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Original Article

Cardiovascular

Left ventricular geometric patterns in end-stage kidney disease: Determinants and course over time

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Abstract

Introduction: While concentric left ventricular hypertrophy (cLVH) predominates in non–dialysis-dependent chronic kidney disease (CKD), eccentric left ventricular hypertrophy (eLVH) is most prevalent in dialysis-dependent CKD stage 5 (CKD5D). In these patients, the risk of sudden death is 5× higher than in individuals with cLVH. Currently, it is unknown which factors determine left ventricular (LV) geometry and how it changes over time in CKD5D.

Methods: Data from participants of the CONvective TRAnsport Study who underwent serial transthoracic echocardiography were used. Based on left ventricular mass (LVM) and relative wall thickness (RWT), 4 types of left ventricular geometry were distinguished: normal, concentric remodeling, eLVH, and cLVH. Determinants of eLVH were assessed with logistic regression. Left ventricular geometry of patients who died and survived were compared. Long-term changes in RWT and LVM were evaluated with a linear mixed model.

Findings: Three hundred twenty-two patients (63.1 ± 13.3 years) were included. At baseline, LVH was present in 71% (cLVH: 27%; eLVH: 44%). Prior cardiovascular disease (CVD) was positively associated with eLVH and ß-blocker use inversely. None of the putative volume parameters showed any relationship with eLVH. Although eLVH was most prevalent in non-survivors, the distribution of left ventricular geometry did not vary over time.

Discussion: The finding that previous CVD was positively associated with eLVH may result from the permanent high cardiac output and the strong tendency for aortic valve calcification in this group of long-term hemodialysis patients, who suffer generally also from chronic anemia and various other metabolic derangements. No association was found between eLVH and parameters of fluid balance. The distribution of left ventricular geometry did not alter over time. The assumption

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that LV geometry worsens over time in susceptible individuals, who then suffer from a high risk of dying, may explain these findings.

Key words: Hemodialysis, left ventricular hypertrophy, left ventricular geometry, mortality, echocardiography

INTRODUCTION

Chronic kidney disease (CKD) is a major risk factor for cardiovascular disease (CVD).[1] Left ventricular (LV) hypertrophy is considered an important contributor of CVD outcome, independent of age, diabetes, blood pressure (BP), lipid profile, and smoking.[2] The worsening of kidney function per se may add to the development of left ventricular hypertrophy (LVH).[3] While its prevalence in CKD varies between 30% and 70%, LVH has been established in >70% of those who start dialysis.[4]

From a geometrical view, 4 patterns of left ventricular mass (LVM) can be distinguished. Hearts with a normal LVM are subdivided into "normal" geometry (NG) and concentric remodeling (CR). Hearts with an increased LVM are subdivided into concentric left ventricular hypertrophy (cLVH) and eccentric left ventricular hypertrophy (eLVH). In contrast to eLVH, relative wall thickness (RWT) is increased relatively to cavity dimensions in cLVH.[5]

Abnormal LV geometry is widespread in renal patients.[3] While most studies,[3,6–8] but not all,[9] reported that cLVH predominates in non–dialysis-dependent (NDD)-CKD, eLVH appears most prevalent in CKD5D.[10,11] Primarily subjects with cLVH, who carry a high risk of stroke,[12] may suffer from the combined deleterious effects of the biochemical and circulatory alterations that occur during the transition from advanced CKD to early CKD5D.[13] Moreover, LV features may change over time as observed both in participants of the Framingham Heart Study (FHS)[14] and CKD patients stage 3 to 4 who took part of the Cardiovascular Risk reduction by Early Anemia Treatment with Epoietin beta (CREATE) trial.[15] During a follow up of 4 years, in FHS, 19% of the patients with cLVH progressed to eLVH, while the other way around was rare. In CREATE more than one third of the patients with cLVH at baseline showed eLVH after 2 years, while less than 10% of the individuals with eLVH at baseline progressed to cLVH. In both studies, some regression to NG and CR was observed as well.

Three studies analyzed the longitudinal course of LV geometry in persons with NDD-CKD[6,7,9,15] and one included patients who progressed from advanced CKD to CKD5D.[8] Results varied between increases in both eLVH and cLVH at the cost of NG,[6,9] regression and progression of abnormal LV geometry,[15] and no change.[7] Since in all these analyses, evaluations were performed at great intervals—up to 2 years—, it is highly likely that the outcome is influenced by survival bias. None of these analyses investigated LV geometric changes in CKD5D patients who survived the first turbulent months of hemodialysis (HD) treatment.

Considering the clinical sequelae of eLVH and cLVH, both types have been associated with a 2- to 3-fold increased CVD risk, if compared to CKD patients without LVH.[6] Yet, In CKD5D, the risk of sudden death, which accounts for one quarter of all deaths and one half of CVD mortality,[16,17] is 5-fold greater in patients with eLVH than with cLVH,[10] So far, however, it is unknown which factors determine LV geometry, and whether and how it changes over time in long-term CKD5D patients. Since we hypothesized that early recognition of an unfavorable LV type and timely intervention may have a beneficial effect on clinical outcome, here we report these issues in patients from the CONvective TRAnsport STudy (CONTRAST) who underwent serial transthoracic echocardiography (TTE).

MATERIALS AND METHODS

Patients

This study includes a subset of CONTRAST patients (NCT00205556) who underwent serial TTE. Patients were recruited between June 2004 and December 2009, and followed until the end of the study (December 31, 2010). After discontinuation of the randomized treatment (renal transplantation, switch to peritoneal dialysis, move to another centre, other reasons), measurements were no longer performed. CONTRAST was designed to compare all-cause mortality and CVD morbidity and mortality between online post-dilution hemodiafiltration and low-flux HD. The design and outcome of CONTRAST are described elsewhere.[18,19]

Data collection

At baseline, patient characteristics [demography, anthropometrics, medical history (diabetes mellitus, CVD,

previous kidney transplantation), medication, laboratory values and hemodynamics), and treatment-related features (vascular access, dialysis vintage, "dry" weight) were collected. CVD was defined as a myocardial infarction, coronary artery bypass graft, percutaneous trans luminal coronary angioplasty, angina pectoris, stroke, transient ischemic attack, intermittent claudication, amputation, percutaneous trans luminal angioplasty, peripheral bypass surgery, and renal percutaneous trans luminal angioplasty. Medication was noted as ß-blockers, renin angiotensin system (RAS) inhibitors, diuretics, calcium antagonists or "others." The mean of 3 consecutive post-dialysis weights was used to calculate "dry" weight. Urine volumes were determined from 24-hour collections; <100 mL was considered anuric. Systolic and diastolic BP were measured before and after 3 consecutive dialysis sessions using a standard electronic sphygmomanometer and the average was used for analysis. Interdialytic weight gain (IDWG) was calculated as the mean net ultrafiltration (UF) of 3 consecutive dialysis sessions. Smoking habit was noted as either ever or never smoker. Laboratory data, hemodynamics, and treatment-related parameters were collected as well after 6, 12, and 24 months (respectively, M6, M12, and M24).

TTE measurements

Two-dimensional TTE was performed on a mid-week non-dialysis day at baseline (M0) and at M6, M12, and M24. From the parasternal long axial position, posterior wall thickness (PWT), septum wall thickness, left ventricular end-systolic diameter (LVESD), and left ventricular end-diastolic diameter (LVEDD) were assessed by an independent echocardiographer at the core laboratory (OK, VU University Medical Center, Amsterdam), who was blinded for all other patient data. Left ventricular mass was calculated using the formula of Devereux and Reicke[20] and modified in accordance with the recommendations of the American Society of Echocardiography.[5] Left ventricular hypertrophy was defined as LVM/height$^{2.7}$ >44 g/m$^{2.7}$ for women and >48 g/m$^{2.7}$ for men.[5] Relative wall thickness was calculated by the formula: RWT = ([2 × PWT]/LVEDD[left ventricular end diastolic diameter]). In patients with LVH the cut-off of RWT was set at 0.42, whereby equal or <0.42 was defined as eLVH and >0.42 as cLVH.[5,21] Ejection fraction (EF) was computed by the echocardiography software. According to the abovementioned definitions, 4 types of LV geometry are distinguished: NG, CR, eLVH, and cLVH. EF was calculated as (LVEDD-LVEDS)/LVEDD. LV systolic dysfunction was defined as an EF < 45%.

Statistical methods

Variables are reported as means with standard deviations, medians with 25th and 75th percentiles, or frequencies and proportions when appropriate. Comparisons between groups were performed with *t*-test, chi-square test, or Mann-Whitney U test, depending on the type of variables and their distributions. A multivariable logistic regression model was developed to investigate the independent relation between demographic and clinical data and the type of LVH. Variables were selected for the multivariable model if they were related with the type of LVH in a univariable regression model, using a cut-off value of $P < 0.2$. For the longitudinal analysis of LV geometry, RWT and LVM/height$^{2.7}$ were analyzed with a generalized linear mixed model with a random intercept. For the different time points (M0, M6, M12, M24) estimated means with 95%-confidence intervals were estimated by entering time in the model as a categorical variable. Annual rates of change were estimated by entering time as a continuous variable in the model. The longitudinal analyses were performed for the total study population and stratified for baseline LV types. Results are considered statistical significant if $P < 0.05$ (2-sided). All calculations were performed with the Statistical Package for Social Sciences software for windows version 20.0 (SPSS, Inc Chicago, IL, USA).

RESULTS

Baseline data

Demographic and clinical characteristics of the CONTRAST and the TTE cohorts

The clinical and demographical data of the group of patients in whom TTE was performed (n = 322) were comparable to the total CONTRAST cohort (n = 714), data not shown. Mean age of the patients was 63.1 ± 13.3 years, 61% of patients were male, dry weight 72.0 ± 14.3 kg, dialysis vintage 2.0 (IQR 1.0–4.0) years.

Echocardiographic and clinical data of the TTE cohort at baseline

Left ventricular hypertrophy was present in 229/322 (71%) patients. Subdivision in LV geometric patterns indicated that eLVH was present in 142(44%), cLVH in 87(27%), CR in 36(11%), and NG in 57(18%). Considering only patients with LVH, 38% had cLVH and 62% eLVH. The clinical, demographical, and

Table 1 Patient characteristics of the 4 left ventricular geometric patterns at baseline

	NG (n = 57)	CR (n = 36)	eLVH (n = 142)	cLVH (n = 87)
Demographics				
Sex (male)	36 (63%)	24 (67%)	84 (59%)	53 (61%)
Age (years)	61.3 ± 14.5	58.3 ± 12.7	65.4 ± 12.8	62.5 ± 13.1
Race (Caucasian)	50 (88%)	26 (72%)	115 (81%)	67 (77%)
Dry weight (kg)	71.9 ± 13.7	73.2 ± 17.8	71.4 ± 14.4	72.4 ± 13.2
Smoker (current or past)	34 (63%)	28 (85%)	91 (68%)	51 (62%)
Dialysis				
HD/HDF (HD)	30 (53%)	15 (42%)	75 (53%)	39 (45%)
Dialysis vintage (years)	2.0 (1.0–4.3)	3.5 (2.3–6.6)	1.9 (0.9–3.7)	1.8 (1.0–3.3)
Residual renal function[a] (yes)	32 (56%)	10 (28%)	78 (55%)	49 (56%)
Interdialytic weight gain (kg)	1.7 (0.9–2.4)	2.4 (1.8–3.0)	1.9 (1.3–2.4)	2.1 (1.5–2.6)
Vascular access (A-V fistula)	45 (79%)	27 (75%)	111 (78%)	73 (84%)
Patient history				
Diabetes Mellitus (yes)	11 (20%)	8 (24%)	43 (31%)	21 (25%)
Previous coronary heart disease (yes)	16 (28%)	17 (47%)	76 (54%)	35 (40%)
Previous kidney transplant (yes)	8 (14%)	7 (19%)	11 (8%)	4 (5%)
Laboratory data				
Hemoglobin (mmol/L)	7.4 ± 0.8	7.3 ± 0.8	7.2 ± 0.8	7.4 ± 0.8
PTH (ρmol/L)	24.0 (11.0–42.0)	34.5 (21.7–59.5)	21.6 (12.9–37.2)	20.7 (10.3–41.6)
Calcium (mmol/L)	2.30 ± 0.19	2.28 ± 0.19	2.29 ± 0.18	2.31 ± 0.17
Phosphate (mmol/L)	1.64 ± 0.43	1.67 ± 0.51	1.66 ± 0.50	1.70 ± 0.55
Albumin (g/L)	41.4 ± 4.6	41.1 ± 3.8	40.4 ± 4.1	40.1 ± 3.6
Magnesium (mmol/L)	1.01 ± 0.21	1.00 ± 0.27	0.99 ± 0.15	0.95 ± 0.20
CRP (mg/L)	3.3 (0.9–11.0)	3.9 (0.7–9.2)	4.9 (1.6–14.0)	3.6 (1.8–8.4)
Medication				
Beta blocker	20 (35%)	16 (44%)	78 (55%)	59 (68%)
RAS inhibitor	17 (30%)	16 (44%)	76 (54%)	53 (61%)
Diuretic	22 (39%)	7 (19%)	63 (44%)	35 (40%)
Calcium antagonist	13 (23%)	11 (31%)	47 (33%)	33 (38%)
Others[b]	26 (46%)	26 (72%)	94 (66%)	59 (68%)
Hemodynamics				
Systolic blood pressure (mmHg)	140 ± 20	149 ± 19	151 ± 22	150 ± 21
Diastolic blood pressure (mmHg)	74 ± 11	80 ± 12	76 ± 12	78 ± 11
LVEDD (mm)	48.4 ± 5.1	40.4 ± 4.8	55.8 ± 5.9	47.1 ± 4.9
LVESD (mm)	31.8 ± 6.6	24.1 ± 5.4	37.8 ± 8.3	30.4 ± 5.9
Ejection fraction (%)	66 (54–73)	70 (61–79)	61 (52–69)	66 (57–72)
Left ventricular mass (g)	171 (145–201)	167 (134–190)	253 (213–297)	251 (220–323)

Data are reported as mean standard deviation, SD; median interquartile range, IQR; or number percentage, %, when appropriate.
cLVH = concentric left ventricular hypertrophy; CR = concentric remodeling; CRP = C-reactive protein; eLVH = eccentric left ventricular hypertrophy; HD = hemodialysis; HDF = hemodiafiltration; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; NG = normal geometry; PTH = parathyroid-hormone; RAS = renin angiotensin system.
[a]Diuresis >100 mL/24 hour.
[b]Others: statin, alpha blocker, or platelet aggregation inhibitor.

echocardiographic data of the geometric LV groups are shown in Table 1.

Determinants of eLVH

To discriminate eLVH from cLVH, univariable logistic regression analysis was performed with potential determinants (Table 2). Variables with a $P < 0.2$ were introduced in the multivariable model. While previous CVD was positively associated with eLVH (OR 2.17 [1.07;4.41]), ß-blocker use showed a negative relationship [OR 0.44 (0.22;0.89]. No association was found between LV geometry and parameters of fluid balance,

Table 2 Univariable and multivariable logistic regression analysis eLVH vs. cLVH

	Univariable model			Multivariable model		
	P value	ODDS-ratio	95%-CI	P value	ODDS-ratio	95%-CI
Demographics						
Sex (male)	0.79	0.93	0.54–1.60			
Age (years)	0.11	1.02	0.996–1.04	0.82	1.00	0.98–1.03
Race (Caucasian)	0.80	0.95	0.65–1.40			
Dry weight (kg)	0.60	1.00	0.98–1.01			
Smoker (past or current)	0.35	1.32	0.74–2.35			
Dialysis						
HD/HDF (HD)	0.24	1.38	0.81–2.35			
Dialysis vintage (years)	0.89	0.99	0.90–1.10			
Residual renal function[a] (yes)	0.84	0.95	0.55–1.62			
IDWG (kg)	0.13	0.79	0.58–1.07	0.13	0.73	0.49–1.10
Vascular access (AV fistula)	0.29	0.69	0.34–1.38			
Patient history						
Diabetes mellitus (yes)	0.33	1.36	0.74–2.50			
Previous CVD (yes)	0.052	1.71	0.996–2.94	0.03	2.17	1.07–4.41
Kidney transplant (yes)	0.36	0.57	0.18–1.86			
Laboratory data						
Hemoglobin (mmol/L)	0.07	0.72	0.50–1.02	0.18	0.74	0.48–1.15
PTH (ρmol/L)	0.90	1.00	0.99–1.01			
Calcium (mmol/L)	0.45	0.56	0.12–2.59			
Phosphate (mmol/L)	0.57	0.86	0.52–1.44			
Albumin (g/L)	0.62	1.02	0.95–1.09			
Magnesium (mmol/L)	0.20	3.40	0.52–22.4			
CRP (mg/L)	0.08	1.02	0.997–1.05	0.15	1.02	0.99–1.05
Medication						
Beta blocker	0.06	0.58	0.33–1.01	0.02	0.44	0.22–0.89
RAS inhibitor	0.27	0.74	0.43–1.27			
Diuretic	0.54	1.19	0.69–2.04			
Calcium antagonist	0.46	0.81	0.46–1.41			
Others	0.80	0.93	0.53–1.64			
Hemodynamics						
Systolic BP (mmHg)	0.78	1.00	0.99–1.01			
Diastolic BP(mmHg)	0.30	0.99	0.97–1.01			

Variables with a $P < 0.2$ in univariable binary logistic regression were introduced in the multivariable model.
BP = blood pressure; CRP = C-reactive protein; HD/HDF = hemodialysis/hemodiafiltration; PTH = parathyroid-hormone; RAS = renin angiotensin system.
[a]Defined as diuresis >100 mL/24 hour.

such as IDWG, UF volume and residual diuresis, or anemia.

Baseline clinical and echocardiographic characteristics of surviving and non-surviving patients

As indicated in Supporting Information Table S1, patients who passed away were more likely to be older and female, and suffered more frequently from prior CVD than surviving patients. These individuals also suffered more frequently from dilated cardiomyopathy (CMP; survivors vs. non-survivors: LVEDD 49.6 ± 7.0 vs. 51.6 ± 8.1, $P = 0.02$; LVESD 31.9 ± 8.0 vs. 35.3 ± 8.7, $P = 0.0001$) and systolic heart failure (survivors vs. non-survivors: EF 64.6 ± 13.8 vs. 59.8 ± 14.2, $P = 0.003$).

Longitudinal analysis

Patient numbers

Three hundred twenty-two out of 714 CONTRAST patients underwent serial TTE. At M6, TEE was available

Table 3 Annual change in RWT and LVM/height$^{2.7}$ in the total patient population and stratified according to baseline left ventricular geometric type

	RWT	P value	LVM index (g/m$^{2.7}$)	P value
Total	0.01 (0.001;0.02)	0.03	0.33 (−1.21;1.87)	0.67
LV categories				
NG	0.04 (0.02;0.06)	0.001	5.47 (2.90;8.04)	0.0001
CR	−0.04 (−0.07;0.01)	0.02	6.88 (0.51;13.25)	0.04
eLVH	0.03 (0.02;0.05)	0.0001	−2.45 (−4.55;−0.36)	0.02
cLVH	−0.03 (−0.05;−0.01)	0.01	−0.84 (−3.76;−2.08)	0.57

Annual changes (95%-confidence intervals) have been estimated with a linear mixed model.
cLVH = concentric left ventricular hypertrophy; CR = concentric remodeling; eLVH = eccentric left ventricular hypertrophy; LV = left ventricular; LVM = left ventricular mass; NG = normal geometry; RWT = relative wall thickness.

in 221 patients. At M12 and M24 these figures were 170 and 98, respectively. During follow up 127 patients died.

Changes in LV geometry over time

Since LV geometry is defined by the values of RWT and LVM (indexed for height$^{2.7}$), these parameters were analyzed over time in the 4 subgroups. Table 3 shows the changes in RWT and LVM/height$^{2.7}$ for the total study population and stratified for each geometric LV type.

Considering LVM, overall no change was observed. Stratified analyses showed significant increases in the NG and CR groups, a decrease in the eLVH group and no change in the cLVH group. In Figure 1a, the estimated means for the 4 different time points are shown, both for the total group and for the separate LV geometric types.

Considering RWT, overall a small but significant increase per year was observed. Stratified analyses showed increases in RWT in the NG and eLVH groups, and decreases in the CR and cLVH groups. In Figure 1b, the estimated means for the 4 different time points are shown, both for the total group and for the separate LV geometric types.

In Figure 2, the annual changes in RWT and LVM-index are simultaneously shown for the 4 geometric LV types. Yearly changes are expressed as percentage of the mean values at baseline for the total study population. In the NG group RWT increased by 0.04/year. Since the mean RWT at baseline was 0.42, the increase/year is 8.66%. Comparable calculations were performed in each RWT and LVH quadrant, and the arrows represent the resultants of these changes.

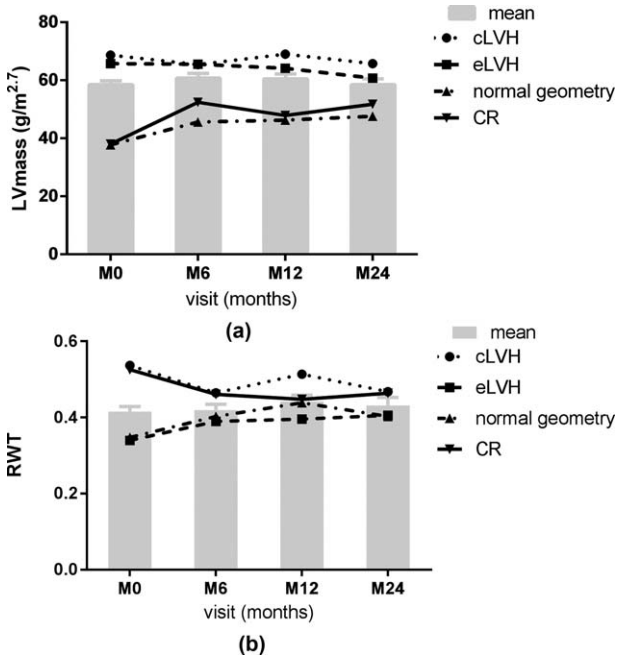

Figure 1 Mean LVM index in g/m$^{2.7}$ (left ventricular mass index, a) and RWT (relative wall thickness, b) at baseline (M0) and during follow up visits at 6, 12, and 24 months (M6, M12, M24). Both are indicated for each geometry group individually and for all patients (bars, mean and 95% CI) (cLVH = concentric left ventricular hypertrophy; CR = concentric remodeling; eLVH = eccentric left ventricular hypertrophy).

DISCUSSION

As far as we know, this is the first report on the longitudinal course of LV geometry in long-term CKD5D patients (median dialysis vintage 2.0 years), who underwent serial (up to 4 times) TTE evaluations. Given the 5-fold higher risk of sudden death in CKD5D patients with eLVH,[10] we first looked for specific determinants of this type of LV geometry.

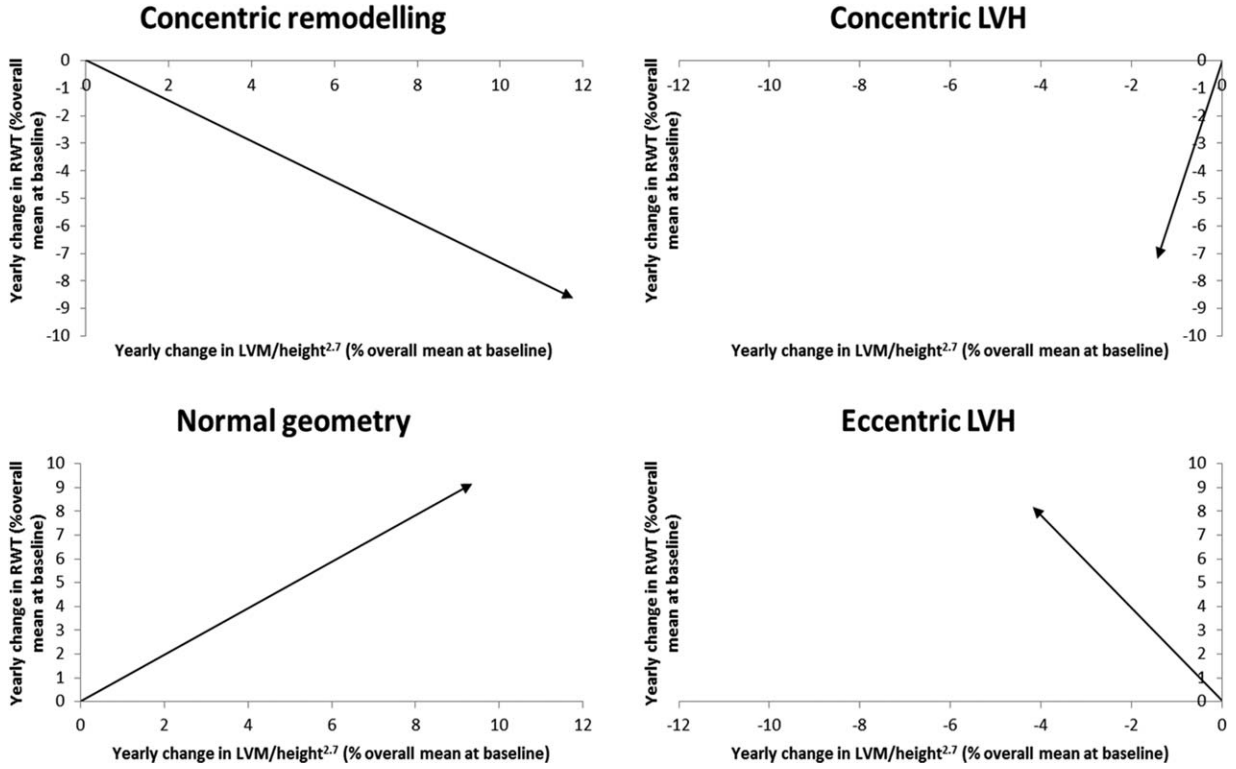

Figure 2 Distribution of left ventricular geometric patterns over time. The direction and the length of the arrows represent the alterations over time. For explanation, see the text (LVH = left ventricular hypertrophy; LVM = left ventricular mass; RWT = relative wall thickness).

Determinants of eLVH at baseline

While in the non-renal population, age, smoking, gender, systolic BP, obesity, and diabetes have been recognized as independent determinants of LVH,[22] in CKD patients, nontraditional risk factors, such as anemia, oxidative stress, IDWG,[23] and a decreased residual kidney function (RKF), have been implicated as well.[24] So far, however, no distinction was made in CKD5D between eLVH and cLVH.

Surprisingly, none of the putative determinants of fluid balance, such as RKF, IDWG, or UF volume,[25] showed any relationship with eLVH. Since this type of LV geometry was most prevalent (44%) in our study group, it is conceivable that HD patients with a long dialysis vintage and declining RKF gradually capture fluid over time without large interdialytic fluctuations and UF demands.

More comprehensible in our opinion is the finding of a positive association between previous CVD and eLVH. As mentioned, the clinical entity "CVD" covers a wide range of heterogeneous conditions, varying from peripheral arterial disease (PAD) to ischemic heart disease. Whereas an association between PAD and eLVH is hard to interpret, preexisting heart failure may result in a dilated LV type, especially in HD patients with a reduced diuresis. In addition, the permanent demand for a high cardiac output, as occurring in long-term HD patients with an arterio-venous (AV) access and poorly controlled anemia,[15] may ultimately lead to heart failure and fluid overload (FO), yet again especially in persons with preexisting CVD.[26] The lack of a direct association between the presence of an AV access and eLVH may be due to the limited number of patients with an intravenous catheter (IVC ± 20%) in our study cohort. Finally, aortic valve calcification, which is a common feature in CKD patients and can lead to an increased LV filling pressure and diameter, may also contribute to the development of a dilated LV type, once again especially in HD patients with previous CVD.

As for ß-blockers, it has been well established that these drugs reduce sympathetic overactivity, which is a common feature in CKD,[27] more effectively than RAS-inhibitors.[28] The inverse association between ß-blockers and eLVH in our study, however, may indicate that their

capacity to reduce the high risk of sudden cardiac death in HD patients with FO is limited.[10] Clinical studies are not very helpful in this respect. Whereas a large observational analysis in >44,000 HD patients reported a higher mortality risk in individuals on a β-blocker-based regimen than a RAS-inhibitor based regimen,[29] opposite findings were found in a RCT, comparing atenolol with lisinopril.[28] As CONTRAST was executed over a timespan of >5 years and the prescription of β-blockers was not prespecified, our results may be confounded by a varying indication and thus not reflect causality.

Longitudinal echocardiographic changes

Against expectations, obvious changes in the distribution of LV geometry were not observed. In fact, LVM increased in the groups without LVH (NG and CR) and tended to decrease in cLVH and eLVH. As for RWT, a decrease was observed in the groups >0.42 (CR, cLVH) and an increase <0.42 (NG, eLVH). Overall, however, RWT increased only trivial (0.01/year), while LVM remained unaltered. Although these changes may result from regression to the mean, an alternative explanation appears more likely. Owing to the long-lasting demand for an unphysiological high cardiac output in chronic HD patients due to AV recirculation and a varying degree of anemia, a decreasing urine output over time and a gradually increasing FO,[25] together with widespread calcifications (vascular and valvular) as well as structural myocardial abnormalities,[15] cardiac dimensions rise progressively in susceptible individuals. As a result, the number of patients with eLVH increases. Yet, since eLVH is associated with a high mortality risk,[30] subsequently its share will decline again. When time elapses, however, other patients may then progress to eLVH.[9] Thus, while LV geometry may worsen over time in susceptible persons, it remains *proportionally* unaffected at the group level.

This view is supported by the data in Supporting Information Table S1. Patients who passed away were older and suffered more frequently from prior CVD than surviving patients. In addition, they suffered more often from dilated CMP and systolic dysfunction those who stayed alive.[31] Additional support is obtained from the longitudinal course of LV geometry, as shown by the direction and length of the arrows in Figure 2, which may represent pure histopathological alterations. It should be noted that out of a total of 322 participants, 127 died during follow up. As previous studies in CKD patients showed that both cLVH and eLVH increase over time at the cost of NG[6,9] and the mortality risk is low in patients with a normal LVM,[2,6] the arrows in the NG and CR quadrants toward the compartments with a high LVM may indeed result from real geometric changes. By contrast, the findings in the cLVH and eLVH quadrants may be the consequences of both geometric changes in surviving patients and drop-out of deceased subjects with an adverse LV type.

Interpretation of changes in LV geometry over time

Since cLVH predominates in advanced CKD and eLVH in CKD5D,[4,10,11,13] the final stage before dialysis may be crucial. Many patients will start dialysis only when dyspnoeic and hypertensive due to FO. Hence, it is conceivable that the LV geometric pattern changes shortly before dialysis, especially in patients with FO. Other putative contributing factors are anemia, high-flow AV fistulae, and poorly controlled uremia.[32] As a result, frail patients may not survive this episode. Various studies have shown a high mortality rate during progression to advanced CKD[33] and following the transition to CKD5D.[34] Since only the fittest patients progress to dialysis, assessment of LV geometry at great intervals[7] may not reveal individual changes. As for our study, it should be realized first, that outcome parameters are influenced by the baseline characteristics of participants. In our study, only patients were included who survived both the transition from advanced CKD to early CKD5D and 2 years of dialysis treatment on average. Second, during follow up, the fittest survived, while the frailest patients died. Third, in individual patients, LV geometry may have changed over time. Thus, both selection, long-term changes and withdrawal due to death, all may influence the distribution of LV geometry over time in CKD5D.

Limitations and strengths

As TTE was measured in specialized centers only, selection bias might occur. Yet, since the baseline features of the study group and the entire CONTRAST cohort were comparable and implementation of TTE was dependent on its local availability, bias by patient selection seems unlikely. More vital perhaps is the absence of data on left atrial dimensions and the lack of mitral inflow velocities, precluding statements on diastolic (dys)function. As for the subdivision in eLVH and cLVH, both cyclic fluctuations in extracellular fluid and hemodynamic parameters, and biochemical deviations may lead to varying LV geometry.[15] Hence, sporadic TTE assessments may represent snapshots rather than a steady state. Other limitations

include the post hoc nature of the study and the substantial number of patients who missed TTE follow up. Important strengths are its multicenter nature and the selective inclusion of chronic HD patients, thus excluding patients in the turbulent transition phase from advanced CKD to early dialysis. Finally, the relatively large sample size, the long follow up, the concise and prospective data collection, and the independent analysis of the TTE recordings by a specialist who was blinded for patient characteristics secures the reliability of our findings.

Summary and recommendations

From this study it appears first, that previous CVD is positively associated with eLVH and ß-blocker use inversely. Neither RKF or IDWG showed any relationship with eLVH. Although eLVH, which was most prevalent at baseline, was associated with the highest mortality rate, the distribution of LV geometry did not alter over time. This apparently paradoxical finding is most likely explained by survival bias. In view of the aforementioned considerations, it is reasonable to assume that strict fluid control will help to reduce the development of eLVH and thus the high death rate in this particular patient group. Only a well-designed prospective study, with more frequent TTE measurements than just once every 1 to 2 per year, may reliably resolve these items.

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AUTHORS CONTRIBUTIONS

Menso J. Nubé, Michiel L. Bots, Peter J. Blankestijn, Marinus van den Dorpel, Piet M. ter Wee, Muriel P.C. Grooteman: Conceived and designed the experiments.

Menso J. Nubé, Michiel L. Bots, Peter J. Blankestijn, Marinus van den Dorpel, Otto Kamp, Piet M. ter Wee, Muriel P.C. Grooteman: Performed the experiments.

Tiny Hoekstra, Camiel L.M. de Roij van Zuijdewijn, Volkan Doganer: Analyzed the data.

Otto Kamp: Contributed analysis tools.

Menso J. Nubé, Tiny Hoekstra, Volkan Doganer, Muriel P.C. Grooteman: Wrote the paper.

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SUPPORTING INFORMATION

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