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Alterations of Left Ventricular Hypertrophy in and Survival of Patients Receiving Hemodialysis: Follow-up of an Interventional Study

GÉRARD M. LONDON,* BRUNO PANNIER,* ALAIN P. GUERIN,* JACQUES BLACHER,† SYLVAIN J. MARCHAIS,* BERNADETTE DARNE,* FABIEN METIVIER,* HASSAN ADDA,* and MICHEL E. SAFAR†

**Service d'Hemodialyse, Hôpital F.H. Manhès, Fleury-Mérogis, and †Service de Médecine Interne, Hôpital Broussais, Paris, France.*

Abstract. Left ventricular (LV) hypertrophy (LVH) is a risk factor for mortality in patients with end-stage renal disease (ESRD). Whether the attenuation of LVH has a positive effect on survival of patients with ESRD has not been documented. The aim of this study was to determine the effect of parallel treatment of hypertension and anemia on LV mass (LVM) and to determine the effect of LVM changes on survival. A cohort of 153 patients receiving hemodialysis was studied. The duration of follow-up was 54 ± 37 mo. All patients had echocardiographic determination of LV dimensions and LVM at baseline and regular intervals until the end of the follow-up period. During the study, BP decreased from (mean ± SD) 169.4 ± 29.7/90.2 ± 15.6 to 146.7 ± 29/78 ± 14.1 mmHg ($P < 0.001$), and hemoglobin increased from 8.65 ± 1.65 to 10.5 ± 1.45 g/dl ($P < 0.001$). The LV end-diastolic diameter and mean wall thickness decreased from 56.6 ± 6.5 to 54.8 ± 6.5 mm ($P < 0.001$), and from 10.4 ± 1.6 to 10.2 ± 1.6 mm ($P < 0.05$), respectively. The LVM decreased from 290 ± 80 to 264 ± 86 g ($P < 0.01$). Fifty-eight deaths occurred, 38 attributed to cardiovascular (CV) disease and 20 attributed to non-CV causes. According to Cox analyses after adjustment for age, gender, diabetes, history of CV disease, and all nonspecific CV risk factors, LVM regression positively affected the survival. The hazard risk ratio associated with a 10% LVM decrease was 0.78 (95% confidence interval, 0.63 to 0.92) for all-causes mortality and 0.72 (95% confidence interval, 0.51 to 0.90) for mortality due to CV disease. These results show that a partial LVH regression in patients with ESRD had a favorable and independent effect on patients' all-cause and CV survival.

Cardiovascular (CV) disease (CVD) is the leading cause of mortality among patients with end-stage renal disease (ESRD) (1,2). Left ventricular (LV) hypertrophy (LVH) and LV dilation determined by echocardiography are frequent cardiac alterations in ESRD and are independent risk factors for mortality (3–7). These alterations develop early during the course of renal insufficiency; their prevalence progresses in parallel with the decline of renal function (8), and LVH is present in 75% of subjects at the start of dialysis (9). These alterations result from the chronic pressure, volume overload, or both, in association with a number of metabolic and neurohumoral abnormalities (10–15). The principal hemodynamic factors responsible for the progression of LVH and LV dilation in patients with renal insufficiency are increased systolic BP (SBP) and anemia (16), and in patients receiving hemodialysis, the arteriovenous (AV) shunts and overhydration further enhance volume overload (3). LV alterations tend to progress over time in the majority of patients (3,16–20). Previous studies showed that treatment of hypertension or anemia could partly reverse LV dilation and LVH, but it has not been demonstrated that this regression has an effect on the survival of these patients (21–24). The aims of this study were to determine the effect of parallel lowering of BP and attenuation of anemia on LV size and function and to determine the effect of LV changes on survival.

Materials and Methods

Patients

The study, which involved a single hemodialysis unit, began in 1990. The mean follow-up period was (mean ± SD) 54 ± 37 mo (range, 10 to 126 mo). Patients were eligible for inclusion if they had been receiving hemodialysis for at least 3 mo (67.7 ± 60.5 mo); if they had a predialysis BP >140/90 mmHg and hemoglobin <11 g/dl; if they had good-quality echocardiography; and if they agreed to participate in the follow-up study, which was approved by our Institutional Review Board. In all, 166 patients met the entry criteria. Because the regression of LVH is a slow process, the final analyses took into consideration only those patients with follow-up periods longer than 9 mo. Thirteen patients were not followed for 9 mo: 3 received a renal transplant, 3 moved, and 7 died (1 accident, 1 sepsis, 1 pulmonary embolism, 2 mesenteric infarction, and 2 acute pulmonary edema). Final analyses were performed on a cohort of 153 patients. Patients who were included in the study who underwent renal

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Correspondence to Dr. Gérard M. London, Hôpital F. H. Manhes, 8 Grande Rue, Fleury-Mérogis, 91712 Cedex, France. Phone: 33169256485; Fax: 33169256525; E-mail: glondon@club-internet.fr
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transplantation and patients who moved were censored on the day of transplantation or departure.

All but 17 patients were white; 62% were men or boys; and 9% had diabetes mellitus. Sixty-four patients had previous history of CVD (27 coronary artery disease, 5 myocardial infarctions, 23 peripheral arterial occlusive disease, aortic aneurysm, or both, and 9 asymptomatic "echocardiographic cardiomyopathy" characterized by a percentage of LV shortening <29%). Data on mortality were obtained for the entire cohort. The mean age of the cohort at inclusion was 51.5 ± 15.3 yr. During the follow-up period, all patients underwent dialysis; the dialysis techniques have been detailed elsewhere (11). Blood chemistries at baseline and at monthly intervals thereafter included blood urea, hemoglobin, serum albumin, blood lipids, calcemia, serum phosphate, and Kt/V, and were determined by standard methods. Since 1994, C-reactive protein (CRP) was measured nephelometrically every 3 mo in 111 patients.

Data Collection

Information compiled from the questionnaire filled out at inclusion included personal and family histories, smoking habits, and history of CVD, including the following: coronary artery disease (angina pectoris, angioplasty, graft), congestive heart failure, aortic and peripheral vascular disease, and cerebrovascular disease. The baseline measurements were made during the 2 wk after inclusion, on the morning before the midweek hemodialysis. BP was measured after 15 min of recumbency with a mercury sphygmomanometer and a cuff of appropriate size in the arm contralateral to the AV shunt. Phases I and V of the Korotkoff sounds were taken as the SBP and diastolic BP (DBP). The mean BP (MBP) was calculated as follows: MBP = DBP + [(SBP − DBP)/3]. The heart rate was determined from the three-lead orthogonal electrocardiogram. Echocardiographic measurements were performed by the same echographer with a Hewlett-Packard Sonos 100 equipped with a 2.25-MHz probe at baseline and at regular intervals (9 mo, 18 mo, 24 mo, and then yearly). Measurements were centralized and read blindly by the same two readers and averaged. LV mass (LVM) measurements were made according to the Penn convention (25) and included the LV end-diastolic diameter (LVEDiD), LV posterior wall thickness (PWTh), and interventricular septal thickness (IVTh). Mean wall thickness (MWTh) was calculated as (PWTh + IVTh)/2, and LV relative wall thickness was calculated as (PWTh + IVTh)/LVEDiD. Three successive complexes were analyzed and averaged. The LVM index was calculated as the ratio LVM/height ($m^{2.7}$) and as the ratio LVM/body surface area (m^2). LV outflow velocity was taken from the apical position, and early (E) and atrial (A) mitral inflow velocities were taken with the signal positioned at the tip of the mitral leaflets. Stroke volume (SV) (ml) was calculated as the aortic annular cross-sectional area multiplied by the velocity integral of LV outflow and cardiac output (L/min) as SV multiplied by heart rate. Total peripheral resistance (TPR) was computed as follows: TPR = MBP × 80/cardiac output. Diastolic filling of the LV was calculated as the E/A ratio. For LVM, intrareader variability was 5.8%, and interreader variability was 8.3%. In a blinded, randomized study, the long-term (1 yr) change of LVM (ΔLVM) under placebo was +4.2% (26).

Aortic stiffness was determined as carotid-femoral pulse wave velocity (PWV) via the foot-to-foot method (27). Transcutaneous Doppler flow-velocity recordings were carried out simultaneously at the base of the neck over the common carotid artery and the femoral artery in the groin with a SEGA M842 8-MHz Doppler unit (SEGA, Paris, France) and a Gould 8188 recorder. The time interval (t) between the feet of the flow waves was determined. The distance traveled by the pulse wave was measured over the body surface as the distance between the two recording sites minus that from the suprasternal notch to the carotid (D). PWV (m/s) was calculated as PWV = D/t.

Interventions

The target of the treatment was to achieve and maintain predialysis BP below 160/90 mmHg or a SBP decrease of >15 mmHg from baseline values. The first step was an attempt to achieve a "dry weight." When this attempt failed, antihypertensive drug therapy was initiated. Patients received as a first-line drug an angiotensin-converting enzyme (ACE) inhibitor or a calcium antagonist. When the BP target was still not achieved, a β-blocker was added. Finally, when elevated BP persisted, ACE inhibitor, calcium blocker, and β-blocker were used in combination. The target BP was achieved after 4 to 14 wk. Recombinant human erythropoietin (EPO) was prescribed at an initial dose of 30 mg/kg per week, provided subcutaneously. The hemoglobin level was monitored bimonthly, and treatment was adjusted accordingly. Hydroxysaccharate iron was administered intravenously to patients with documented iron depletion. The target hemoglobin was set at 10 to 11 g/L, and the mean titration phase lasted 10 wk.

Statistical Analyses

All data are expressed as means ± SD. The D'Agostino Omnibus test was used to assess the shape of distribution curves. Continuous variables were compared by *t* test or Wilcoxon's rank-sum tests as appropriate. ANOVA was used for multiple-group comparisons of normally distributed variables at baseline and follow-up. Differences in frequencies were tested by χ^2 analysis. Gender (0, male; 1, female), and previous CVD (0, no; 1, yes) were used as dummy variables. Multiple correlation–regression analysis was used to test the association of parameters related to ΔLV dimensions or ΔLVM by the least-squares method.

The outcome events studied were all-cause and CV mortality. The primary analysis concerned the survival curves and the Cox proportional hazards model. Survival was estimated by the Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. Factors prognostic of survival were identified by the Cox proportional hazards regression model. The assumption of proportional hazards over time was verified before the analyses and was met by all covariates. The assumption concerning linearity of continuous covariates was also verified before analysis. Because ΔLVM data were not normally distributed, they were converted for the statistical analyses into normally distributed percentage changes from baseline (baseline value − final value/baseline value). Variables were considered to be prognostic when they were found to be statistically significant ($P < 0.05$) in the Cox proportional hazards regression model. Adjusted hazard risk ratios were calculated as the antilogarithm of the β coefficient of the Cox regression of the outcome events with all of the prognostic variables entered into the models (age, duration of dialysis before inclusion, baseline BP, ΔBP, history of CVD, changes in blood chemistries). The 95% confidence intervals for the adjusted risk ratio estimates were obtained with the following formula: antilogarithm (β ± 1.96SE), where SE is the standard error of β. To predict the cutoff values of ΔLVM, we used the receiver operating characteristic curves. The optimal ΔLVM cutoff was defined as the maximization of the sum of sensitivity and specificity (28). All analyses were performed by NCSS 7.0. software (Kaysville, UT).

Results

Overall Population

The clinical and hemodynamic characteristics of the entire cohort at inclusion and end of follow-up are shown in Table 1. Target BP was obtained by adjustment of "dry weight" in 45 patients; antihypertensive drugs alone or in combination were prescribed to 108 patients receiving an average of 1.3 ± 0.9 antihypertensive drugs. BP decreased significantly in the entire cohort. In a multivariate analysis, the ΔSBP were correlated to ΔPWV ($r = 0.498$; $P < 0.001$) and to lesser degree to ΔSV ($r = 0.204$; $P = 0.048$). Similarly, the changes in pulse pressure were correlated to ΔPWV ($r = 0.3582$; $P < 0.001$) and SV changes ($r = 0.236$; $P = 0.0142$). The hemoglobin level increased significantly and the levels achieved corresponded to the therapeutic target. At baseline, the LVEDiD and MWTh were in the upper range of normal values, with normal relative wall thickness. LVM was increased in the overall population. LVH (LVM index >50 g/m$^{2.7}$ and >132 g/m^2 for boys and men, >47 g/m$^{2.7}$ and >110 g/m^2 for women and girls) was present in 138 patients, and 15 patients had LVM indexes within normal range. Nine months after the start of follow-up, the LVM did not change significantly in the entire population (278 ± 78 g). At the end of follow-up, moderate but significant decreases of LVEDiD, MWTh, LVM, and LVM indexes were observed in the entire population (Table 1).

Table 2 shows the multiple correlation between ΔLVM, ΔPWV, and hemoglobin changes (the correlations with ΔSBP were NS when adjusted for ΔPWV). Cardiac output decreased significantly due to lower SV and heart rate. SV changes were correlated with hemoglobin changes ($r = -0.2912$; $P < 0.001$). The percentage of LV shortening moderately decreased, and the E/A ratio moderately increased.

Outcome and Prognostic Effect of ΔLVM

During the follow-up period, 58 deaths occurred, including 38 deaths due to CV failure. According to the Cox analysis, the only significant and independent covariates retained for all-cause mortality were age and history of CVD (positive influence) and decrease of LVM (negative influence) (Table 3). Similar results were observed for CV mortality. Gender, smoking, time on dialysis, blood chemistry abnormalities, and Kt/V were NS independent factors. According to receiver operating

Table 1. Characteristics of the entire population

Parameter	Baseline	End of Follow-Up
Systolic BP (mmHg)	169.4 ± 29.7	146.7 ± 29[b]
Diastolic BP (mmHg)	90.2 ± 15.6	78 ± 14[b]
Pulse pressure (mmHg)	78 ± 23	69 ± 24[b]
Mean BP (mmHg)	116.2 ± 19.1	103.0 ± 17.2[b]
Heart rate (beats/min)	75 ± 13	71 ± 11[b]
Stroke volume (ml)	99.8 ± 22.9	93.7 ± 27.8[b]
Cardiac output (L/min)	7.40 ± 2.0	6.6 ± 2.0[b]
Total peripheral resistance (dyne · s · cm^{-5})	1346 ± 447	1364 ± 478
Pulse wave velocity (m/s)	11.15 ± 2.70	11.03 ± 3.18
LV shortening (%)	35.4 ± 6.7	34 ± 6.4[c]
E/A (ratio)	0.87 ± 0.36	0.93 ± 0.35[d]
LV mass (g)	290 ± 80	264 ± 86[d]
LV mass index (g/m$^{2.7}$)	77.0 ± 19.9	70.5 ± 22.1[d]
LV mass index (g/m^2)	174 ± 45	162 ± 45[b]
LV end-diastolic diameter (mm)	56.6 ± 6.5	54.8 ± 6.5[b]
LV end-systolic diameter (mm)	36.7 ± 7.2	36.4 ± 6.4
LV mean wall thickness (mm)	10.4 ± 1.6	10.2 ± 1.6[c]
LV relative wall thickness (ratio)	0.37 ± 0.07	0.38 ± 0.07
Body weight (kg)	61.8 ± 13	61.5 ± 13
Body height (cm)	163.9 ± 10	163.8 ± 9.9
Body surface area (m^2)	1.66 ± 0.20	1.65 ± 0.20
Hemoglobin (g/100 ml)	8.65 ± 1.65	10.5 ± 1.45[b]
Interdialytic weight gain (kg)	2.51 ± 0.67	2.53 ± 0.64
Total cholesterol (mmol/L)	5.28 ± 1.13	5.13 ± 1.14[c]
HDL cholesterol (mmol/L)	1.10 ± 0.30	1.08 ± 0.37
Triglycerides (mmol/L)	1.69 ± 0.94	1.78 ± 0.92
Serum albumin (g/L)	40.5 ± 2.2	40.3 ± 3.0

[a] Values are means ± standard deviation.
[b] $P < 0.001$.
[c] $P < 0.05$.
[d] $P < 0.01$.

Table 2. Multiple regression for changes of left ventricular mass as a dependent variable during follow-up

Parameter	β Coefficient	*t* Value	*P* Value	Sequential r^2	Partial r^2
Δ Pulse wave velocity (m/s)	4.10	7.43	0.00001	0.3059	0.2703
Δ Hemoglobin (g/L)	−3.12	−3.47	0.00068	0.3578	0.0747
		$r^2 = 0.3578$; F ratio = 41.5; $P < 0.00001$			

Table 3. Proportional hazards risk ratios for all-cause and cardiovascular mortality as censor variables for an entire population

Parameter	RR (95% CI)	*z* Statistic	*P* Value	Pseudo-r^2
All cause				
age (yr)	1.05 (1.02–1.08)	3.90	0.0001	0.1330
Δ LVM (10% decrease)	0.78 (0.63–0.92)	3.24	0.0012	0.0957
prior CVD (0, no; 1, yes)	2.42 (1.25–4.67)	2.62	0.0088	0.0649
		$\chi^2 = 65.6$; $P < 0.00001$; pseudo $r^2 = 0.3984$		
Cardiovascular				
Δ LVM (10% decrease)	0.72 (0.51–0.90)	3.16	0.0016	0.1048
prior CVD (0, no; 1, yes)	3.90 (1.60–9.82)	2.89	0.0039	0.0894
age (yr)	1.04 (1.01–1.07)	2.46	0.0141	0.0662
		$\chi^2 = 51$; $P < 0.00001$; pseudo $r^2 = 0.3750$		

[a] RR, relative risk; LVM, left ventricular mass; CVD, cardiovascular disease; CI, confidence interval.

characteristic curves, the best cutoff value for all-cause survival was a 4.5% decrease of LVM with a sensitivity of 80%, specificity of 69%, positive predictive value of 61%, and negative predictive value of 84%. The cutoff value for CV survival was a 6.7% decrease in LVM with similar sensitivity and specificity.

Because the prevalence of history of CVD had a very strong effect on mortality, a Cox analysis of patients with no history of CVD ($n = 89$; receiving dialysis 63.3 ± 58.6 mo; aged 44.4 ± 15.4 yr; follow-up period 54.3 ± 34 mo) was also performed. Results (Table 4) indicate that a decrease of LVM in this population was also associated with lower all-cause and CV mortality.

Comparisons of Responders and Nonresponders

Previous prospective blinded and randomized interventional studies (21,27) performed in our department, which aimed at assessing the different components of the variability of repeated measurements of LVM and LVM index, showed that an 8.6% decrease from the baseline LVM was the limit of the regression to the mean when patients were selected on the basis of the presence of LVH (29). Therefore, in the study presented here, the patients whose LVM decreased by >10% were considered to be responders, and those whose LVM increased or decreased by <10% were considered to be nonresponders. On the basis of this cutoff value, patients were divided as follows: 70 responders and 83 nonresponders (LVM was stable in 33 patients and increased in 50) (Table 5). During follow-up, 48 nonresponders died *versus* 10 responders ($P < 0.001$) (Figure 1).

At baseline, the nonresponders had been on dialysis for 50 mo (4 to 237 mo) in comparison with 37 mo (4 to 225 mo) for responders (NS). Nonresponders were older (54 ± 15 *versus* 49 ± 16 yr, $P < 0.05$), with higher proportions of girls and

Table 4. Proportional hazard risk ratios for all-cause and cardiovascular mortality as censor variables for patients with no history CVD[a]

Parameter	RR (95% CI)	*z* Statistic	*P* Value	Pseudo-r^2
All cause				
age (yr)	1.08 (1.02–1.14)	2.70	0.0069	0.1450
Δ LVM (10% decrease)	0.69 (0.52–0.83)	2.39	0.0182	0.1141
		$\chi^2 = 18.5$; $P = 0.00012$; pseudo $r^2 = 0.2992$		
Cardiovascular				
Δ LVM (10% decrease)	0.52 (0.23–0.75)	2.38	0.0204	0.1167
age (yr)		1.63	NS	
		$\chi^2 = 5.80$; $P = 0.0204$; pseudo $r^2 = 0.1167$		

[a] RR, relative risk; CI, confidence interval; LVM, left ventricular mass; NS, not significant.

Table 5. Hemodynamic characteristics of responders and nonresponders at baseline and follow-up[a]

Parameter	Responders ($n = 70$)		Nonresponders ($n = 83$)	
	Baseline (1)	Follow-up (2)	Baseline (3)	Follow-up (4)
Systolic BP (mmHg)	168.4 ± 28.4	137.3 ± 28.4C	168.4 ± 31.6	154.2 ± 27.0C, H
Diastolic BP (mmHg)	90.4 ± 16.7	76.7 ± 13.4C	88.6 ± 16.1	80.0 ± 14.2C
Mean BP (mmHg)	116.5 ± 20.0	99.6 ± 16.7C	114.6 ± 18.9	104.6 ± 16.4C
Pulse pressure (mmHg)	75.8 ± 21.4	60.6 ± 21.7C	79.4 ± 23.7	75.1 ± 23.0A, H
Heart rate (beat/min)	73.8 ± 13.7	69.2 ± 10.5A	76.0 ± 11.7	72.0 ± 10.7B
Stroke volume (ml)	100.3 ± 23.2	85.3 ± 23.0C	99.4 ± 22.8	102.0 ± 29.7H
Cardiac output (L/min)	7.31 ± 2.00	5.92 ± 1.71C	7.49 ± 1.98	7.21 ± 2.10A, H
TPR (dyne · s · cm^{-5})	1383 ± 466	1456 ± 519	1314 ± 431	1280 ± 423G
Aortic PWV (m/s)	11.37 ± 2.80	10.18 ± 2.57C	10.96 ± 2.58	11.81 ± 3.50C, H
% LV shortening	36.0 ± 7.2	35.2 ± 6.0	35.1 ± 6.1	32.9 ± 6.5A, F
E/A (ratio)	0.92 ± 0.31	0.97 ± 0.31	0.84 ± 0.38	0.87 ± 0.37
LV mass (g)	310 ± 85	239 ± 74C	272 ± 73D	296 ± 87B, H
LV mass index ($g/m^{2.7}$)	80.5 ± 20.8	61.2 ± 17.2C	72.6 ± 18.4D	79.5 ± 22.5B, H
LV mass index (g/m^2)	185 ± 47	140 ± 40C	165 ± 41D	182 ± 50B, H
LV diastolic diameter (mm)	56.5 ± 6.8	52.4 ± 6.5C	56.7 ± 6.4	57.2 ± 6.4H
LV systolic diameter (mm)	36.5 ± 7.8	34.0 ± 7.5C	36.9 ± 6.7	38.6 ± 6.3H
LV mean wall thickness (mm)	11.0 ± 1.8	10.0 ± 1.9C	10.0 ± 26E	10.5 ± 1.5B, F
LV relative wall thickness	0.40 ± 0.08	0.39 ± 0.08	0.35 ± 0.06E	0.37 ± 0.06
Interdialytic weight gain (kg)	2.56 ± 0.74	2.55 ± 0.70	2.42 ± 0.62	2.45 ± 0.50H
Hemoglobin (g/100 ml)	8.50 ± 1.60	10.80 ± 1.20C	8.85 ± 1.75	10.15 ± 1.50C, G
Serum albumin (g/L)	40.5 ± 2.9	40.7 ± 2.8	39.8 ± 3.0	39.7 ± 3.2
CRP (mg/L)	4.8 ± 2.4	5.3 ± 2.7	11.9 ± 9E	12.2 ± 12.1H
Body height (cm)	165.0 ± 10.3	165.0 ± 10.3	163.0 ± 9.5	162.8 ± 10.0
Body weight (kg)	63.1 ± 14.0	63.6 ± 14.0	60.6 ± 11.7	59.7 ± 11.9
Body surface area (m^2)	1.68 ± 0.20	1.70 ± 0.21	1.65 ± 0.18	1.63 ± 0.18F

[a] BP, blood pressure; TPR, total peripheral resistance; PWV, pulse wave velocity; LV, left ventricular; CRP, C-reactive protein ($n = 111$). Values are means ± standard deviation. Letters indicate significance: 1 *versus* 2; 3 *versus* 4: A, $P < 0.05$; B, $P < 0.01$; C, $P < 0.001$; 1 *versus* 3: D, $P < 0.05$; E, $P < 0.01$; 2 *versus* 4: F, $P < 0.05$; G, $P < 0.01$; H, $P < 0.001$.

women (38 of 83 *versus* 22 of 70, $P < 0.05$), patients with previous CVD (46 of 83 *versus* 18 of 70, $P < 0.01$), and patients with aortic disease, peripheral artery disease, or both (18 of 83 *versus* 5 of 70) ($P < 0.01$). Responders and nonresponders received on average, respectively, 1.3 and 1.2 antihypertensive drugs (NS). For the maintenance of target hemoglobin, responders received 2707 ± 2000 U/wk (49 ± 31 U/kg per week) of EPO *versus* 5629 ± 3830 (87 ± 50 U/kg per week) for nonresponders ($P < 0.01$). Hemodynamic parameters were similar, with the exception of baseline LVM, which was lower in nonresponders ($P < 0.05$). In nonresponders, the LVM increased during the follow-up. In nonresponders, these changes were attributed to the persistent increase of hemodynamic overload due to increased aortic stiffness, and to higher SV and cardiac output associated with lower hemoglobin.

Although the SBP, DBP, and MBP decreased significantly in both groups, SBP remained higher in nonresponders ($P < 0.001$). The principal difference concerned the changes of pulse pressure, which were not influenced by treatment in nonresponders. The persistence of high pulse pressure in nonresponders reflected principally increased aortic stiffness in parallel with higher SV. Blood chemistry parameters remained stable during the follow-up period (data not shown). CRP was higher in nonresponders. For the entire population, the ΔPWV was correlated with serum CRP levels (Figure 2) and decrease of PWV in response to BP decrease was associated with lower CRP, whereas the absence of BP responsiveness was associated with higher CRP ($P < 0.01$). For the entire population, CRP was positively correlated with the weekly dose of EPO needed to maintain target hemoglobin levels ($r = 0.252$; $P = 0.012$).

Discussion

LVH is common in patients with ESRD and was present in 90% of patients in the study presented here. The structural LV alterations occur early during the course of renal insufficiency and result in large part from volume and pressure overloads (3,4,8,9). Although the association between cardiac alterations and hemodynamic overload was principally documented by cross-sectional studies, a recent prospective study by Levin *et al.* (16) demonstrated that the decline of the hemoglobin level and increase of SBP were independent predictors of LVM growth in early renal insufficiency. In the general population (30) and in patients with ESRD, increased LVM is an inde-

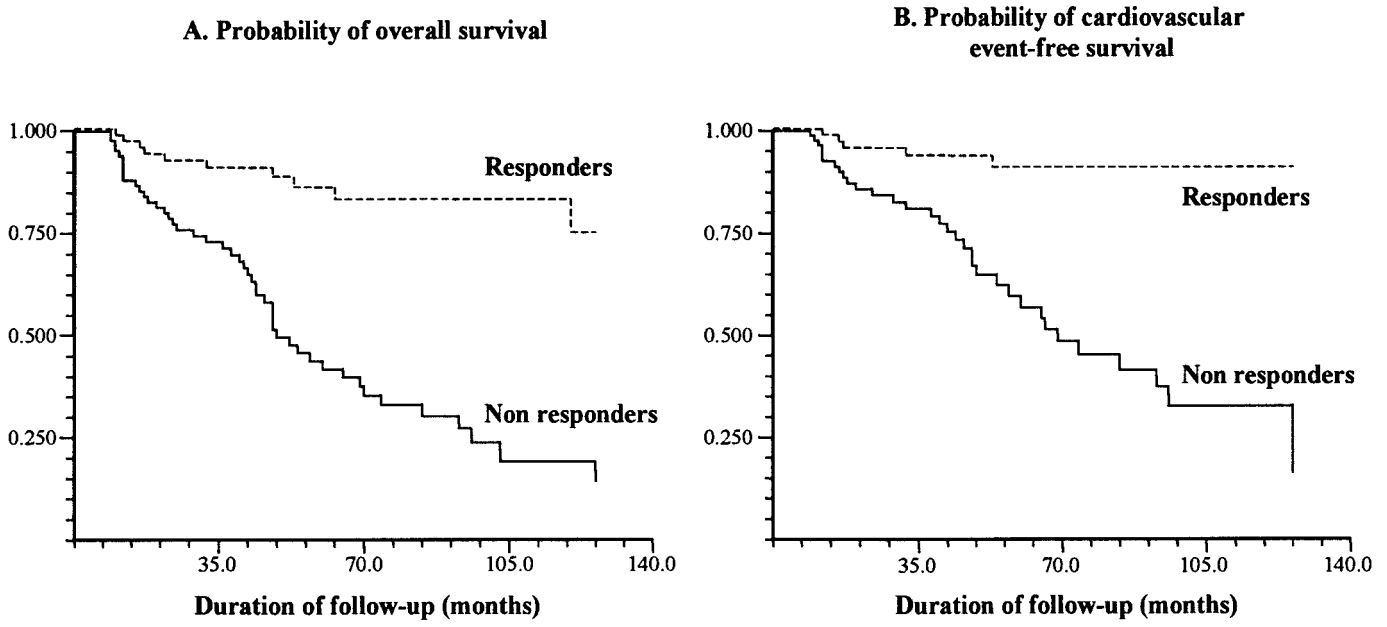

Figure 1. Probability of (A) overall survival and (B) cardiovascular event-free survival in responders and nonresponders. Comparisons between survival curves were highly significant ($\chi^2 = 30.1$ for overall survival and $\chi^2 = 31.5$ for event-free survival; $P < 0.001$ for both).

pendent predictor of death (5,6). The expected consequence of reversing LVH should be improved patient survival.

In patients with essential hypertension and ESRD, a reduction of LVM was a favorable prognostic marker that predicted a lower risk for subsequent nonfatal CV morbid events (20,31,32). This study showed that reversal of LVH was a favorable marker that predicted a lower risk for subsequent death of patients with ESRD receiving hemodialysis. Our results indicate that prolonged survival is essentially linked to decreased LVM as such, and the beneficial effect of LVM reduction was also verified in patients receiving hemodialysis with no CV complications before inclusion into the study (Table 4).

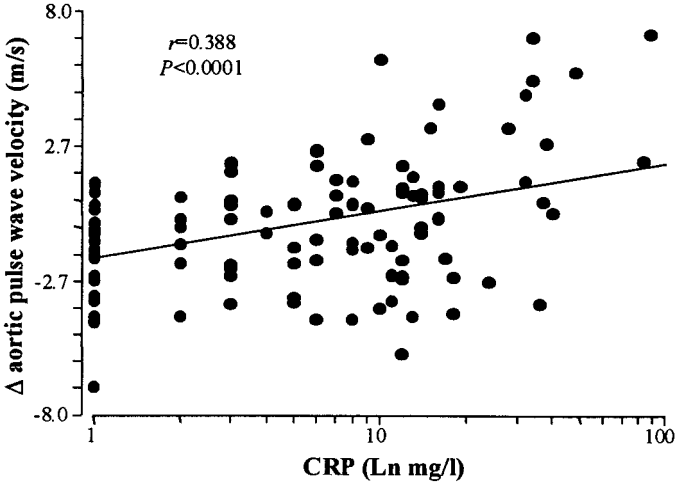

Figure 2. Scatter plot showing the correlation between the changes of aortic pulse wave velocity and the C-reactive protein (CRP) level (mg/L, log scale) at the end of follow-up.

Treatment of hypertension in patients with ESRD induces partial regression of LVH (21,22). Although several studies showed that attenuation of anemia induced a partial regression of LVH (23,24), that finding was challenged by Foley *et al.* (33), who showed that normalization of hemoglobin in patients with asymptomatic cardiomyopathy prevented the development of further LV dilation with a limited effect on LVM as such (33). For our entire cohort, the LVM decrease was significant and attributed to changes of hemoglobin and changes of arterial stiffness, which is an important vascular alteration opposing LV ejection in these patients. LVM changes were moderate, and a significant LVH reduction (responders) was observed in only 46% of the patients, a percentage close to that reported by Foley *et al.* (20). This is not surprising because many patients did not respond to treatment, and the correction of hemodynamic overload was largely incomplete. Indeed, anemia was only partly corrected and overhydration (interdialytic change in body weight) and AV shunts were still present. BP changes were significant in the entire population and within the two subgroups. The principal factor responsible for the MBP decrease was decreased cardiac output because the TPR did not change significantly. The relative stability of TPR resulted from the opposite effects of increased viscosity due to attenuation of anemia and due to the use vasodilating antihypertensive drugs.

For the entire population, another reason for the modest response of LVM to therapeutic intervention was the increased arterial stiffness observed in nonresponders. The most visible consequences of this abnormality were the persistent increases of SBP and pulse pressure in these patients. The appropriate

term to define the arterial factor or factors opposing LV ejection is "aortic input impedance," which depends principally on TPR, the distensibility of the aorta and large central arteries, the intensity of arterial wave reflection, and inertance of the blood column in the arteries (34,35). Stiffening of the arterial system in patients receiving dialysis is an important factor contributing to pressure overload (11,12), and stiffening of arterial walls is an independent determinant of CV and all-cause mortality of patients receiving hemodialysis (36,37). Moreover, in a recent study, it was shown that nonresponsiveness of aortic stiffness to lowered BP was associated with shorter survival of patients with ESRD (38). The maintenance of an abnormally high pulse pressure in nonresponders was the direct consequence of the progressive increase of aortic stiffness. Pulse pressure is an independent CV risk factor (39,40) and could account for the higher mortality of nonresponders.

The reasons for the progressive increase of aortic stiffness in nonresponders are not clear. A possible explanation is that these subjects have advanced BP-insensitive "uremic arteriopathy" (41). The association of CRP level with the smaller response of aortic PWV to BP changes could suggest that chronic microinflammation might be associated with resistance to treatment (Figure 2). Furthermore, nonresponders had lower final hemoglobin levels despite significantly higher weekly doses of EPO, which were positively correlated with CRP. These results suggest that in patients receiving hemodialysis, microinflammation through its influence on EPO efficacy and its association with progressive arteriosclerosis participate in the maintenance of hemodynamic overload and limited efficacy of therapeutic interventions. LVM changes were accompanied by a small decrease of the percentage of LV shortening, which is in agreement with the decreased cardiac inotropic function associated with the correction of anemia (42).

This study has several limitations. The first limitation is the absence of a parallel control group (omitted for obvious ethical reasons), and comparisons can only by made with previous publications that evaluate the spontaneous evolution of LV changes during dialysis before the introduction of EPO. In the long run, progressive LV dilation with compensatory hypertrophy is a characteristic spontaneous evolution of cardiomyopathy in patients receiving dialysis (3,16,20,27). In a previously published 48-mo follow-up study performed in our unit, we observed the same evolution with progressive increases of LV diameter and LVM (3). The results of this study indicate that therapeutic intervention aimed at stabilizing or reversing LVH can be successful and can thwart the natural evolution of LV alterations.

The volume overload in patients with ESRD is not attributable to anemia alone but is also a consequence of overhydration and AV shunt flow (3). Although interdialytic body weight changes were similar at baseline and at the end of the follow-up period, and although they were not associated with LVM changes, the AV shunt flows were not evaluated. Previous studies have shown that AV shunt flow is one of the factors of volume overload associated with the increases of LVEDiD and LVM (3,15). The persistence of AV shunts in patients is a factor that limits the therapeutic efficacy of treatments aimed at reducing the mechanical cardiac overload. AV shunt-induced volume overload develops over time, but because the total duration of hemodialysis was similar for responders and nonresponders, there are no arguments supporting the presence of higher AV shunt flow in the latter group.

Although M-mode echocardiography can be used to evaluate LV dimensions and thereby estimate LV volume or LVM, many errors can occur in their calculations because many assumptions are required to assess these parameters. As a result of the "weight" of the LVEDiD in the formula used for the calculation of LVM, an increased internal diameter of the LV, like that frequently observed in patients with ESRD, tends to overestimate the LVM in comparison with other techniques (43). Because the LVEDiD is influenced by volume status (3,15) and decreases during the hemodialysis session (44), it is essential to perform the follow-up echocardiographic studies with the same timing in relationship to the hemodialysis session.

Another problem with the serial evaluations of LVM could be the "regression-to-the-mean" phenomenon (29,45). This phenomenon occurs when a study sample is selected on the basis of an increased (or decreased) value of a given parameter (*e.g.,* LVM), which is taken as an expression of a specific alteration (*e.g.,* LVH). When the first determination of that variable is extreme to the limits of its distribution, the subsequent measurements will tend to be closer to the center of the distribution. The regression-to-the-mean phenomenon in this study is unlikely for several reasons. The inclusion criteria for the study were not based on the presence or absence of LVH, and at inclusion, 15 patients had LVM indexes within the normal range (LVM decreased in 9 of these patients). The separation of responders and nonresponders was based on evaluation of the regression to the mean, which was based on the results of a previously conducted controlled and randomized study in patients with uremia selected for the presence of LVH (21).

The ability to generalize the results of this study may be limited because of the inclusion criteria and the demographic and clinical characteristics. Patients included in the study had good-quality and reproducible echocardiographies; several patients with poor images were not included. Their exclusion could have introduced some bias in the population selection (45). Patients with ESRD are a high-risk population with CV mortality up to 20 times higher than that of the general population without uremia (1). Moreover, the percentage of patients with diabetes among patients with ESRD, although steadily increasing in France, was lower than in North America and in northern Europe. Finally, the LV systolic function was within the normal range, with only a moderate alteration of diastolic filling.

In conclusion, the results of this study demonstrate the following: (*1*) attenuation of hemodynamic overload reduced LVH in patients receiving hemodialysis; (*2*) LVH regression had a positive effect on survival of patients receiving hemodialysis; and (*3*) failure of LVH to respond to treatment was associated with persistent hemodynamic overload due to progressive aortic stiffening and poorer response of anemia to

EPO in patients with chronic microinflammation. The data showed that the attempts to correct hemodynamic overload should be more aggressive and should start earlier in the course of renal insufficiency because late intervention, such as that found in this study, has limited efficacy. Another approach would be to elucidate the reasons for progressive arterial stiffening and the cause or causes of microinflammation, and to propose an appropriate therapeutic strategy.

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