.16
ADMA	1 μmol/L	1.06 (0.97–1.16)	0.19
systolic pressure	1 mmHg	1.01 (0.99–1.02)	0.36
diabetes	yes/no	0.83 (0.51–1.36)	0.46
albumin	1 g/L	1.01 (0.97–1.06)	0.54
CRP	10 mg/L	1.00 (0.92–1.09)	0.92
	Units	Hazard ratio (95% CI)	*P*
Midwall fractional shortening–based model[d]			
age	1 yr	1.03 (1.02–1.05)	<0.001
previous CV events	yes/no	1.87 (1.26–2.77)	0.002
midwall fractional shortening	1% decrease	1.11 (1.03–1.19)	0.003
smoking	yes/no	1.40 (0.94–2.07)	0.09
treatment modality	CAPD/HD	1.63 (0.90–2.96)	0.11
antihypertensive treatment	yes/no	1.41 (0.90–2.21)	0.13
ADMA	1 μmol/L	1.06 (0.97–1.16)	0.21
albumin	1 g/L	1.02 (0.97–1.06)	0.46
circumferential end systolic stress	1 kdynes/cm^2	1.00 (0.99–1.01)	0.50
diabetes	yes/no	0.88 (0.54–1.42)	0.60
systolic pressure	1 mmHg	1.00 (0.99–1.01)	0.76
CRP	10 mg/L	1.00 (0.92–1.09)	0.91

[a] The *P* value of each predictor included in the table is derived from the Wald statistic [(*i.e.* regression coefficient/SE of the regression coefficient)^2]. Factors are ranked according to the strength of their link with the outcome.
[b] −2 log likelihood: 1143.686.
[c] −2 log likelihood: 1143.928.
[d] −2 log likelihood: 1144.934.

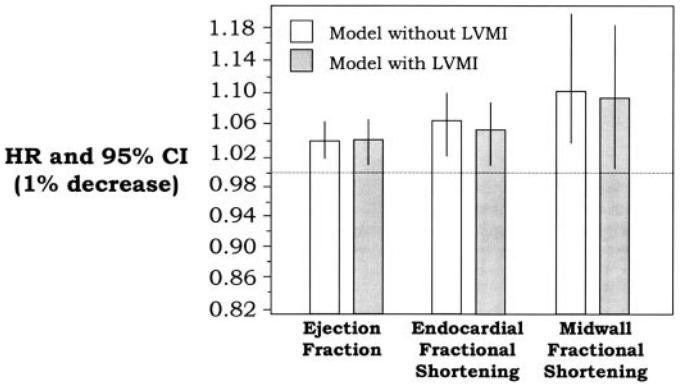

Figure 2. Hazard ratios for incident CV events associated with a 1% decrease in LV function in each estimator. White columns, hazard ratios adjusted for all covariates listed in Table 3 except LVMI; gray columns, hazard ratios adjusted for all covariates listed in Table 3 and for LVMI.

ever, the prevalence of systolic dysfunction in asymptomatic patients with ESRD is unknown, and it is still undefined whether the detection of this alteration by echocardiography conveys prognostic information additional to background CV complications, LVH, and other established risk factors. By the same token, it is unknown whether the study of systolic function based on midwall mechanics (mwFS) is of greater prognostic value in these patients than that of classical indicators based on measurements made at endocardial level (EF and endoFS). This problem is important because due to the nonuniform wall thickening of LV walls during systole, midwall fractional shortening provides better estimates of myocardial contractility than ejection fraction or endocardial fractional shortening when wall thickness is increased by hypertrophy (14,15), which is a notoriously common alteration in ESRD (3,4,6).

Our study was based on a cohort of asymptomatic patients without clinical history of heart failure and with an ejection fraction greater than 35% at baseline. On the basis of the estimate made by indicators based on measurements made at endocardial level (endoFS and EF), we found that the proportion of patients with LV systolic dysfunction was about 7 times higher in ESRD patients than in coeval cohorts in the community (28). Of note, fractional shortening at midwall was subnormal in as much as 48% of our asymptomatic ESRD patients. The much greater proportion of patients identified as having systolic dysfunction by this method in comparison to fractional shortening at endocardial level (26%) depends on the high prevalence of LVH in the dialysis population (77% in the present study), which is of con-

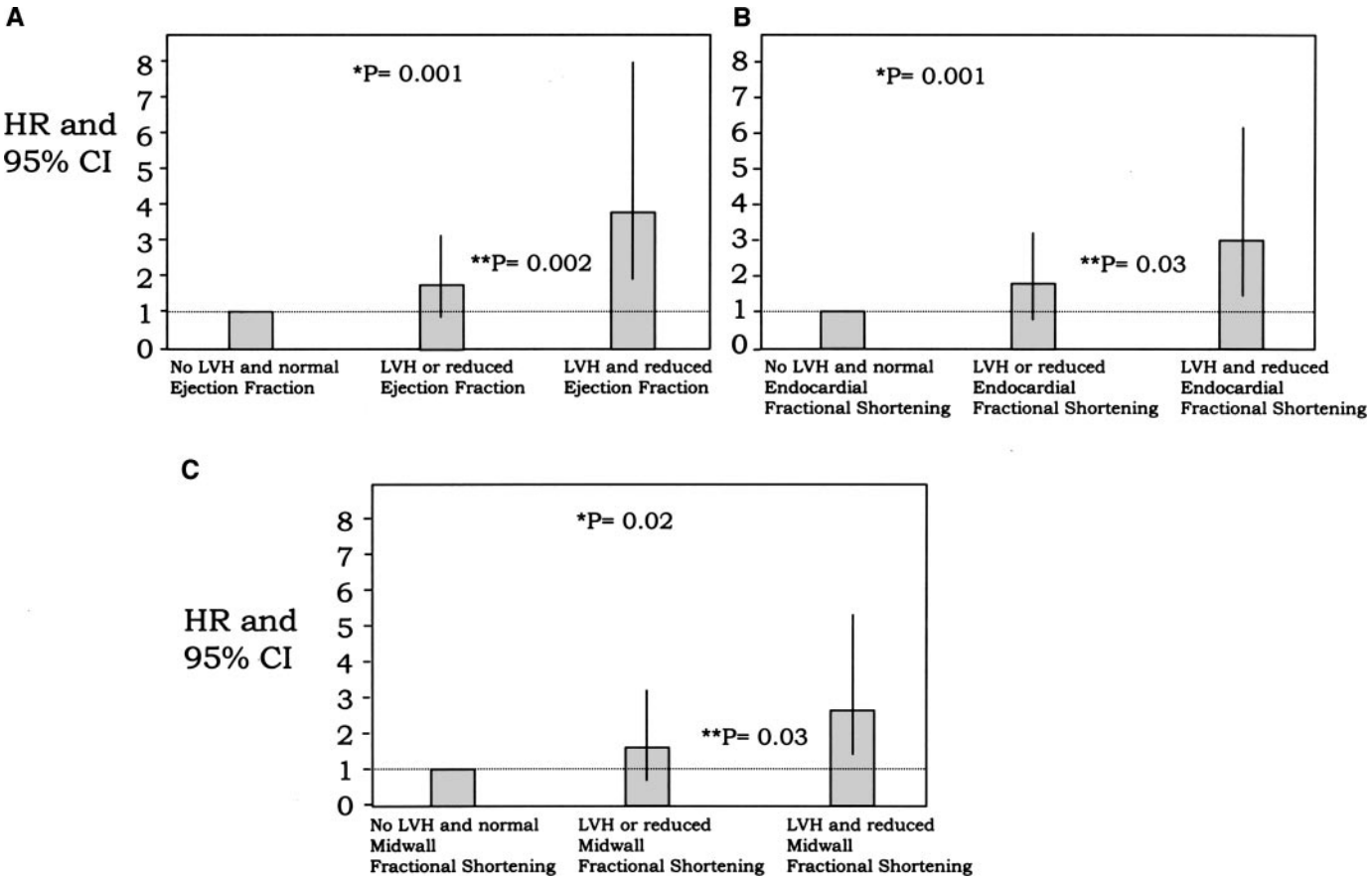

Figure 3. Interaction between systolic dysfunction and LVH in the prediction of incident CV events. Data are adjusted for all covariates listed in Table 3. *P for trend; **P derived from a modified Wald test comparing patients with LVH *or* systolic dysfunction (second column) with those displaying both LVH *and* systolic dysfunction (third column).

centric type in about half of cases. Indeed, as previously noted in essential hypertensive patients (29), we found that, at comparable levels of midwall fractional shortening, both ejection fraction and fractional shortening at endocardial level systematically overestimate systolic function in patients with concentric hypertrophy or remodeling.

Systolic Dysfunction and Cardiovascular Outcomes

The ability to predict the outcome is the basic requirement of any factor (risk factor) that is suspected to influence a given outcome in a given population (30). Thus it is important to test the prognostic value of echocardiographic indicators of systolic function, specifically in the ESRD population. Furthermore, the detection of systolic dysfunction appears particularly relevant in asymptomatic individuals where myocardial disease may progress despite compensatory mechanisms involving the autonomic system, neurohormones, and changes in cardiac function and structure. In this regard, our study is the first showing that LV systolic function either measured by classical indicators (EF and endoFS) or by midwall fractional shortening (mwFS) predict incident CV events in a large population of asymptomatic ESRD patients. The prediction power of these indicators was largely independent of traditional and novel risk factors in ESRD such as CRP and ADMA. In this regard, it is important to note that ADMA, a factor that has been strongly associated both with systolic dysfunction (31) and cardiovascular outcomes (32), failed to independently predict the outcome in models including LV function (Table 3). This phenomenon suggests that LV dysfunction represents not only a prognostic marker but also an intermediate mechanism whereby ADMA may cause cardiovascular complications in ESRD patients. Interestingly, the prediction power of LV dysfunction remained unmodified after adjustment for LVMI, which is considered the strongest predictor of CV complications in this population (33,36). In this regard, it is noteworthy that systolic dysfunction interacted with LVH in predicting such events. Indeed there was a graded increase in CV risk depending on the presence of raised LVMI and compromised LV systolic function, the risk being maximal in individuals who displayed both of these alterations. Our finding that systolic dysfunction interacts with LVH in the prediction of adverse CV outcomes contrasts with studies performed in uncomplicated essential hypertension (34), but it is in keeping with the results of the Cardiovascular Health Study, a population based study of elderly subjects (35).

Comparison of Methods of Measurement of Systolic Function

An objective of our study was to determine which echocardiographic variables of LV function predicted adverse outcomes. We hypothesized that depressed midwall shortening would detect individuals with a normal EF or endoFS at risk for subsequent CV events. This hypothesis was suggested by studies demonstrating that endoFS overestimates systolic function in the presence of concentric LVH or remodeling and that mwFS is a stronger predictor of cardiovascular mortality in essential hypertensive patients (15). Although we confirmed in the dialysis population that mwFS is an independent predictor of cardiovascular outcomes, this indicator did not perform any better than EF or conventional endoFS. Such discrepancy may depend on the fact that dialysis patients have a much shorter CV event-free survival than essential hypertensives. Therefore, the prognostic superiority of mwFS may be apparent only in patients in the early phases of myocardial disease (*i.e.*, those with a long cardiovascular event-free survival), such as in individuals with uncomplicated hypertension. Furthermore the overestimation of systolic function by EF and endoFS may be less problematic in a population with a high frequency of systolic dysfunction (26% by endoFS in this study) than in a population with a low prevalence of this disturbance, like in essential hypertensive patients (3.6% by the same indicator [36]). The difference in the loading conditions of the LV (28) between ESRD patients and essential hypertensive patients may be another reason for the lack of superiority of midwall shortening in ESRD. Whatever the explanation for this phenomenon noted also in other populations (34,35), our data emphasize the importance of testing risk markers specifically in the ESRD population and suggest that simple systolic function parameters can predict adverse CV outcomes in asymptomatic dialysis patients.

The study of myocardial contractility by echocardiography provides prognostic information that is independent of LV mass and other risk factors in ESRD. Risk stratification by any of the systolic function indicators tested in this study may prove useful in secondary prevention strategies in these patients.

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