Original Article

Presence of Chronic Kidney Disease and Subsequent Changes of Left Ventricular Geometry over 4 Years in an Apparently Healthy Population Aged 60 and Older

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Chronic kidney disease (CKD) is associated with increased cardiovascular (CV) risk. Left ventricular geometry (LVG) is a predictor for CV events. However, the influence of CKD on LVG changes in the elderly remains unclear. In this study, we performed echocardiography to evaluate LVG at baseline and at 2 and 4 years after baseline in 120 apparently healthy elderly Chinese who were recruited from a screening of 1,500 individuals. No subjects had a history of organic heart disease or chronic medication. CKD was defined as a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m², as calculated using the Modification of Diet in Renal Disease (MDRD) study equation. The mean age was 71.5±3.9 years (range: 60–81 years). The prevalences of CKD, concentric remodeling, eccentric hypertrophy and concentric hypertrophy were significantly increased after 4 years (all $p \leq 0.033$). The LVG changes were only significant in subjects with CKD at baseline ($p=0.039$). If we stratified subjects into those with favorable (normal and concentric remodeling) and those with unfavorable LVG (eccentric hypertrophy and concentric hypertrophy), the presence of CKD was an independent predictor for unfavorable LVG after 4 years both in univariate and multivariate analysis (odds ratio [OR]=3.18 and 3.70, $p=0.011$ and 0.015, respectively). This longitudinal study showed that aging was related to increased prevalence of CKD and changes of LVG. The presence of CKD is associated with changes of LVG toward unfavorable forms. These findings might partially explain why subjects with CKD have a higher CV risk and could provide knowledge essential to the assessment of cardiac structure and disease in older subjects. (*Hypertens Res* 2008; 31: 913–920)

Key Words: left ventricular geometry, chronic kidney disease, aging

Introduction

Aging is associated with higher cardiovascular (CV) morbid-

ity and mortality, partially as a result of unfavorable changes in cardiovascular disease (CVD) risk factors (*1*). Left ventricular mass (LVM), as measured by M-mode echocardiography, is a major independent risk factor for cardiovascular

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morbidity and mortality (2). Left ventricular (LV) geometry (LVG), determined by LVM and relative wall thickness (RWT), is considered to be an indicator of cardiovascular prognosis and extracardiac target organ damage (3, 4). In the Framingham Heart Study, Krumholz *et al.* found that the healthy participants with concentric hypertrophy had the worst prognosis for incident cardiovascular disease (5).

Decreased kidney function is increasingly recognized as a risk factor for CVD mortality and all-cause mortality in the elderly (6). Large epidemiological studies have shown that those with chronic kidney disease (CKD), defined as a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m², are at risk for progression of kidney disease and development of end-stage renal disease (ESRD) (7). Furthermore, other studies have reported a graded association between a reduced estimated GFR and the risk of death, cardiovascular events, and hospitalization which was independent of the known risk factors, a history of cardiovascular disease, and the presence of documented proteinuria (8, 9).

Left ventricular mass growth is associated with worse GFR, and left ventricular hypertrophy (LVH) develops during the early stages of CKD (10). Despite the high prevalence of LVH in patients with CKD, progression of LV morphological derangement in those with earlier stages of CKD is under-reported. Furthermore, the majority of studies of LVG in patients with kidney diseases have been performed in patients with ESRD on dialysis therapy or established cardiac diseases (11).

To our knowledge, there has been no study exploring the association between CKD and LVG changes in elderly individuals who were free of cardiovascular events at study entry. We previously conducted a prospective study to investigate several physiological parameters in an elderly Chinese population living in Taiwan. In that study, we demonstrated that aging significantly alters LV structure and LVG, and we disclosed an association between the renin-angiotensin system (RAS) gene polymorphism, especially the angiotensin converting enzyme (ACE) insertion/deletion (I/D) genotype, and LVM change and geometry (12). In the present study, we proposed to test for the relationship between the presence of CKD and subsequent changes of LV geometry using the same cohort.

Methods

Study Population

The subjects were from a community-based longitudinal cohort study (Gerontology Research Laboratory: The Longitudinal Study of Aging) that was designed to measure changes in several physiological functions and structures during the aging process in healthy elderly subjects. This working group was first initiated in 2000 and included several co-investigator physicians specializing in chest medicine, orthopedics and cardiology. Each co-investigator physician was

responsible for one specific examination of the elderly participants. Each participant had to be free of disease at baseline in order to be recruited into the normal aging group. Participants were invited from several senior activity centers in Kaohsiung city, Southern Taiwan. Baseline examinations were performed from October 1, 2000 to March 31, 2001.

The screening process included three stages. Figure 1 demonstrates the numbers of participants at each stage of screening or examination. Inclusion criteria for healthy elderly subjects were as follows: 1) an age of 60 years or more; 2) an active lifestyle, with no limitations in daily life; 3) no history of previously diagnosed diabetes, hypertension, ischemic heart disease or cerebrovascular accident; 4) not receiving any chronic medications. Initially there were 1,500 potential candidates. After interview by senior nurses using a constructed questionnaire, 694 out of 1,500 elderly were qualified for entry into the study. However, only 434 elderly candidates were willing to visit Kaohsiung Medical University Hospital (KMU) to participate in the first-stage biochemical tests and physiological examinations. Two senior physicians carefully examined the results of the laboratory tests and chest X-rays. Among the 434 cases, 254 were qualified as being healthy elderly, while 180 cases did not meet the criteria. An additional 33 patients dropped out before the bone density (BMD) evaluation in the second-stage, leaving 221 subjects. The BMD evaluation excluded 7 unqualified subjects and 6 subjects were lost to follow-up, leaving 208 subjects who participated in the third-stage examinations of electrocardiography (ECG) and echocardiography. Among the 208 subjects, 193 cases were qualified with normal ECG and echocardiographic data and were enrolled into the cardiology study population, while 15 cases did not meet the criteria. The Institutional Review Board of Kaohsiung Medical University Hospital approved this study. All enrolled patients gave their informed consent.

Blood pressures were taken after subjects had rested comfortably for 10 min. A computerized automatic mercury-sphygmomanometer (CH-5000; Citizen, Tokyo, Japan) was used on the right arm, with participants in a seated position. The reading was repeated and the mean of these two readings was used. Body weight and height were measured and body mass index (BMI) was calculated. A blood sample was drawn for determination of hemoglobin, total cholesterol, sugar, blood urea nitrogen (BUN) and creatinine after an 8-h overnight fast. All of the measurements were repeated every 2 years. The examinations were usually scheduled in the same month as the first visit to assure the same interval of follow-up.

Echocardiographic Methods

A single experienced cardiologist (WV) blinded to the clinical data performed the two-dimensional echocardiography with quantitative LV analysis. Echocardiographic examinations were performed using commercially available instru-

Fig. 1. Trial profile.

ments (HP Sonos 5500; Hewlett-Packard, Andover, USA) equipped with a 2–4 MHz imaging transducer. The LVM was calculated according to the formula of Devereux and Reichek (13). The ratio of LVM to body surface area (BSA) was used as the LVM index (LVMI) to adjust for body size. Increased LVMI was defined as $\text{LVMI} > 122.4 \text{ g/m}^2$ (i.e., 2 SD above the mean LVM value in the normotensive Chinese group) (14). Relative wall thickness (RWT) was calculated as $[2 \times \text{left ventricular posterior wall (LVPW)}] / \text{LV end-diastolic dimension (LVEDD)}$. Increased RWT was defined as an RWT of more than 0.45 (3). From these calculations, the participants were categorized into four groups: 1) normal (normal LVMI and RWT); 2) concentric remodeling (normal LVMI and increased RWT); 3) eccentric hypertrophy (increased LVMI and normal RWT); and 4) concentric hyper-

trophy (increased LVMI and increased RWT). We further stratified subjects into favorable (normal and concentric remodeling) and unfavorable LVG (eccentric hypertrophy and concentric hypertrophy) groups for binary logistic regression analysis. The LVM intraobserver error, calculated by dividing the difference between two measurements by the mean of two measurements from 10 randomly selected cases, was $13 \pm 9\%$ in this study.

Calculation of Kidney Function and Definition of CKD

The estimated GFR was calculated with the Modification of Diet in Renal Disease (MDRD) Study equation $[\text{GFR} = 186.3 \times (\text{serum creatinine in mg/dL})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if$

Table 1. Patients' Characteristics, Renal and Left Ventricular Parameters

	Baseline	2nd year	4th year	<i>p</i> value	
				Year 2 vs. baseline	Year 4 vs. baseline
Age (years)	71.5±3.9	73.5±3.9	75.5±3.9		
BMI (kg/m ²)	23.2±3.0	23.0±2.9	22.9±3.3	0.109	0.046
SBP (mmHg)	126.5±13.1	123.5±13.9	126.7±16.0	0.021	0.900
DBP (mmHg)	72.9±8.5	72.7±10.6	73.5±12.1	0.851	0.531
Hemoglobin (mg/dL)	14.0±1.1	14.0±1.2	14.2±1.3	0.145	0.005
Cholesterol (mg/dL)	192.9±32.4	192.1±29.1	187.9±30.2	0.675	0.025
Glucose (mg/dL)	101.0±8.5	99.5±10.9	104.6±12.0	0.112	<0.001
BUN (mg/dL)	15.68±3.15	15.69±3.39	16.08±3.69	0.993	0.262
Creatinine (mg/dL)	1.10±0.18	1.15±0.18	1.17±0.17	<0.001	<0.001
MDRD GFR	68.1±10.1	65.6±10.0	62.1±9.1	0.006	0.018
CKD (%)	23	34	43	0.007	0.001
LVIVS (mm)	8.8±1.8	8.8±1.7	8.6±1.5	0.996	0.178
LVPW (mm)	8.9±1.8	9.4±1.8	9.5±1.9	0.029	0.001
LVEDD (mm)	47.3±4.5	46.1±4.2	47.7±4.5	0.003	0.278
LVESD (mm)	27.3±4.2	25.8±4.6	26.3±4.3	<0.001	0.012
LVMI (g/m ²)	98.5±26.2	99.0±26.6	104.5±28.1	0.851	0.008
RWT (%)	38	41	40	<0.001	<0.001
LV geometry (%)				0.427	0.033
Normal	70.8	61.7	58.3		
Concentric remodeling	12.5	20.0	13.3		
Eccentric hypertrophy	9.2	5.8	16.7		
Concentric hypertrophy	7.5	12.5	11.7		

Total No.: 120. Male: 94 (78.3%). Values are mean±SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; MDRD, modification of diet in renal disease (mL/min/1.73 m²); GFR, glomerular filtration rate; CKD, chronic kidney disease; LVIVS, left ventricular interventricular septum dimension; LVPW, left ventricular posterior wall dimension; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVMI, left ventricular mass index; RWT, relative wall thickness; LV, left ventricular.

female)] (15). Chronic kidney disease was defined as a GFR of less than 60 mL/min/1.73 m². This range corresponds to stage 3 or higher CKD by the National Kidney Foundation's classification scheme and helps to identify individuals with clinically significant CKD (7). Follow-up every 2 years was selected on the basis of a previous recommendation for an observation period of at least 2 years for valid determination of the rate of decline in GFR (16).

Statistical Analysis

All data are expressed as the mean±SD. The paired *t*-test and McNemar test were used to evaluate the change of continuous variables and differences of prevalence of CKD and LVG during the 4-year follow-up. We further stratified subjects into favorable (normal and concentric remodeling) and unfavorable LV geometry (eccentric hypertrophy and concentric hypertrophy) groups. Our independent covariates to correlate with the 4th year LVG (unfavorable=1, favorable=0) included age, sex (male=1, female=0), BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), cholesterol, glucose, BUN, creatinine, hemoglobin, interventricular sep-

tum (IVS), LVPW, LVEDD, LV end-systolic dimension (LVESD), RWT, LVG, LVMI, MDRD and CKD status (presence=1, absence=0) at baseline. Subsequently, significantly correlated variables in the univariate analysis were further analyzed by binary logistic regression analysis to identify predictors for unfavorable geometry at year 4. All tests were two-sided, and the level of significance was established as *p*<0.05. The Statistical Package for the Social Sciences (SPSS) 11.0 for Windows (SPSS Inc., Chicago, USA) was used for statistical analysis.

Results

Clinical Characteristics

One-hundred and ninety-three subjects were enrolled initially (Fig. 1). Among them, 120 subjects who completed the 4 years of examinations with all biochemistry data and an adequate echocardiographic window for LV measurements were finally included in the current study. Table 1 summarizes the demographic information at the baseline and the 2nd and 4th years.

Table 2. Baseline CKD and Changes of Prevalence of Geometry

	Baseline	4th year	p value
Left ventricular geometry (%)			
CKD (+)			0.039
Normal	70.4	48.1	
Concentric remodeling	14.8	3.7	
Eccentric hypertrophy	11.1	25.9	
Concentric hypertrophy	3.7	22.2	
CKD (–)			0.256
Normal	71.0	61.3	
Concentric remodeling	11.8	16.1	
Eccentric hypertrophy	8.6	14.0	
Concentric hypertrophy	8.6	8.6	

CKD, chronic kidney disease.

The subjects included 94 men and 26 women (male 78.3%). Ages at the enrollment of the study ranged from 60 to 81 years (mean: 71.5 ± 3.9 years). There was no significant change of SBP and DBP after 4 years. At the 4-year follow-up, BMI was reduced ($p=0.046$). Although the total cholesterol level slightly decreased ($p=0.025$ compared to baseline), the fasting glucose and hemoglobin levels increased significantly ($p<0.001$ and 0.005 compared to baseline, respectively).

Kidney Function Data

The serum creatinine was gradually increased both at year 2 (1.10 ± 0.18 to 1.15 ± 0.18 mg/dL, $p<0.001$) and year 4 (1.10 ± 0.18 to 1.17 ± 0.17 mg/dL, $p<0.001$) compared to baseline. The estimated renal function MDRD between baseline and the follow-up period also demonstrated the same pattern, declining from 68.1 ± 10.1 to 65.6 ± 10.0 mL/min/ 1.73 m² at year 2 and from 68.1 ± 10.1 to 62.1 ± 9.1 mL/min/ 1.73 m² at year 4 ($p \leq 0.001$ for both). There was no significant change of BUN during the study period (Table 1).

The prevalence of CKD significantly increased during follow-up, from 23% at baseline to 34% at year 2 ($p=0.007$) and 43% at year 4 ($p=0.001$ vs. baseline). The presence of CKD at baseline was not correlated with initial LV parameters, including IVS, LVPW, LVEDD, LVESD, RWT and LVMI (all $p \geq 0.202$).

Echocardiographic Data

There was an increase in the RWT and LVMI (38% to 40% and 98.5 ± 26.2 to 104.5 ± 28.1 g/m², both $p \leq 0.008$) at the third examination (Table 1). The prevalence of all three geometries increased with aging in the overall population ($p=0.033$ at year 4). However, when subjects were stratified by the initial presence or absence of CKD, the CKD group demonstrated significant changes of LVG ($p=0.039$) after 4 years but the

group without CKD did not ($p=0.256$) (Table 2).

Univariate and Multivariate Regression Analysis for Presence of Unfavorable LVG

In univariate analysis, presence of CKD at baseline (odds ratio [OR]=3.18, confidence interval [CI]: 1.30–7.81; $p=0.011$), male sex (OR=3.77; 95% CI: 1.05–13.54; $p=0.042$), baseline SBP (OR=1.04; CI: 1.00–1.07; $p=0.042$), baseline LVIVS (OR=1.32; CI: 1.05–1.66; $p=0.020$), baseline LVPW (OR=1.41; CI: 1.12–1.79; $p=0.004$), baseline LVEDD (OR=1.23; CI: 1.10–1.37; $p<0.001$), baseline LVESD (OR=1.24, CI: 1.11–1.39, $p<0.001$), baseline LVMI (OR=1.05, CI: 1.03–1.07, $p<0.001$) and baseline unfavorable geometry (OR=9.33; CI: 3.19–27.33; $p<0.001$) were associated with the presence of unfavorable geometry at year 4.

Binary logistic regression analysis identified presence of CKD at baseline (OR=3.70; CI: 1.28–10.68; $p=0.015$), baseline LVESD (OR=1.22, CI: 1.07–1.40; $p=0.003$) and baseline LVMI (OR=1.05; CI: 1.02–1.07; $p<0.001$) as the factors associated with the presence of unfavorable geometry at year 4. The percentage of unfavorable geometry variance explained by these variables was 44.1% (Table 3).

Discussion

There were three main findings in this 4-year longitudinal study. First, the aging process was associated with an increase of CKD prevalence and changes of LVG in our elderly subjects. Second, the changes of LVG were only significant in subjects with CKD at baseline. Third, the presence of CKD was an independent predictor for subsequent changes of LVG toward an unfavorable form at year 4.

Some observations in humans have indicated that myocytes retain the capacity to undergo hypertrophy and proliferate in the senescent heart (17). Previous cross-sectional studies have not reached a conclusion regarding whether aging is associated with LVMI (18, 19). However, our prospective study may have been less subject to ascertainment bias than such cross-sectional studies. It was found that aging was associated with increased stiffness in the large arteries, which increases afterload and thereby contributes to an increase in LVMI (20). In addition, in the present study we investigated elderly persons, and the elderly may be more likely to be predisposed to LVM alternation. A recent study concluded that LVG was a better indicator of cardiovascular prognosis than LVM (3). In the Framingham Heart Study, Krumholz *et al.* found that the healthy participants with concentric hypertrophy had the worst prognosis for incident cardiovascular disease (5). Age has also been positively related to the LVPW thickness and RWT (21). In this prospective study, we found that aging was associated with an increase in LVMI. Both findings may explain the relationship between aging and the increased prevalence of concentric remodeling, eccentric hypertrophy,

Table 3. Univariable and Multivariable Factors for Predictors of Unfavorable Geometry

	Univariable factors		Multivariable factors	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age	1.11 (0.99–1.25)	0.074		
Sex	3.77 (1.05–13.54)	0.042		
BMI	1.04 (0.91–1.19)	0.526		
SBP	1.04 (1.00–1.07)	0.037		
DBP	1.01 (0.96–1.05)	0.819		
Cholesterol	0.99 (0.98–1.00)	0.093		
Glucose	1.03 (0.98–1.08)	0.269		
Hb	1.03 (0.72–1.46)	0.877		
LVIVS	1.32 (1.05–1.66)	0.020		
LVPW	1.41 (1.12–1.79)	0.004		
LVEDD	1.23 (1.10–1.37)	<0.001		
LVESD	1.24 (1.11–1.39)	<0.001	1.22 (1.07–1.40)	0.003
RWT	14.42 (0.13–1,655.63)	0.270		
LVMi	1.05 (1.03–1.07)	<0.001	1.05 (1.02–1.07)	<0.001
Geometry	9.33 (3.19–27.33)	<0.001		
BUN	1.07 (0.94–1.22)	0.284		
Cr	0.32 (0.03–3.06)	0.323		
MDRD	0.97 (0.93–1.01)	0.127		
CKD	3.18 (1.30–7.81)	0.011	3.70 (1.28–10.68)	0.015

OR, odds ratio; CI, confidence interval; BMI, body mass index; SBP, baseline systolic blood pressure; DBP, baseline diastolic blood pressure; BUN, baseline blood urea nitrogen; MDRD, baseline modification of diet in renal disease; CKD, chronic kidney disease at baseline; LVIVS, baseline left ventricular interventricular septum dimension; LVPW, baseline left ventricular posterior wall dimension; LVEDD, baseline left ventricular end-diastolic dimension; LVESD, baseline left ventricular end-systolic dimension; LVMi, baseline left ventricular mass index; RWT, baseline relative wall thickness.

and concentric hypertrophy in the present study.

Physiological characteristics may change with time to influence the changes of renal parameters (22). Aging is associated with a decrease in the number of nephrons and tubular cells (23, 24). There is also a decline in the renal blood flow as well as the glomerular filtration rate with age (25). Although aging is associated with a decrease in renal function, a previous study reported that renal function did not deteriorate with age in a third of an elderly population, which is comparable to the findings in our study (31.7%) (26). In the present study we used the MDRD Study equation, which has been shown to yield more accurate GFR values than the Cockcroft-Gault formula in elderly subjects (27). Therefore, our data provide more reliable evidence for evaluating the effect of aging on renal parameters. We thus found that the aging process was associated with a decline of renal functional parameters in our elderly subjects.

Left ventricular hypertrophy is highly prevalent in CKD even in the early stages (10). Many epidemiological studies have demonstrated that LVH is common in patients with renal insufficiency even before they progress to dialysis, and that the prevalence of LVH correlates with the degree of renal functional impairment. This is mainly due to the multifactorial pathogenesis of LVH in renal patients, in whom both hemodynamic and non-hemodynamic stimuli act synergically

to induce either an increase in left ventricular mass or an LV dilation. Anemia and arterial hypertension seem to be the most important factors in this process (28). Interventional studies have shown that partial correction of anemia through epoetin, together with a successful arterial hypertension therapy using ACE inhibitors or other drugs acting on the RAS, can induce LVH regression in CKD. In our present study population, multivariate analysis indicated that blood pressure and hemoglobin level were not independent predictors for the presence of unfavorable geometry in the 4th year of follow-up. In addition to these factors, something else must have contributed to the geometric changes.

The RAS is frequently activated in CKD. The findings in a previous animal study suggest that the RAS plays an important role in the pathogenesis of renal damage and cardiac hypertrophy (29). Previously we disclosed an association between the RAS gene polymorphism, especially the angiotensin converting enzyme (ACE) I/D genotype, LVM change and geometry in an elderly Chinese cohort (12). The use of ACE inhibitors in diabetic patients may be beneficial when renal dysfunction and/or cardiac hypertrophy are present (30). In the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial, treatment with RAS blockade reduced CV events only in patients with reduced renal function (31). Many major clinical trials have also reported

that the RAS plays an important role in the pathogenesis of CV disease in subjects with CKD. These findings may partly explain why the changes of LVG were only significant in subjects with CKD in the present study, and why the presence of CKD was an independent predictor for subsequent changes of LVG toward an unfavorable form in the 4th year of follow-up.

There were four important limitations in this study. First, we did not collect data on RAS activity, which could have helped us to clarify whether CKD itself was a direct cause of the changes of geometry or merely a surrogate marker. Second, there were no clearance measurements, urinary analyses, or albuminuria/proteinuria and renal sonography examinations, which limited our further analysis of their association with LVG. Third, the original MDRD equation has not been validated in a Chinese population. However, the MDRD Study equation has been shown to yield more accurate GFR measurements than the Cockcroft-Gault formula in elderly subjects. Fourth, our investigation involved a comparatively small number of patients, which may have caused systematic non-random error or bias. To minimize such noise, it will be necessary to obtain further sufficiently large random samples using a suitable sampling frame. Furthermore, investigations using larger cohorts and longer follow-up periods may identify additional factors associated with changes of geometry. Although our findings are of interest, the results need to be replicated for confirmation.

In conclusion, this longitudinal study showed that the aging process was related to an increased prevalence of CKD and changes of LVG. The presence of CKD is associated with subsequent changes of LVG toward unfavorable forms. These findings might partially explain why subjects with CKD have a higher CV risk and may provide further knowledge essential to the assessment of cardiac structure and disease in older subjects. Indeed, the adverse outcome in patients with unfavorable geometry, whose survival is reduced and incidence of fatal and non-fatal CV events increased, can be reversed if the risk factors can be identified early. It seems that the most promising strategy of reducing CV risk is to correct screening of risk factors as well as prompt treatment in the early stages of CKD, with the aim of improving general and CV prognosis among the elderly.

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