Original Paper

Early Left Ventricular Dysfunction Detected by Speckle Tracking in Long-Term Hemodialysis Patients with Valvular Calcification

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Keywords

Two-dimensional strain tracking imaging · Hemodialysis · Cardiac valve calcification · End-stage renal disease

Abstract

Purpose: Cardiac valve calcification (VC) is very common in patients on hemodialysis. However, the definite effect of VC on left ventricular (LV) geometry and function in this population is unknown, especially when LV ejection fraction (LVEF) is normal. The aim of this study was to determine the effect of VC on LV geometry and function in long-term hemodialysis patients by conventional echocardiography and two-dimensional speckle tracking echocardiography (2D-STE). **Methods:** A total of 47 hemodialysis patients (2–3 times weekly for 5 years or more) were enrolled in this study. Cardiac VC was defined as bright echoes of more than 1 mm on one or more cusps of the aortic valve or mitral valve or mitral annulus using echocardiography as the screening method. LV longitudinal global strain (GLS) was assessed on the apical four-chamber view and calculated as the mean strain of 6 segments. LV global circumferential strain was acquired on the LV short axis view at the level of papillary muscles. **Results:** Twenty-five patients with VC had higher mean values of interventricular septum thickness, LV posterior wall thickness, LV mass index, relative wall thickness, and LV mass/end-diastolic volume than 22 patients without VC ($p < 0.05$, respectively), indicating more obvious LV hypertrophy (LVH). VC patients had higher mitral annular E/E' values, especially at the septal side representing increased LV filling pressure compatible with diastolic dysfunction, while only the E/E' ratio of the septal side was significantly different between the 2 groups (16.7 ± 4.1 vs. 12.3 ± 4.4 , $p < 0.01$). When assessed by GLS, LV longitudinal systolic function was also lower in patients with VC compared with those without VC (-0.18 ± 0.03 vs. -0.25 ± 0.04 ; $p < 0.01$). **Conclusions:** Cardiac VC diagnosed by echocardiography when it occurs in long-term hemodialysis pa-

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tients may indicate more severe LVH, myocardial damage, and worse heart function in comparison to those without VC. Tissue Doppler imaging and 2D-STE can detect the subtle change of heart function in this population in the early stage of LV dysfunction when LVEF is normal.

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Introduction

Cardiac valve calcification (VC) is a very common phenomenon in patients with end-stage renal disease (ESRD), especially in those on dialysis in whom calcification progresses rapidly [1, 2], and it is a powerful predictor of mortality and fatal cardiovascular events [3–5]. Cardiac VC is also associated with the presence and severity of coronary artery diseases in chronic kidney diseases [3, 6]. Using echocardiography as the screening method, cardiac VC is a frequent complication with a prevalence of at least 30% in the ESRD patients [3].

However, the definite effect of cardiac VC on left ventricular (LV) geometry and function in this population is unknown, especially in the early stage of LV dysfunction when LV ejection fraction (LVEF) is normal. The development of two-dimensional (2D) speckle tracking echocardiography (STE) has facilitated the simple and angle-independent measurement of LV myocardial deformation in the longitudinal, circumferential, and radial directions, which can be used to detect subclinical uremic cardiomyopathy when LVEF is normal [7, 8]. LV strain has been proposed as a novel indication of systolic function. Our study aimed to determine the effect of VC on LV geometry and function in long-term hemodialysis patients by conventional echocardiography, pulse Doppler, tissue Doppler imaging (TDI), and 2D-STE.

Materials and Methods

Study Participants

Long-term hemodialysis patients (2–3 times weekly for 5 years or more) in the Nephrology Department of China-Japan Friendship Hospital, Beijing, China, were enrolled in this study. Patients with myocardial infarction, heart failure, atrial fibrillation, aortic stenosis (transaortic flow velocity >2.5 m/s), rheumatic valvular disease, prosthetic valves, bicuspid aortic valves, congenital heart disease, bacterial endocarditis, hypertrophic obstructive cardiomyopathy, and poor acoustic windows were excluded from the study. Cardiac VC was defined as bright echoes of more than 1 mm on one or more cusps of the aortic valve or mitral valve or mitral annulus by echocardiography [9].

Echocardiography

Conventional Echocardiography

Echocardiography was performed within 12 h of hemodialysis. Conventional parameters were obtained in the left decubitus position according to the recommendations of the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) [10] using a Philips iE33 echocardiographic machine (Philips Medical System, N.A., Bothell, WA, USA) equipped with an S5–1 and an X3–1 probe. Three beats were stored digitally and analyzed offline with Q-Lab software. These measurements were performed three times continuously by a single experienced cardiologist who was blinded to all clinical details. LV end-diastolic diameter (LVEDD), LV end-systolic diameter, interventricular septum thickness (IVST), LV posterior wall thickness (LVPWT), and LV fractional shortening were measured by M-mode echocardiography. LVEF was calculated using biplane Simpson's method. LV mass (LVM) was calculated using the 2D area-length method, and LVM index (LVMI) was LVM indexed to the body surface area. Prevalence of LV hypertrophy (LVH) was defined as LVMI >115 and 95 g/m² for males and females, respectively. Relative wall thickness (RWT) was calculated as follows: $RWT = 2 \times LVPWTd / LVEDD$ [11]. Peak early diastolic velocity (E), peak atrial systolic velocity (A), E wave deceleration time, and the E/A ratio were assessed from the mitral flow velocity pattern with the pulse Doppler method. Pulmonary vein flow S velocity and D velocity ratio and pulmonary vein atrial reversal flow velocity were assessed from the pulmonary vein flow velocity

pattern. Pulmonary artery systolic pressure was estimated by tricuspid valve regurgitation peak velocity and right atrium pressure. Average peak early diastolic velocity (E') and systolic velocity of mitral valve annulus (S') were obtained from the septal and lateral sides of the mitral annulus in the apical four-chamber view with proper pulsed-wave TDI settings. The E/E' ratio was calculated to estimate LV filling pressures. Left atrium volume was measured using the biplane area-length method.

2D Speckle Tracking Echocardiography

Standard 2D ultrasound images were recorded with a frame rate of >70 frames per second from the apical four-chamber view and short axis view at papillary muscle level. The recordings were digitally stored for offline analysis by EchoPAC 2D strain software. After manual tracing of endocardial borders, the software automatically traced the region of interest (ROI). To optimize tracking, the ROI width was adjusted when necessary. Myocardial motion in ROI was traced every frame after running the program. LV longitudinal global strain (GLS) was assessed on the apical four-chamber view, and calculated as the mean strain of 6 segments (basal septum, mid-septum, apical septum, basal lateral, mid-lateral, and apical lateral). LV global circumferential strain (GCS) was acquired on the LV short axis view at the level of papillary muscles. GLS and GCS are negative values and thus represent shortening. A less negative, i.e. a “higher” value, indicates less shortening, indicative of worse systolic LV function.

Real-Time 3D Echocardiographic Imaging

It was performed from the apical four-chamber view. Real-time full-volume 3D dataset triggered by electrocardiogram was acquired automatically. Three orthogonal sections were adjusted to ensure the coronal and sagittal planes in the middle of LV and the transverse plane at the level of mitral annulus with Qlab 3DQ ADV software. Five points were selected at mitral annulus and LV apex, respectively, and the LV endocardium was traced automatically. The tracings were refined with further manual adjustment. End-diastolic volume (EDV), end-systolic volume (ESV), LVEF and single volume (SV) were acquired after sequence analysis and LVM/EDV was calculated. The LVEF was calculated as $EF = (EDV - ESV)/EDV \cdot 100\%$.

Statistical Analysis

All statistical analyses were performed using SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA). All data were presented as the mean $\pm$ standard deviation. Comparison of numerical variables between the study groups was made using Student's t test for independent samples in comparing 2 groups when normally distributed and Mann-Whitney U test for independent samples when not normally distributed. $p < 0.05$ was considered significant.

Results

Clinical Characteristics

A total of 47 patients were included, 29 women and 18 men. Age ranged from 33 to 77 years. VC was found in 25 patients, 76% located to the aortic valve, 64% to the mitral valve, and 40% located to both valves. No statistically significant differences were found between the groups with VC and without VC with regard to age, duration of hemodialysis, blood pressure, diabetes, current smokers, hemoglobin, blood creatine, calcium, phosphate, and calcium $\times$ phosphate product (Table 1).

Echocardiographic Index for LV Geometry

The echocardiographic findings of LV geometry in patients with and without VC are shown in Table 2. Patients with VC had higher mean values of IVST, LVPWT, LVMI, RWT, and LVM/EDV than those without VC (13.4 ± 2.2 mm, 11.8 ± 2.1 mm, 132.3 ± 34.5 g/m², 0.48 ± 0.08 and 3.2 ± 0.89 g/mL vs. 11.2 ± 1.3 mm, 10.7 ± 1.3 mm, 101.9 ± 25.3 g/m², 0.44 ± 0.05 and 2.1 ± 0.76 g/mL, $p < 0.05$, respectively), indicating more obvious LVH. In the VC group, RWT was over 0.42, and LVH was mainly concentric hypertrophy [11]. There were no significant differences in EDV and ESV between the two groups.

Table 1. Baseline clinical features in patients with and without VC

Characteristics	VC (n = 25)	Without VC (n = 22)	p
Age, years	55.0±12.0	53.7±11.9	0.718
Duration of hemodialysis, years	9.7±4.4	10.4±2.7	0.594
Systolic blood pressure, mm Hg	144±15.3	142.2±23.9	0.062
Diastolic blood pressure, mm Hg	81.5±12.3	73.1±14.2	0.607
Hemoglobin	101.5±17.5	100.3±17.4	0.988
Blood creatine, µmol/L	662.7±377.1	735.9±291.3	0.473
BUN, mmol/L	19.8±11.7	21.7±7.8	0.072
Serum calcium, mmol/L	2.4±0.2	2.3±0.3	0.085
Serum phosphate, mmol/L	1.7±1.0	2.0±0.6	0.125
Bicarbonate, mmol/L	21.7±4.8	22.4±3.8	0.653
Calcium × phosphate product	3.96±2.33	4.71±1.75	0.423
Diabetes, n (%)	5 (20.0)	4 (18.2)	0.874
Current smokers, n (%)	1 (4.0)	1 (4.5)	0.926

Data are presented as mean ± standard deviation or as stated. VC, valve calcification.

Table 2. Echocardiographic parameters of left ventricular geometry in patients with and without VC

Characteristics	VC (n = 25)	Without VC (n = 22)	p
LVEDD, mm	48.7±4.5	48.2±3.0	0.689
LVESD, mm	30.3±3.9	29.4±3.0	0.374
IVST, mm	13.4±2.2	11.2±1.3	<0.001
LVPWT, mm	11.8±2.1	10.7±1.3	0.036
RWT	0.48±0.08	0.44±0.05	0.044
LVMI, g/m ²	132.3±34.5	101.9±25.3	0.017
EDV, mL	69.8±21.1	75.7±25.1	0.586
ESV, mL	25.0±9.3	28.5±9.7	0.424
LVM/EDV, g/mL	3.2±0.89	2.1±0.76	0.004

Data are presented as mean ± standard deviation. VC, valve calcification; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVST, interventricular septum thickness; LVPWT, left ventricular posterior wall thickness; RWT, relative wall thickness; LVMI, LV mass index; EDV, end-diastolic volume, ESV, end-systolic volume; LVM, LV mass.

Cardiac Function Evaluation by Different Modalities

The echocardiographic parameters for LV function evaluation are summarized in Tables 3 and 4. Patients in the VC group had significantly higher mean mitral annular E/E' value when compared to the group without VC, including values above 15 at the septal side representing increased LV filling pressure compatible with diastolic dysfunction (16.7 ± 4.1 vs. 12.3 ± 4.4 , $p < 0.01$). To evaluate LV systolic function, we measured LVEF, fractional shortening, and SV. These parameters were not significantly different among the 2 groups. The S' from the septal side by TDI was higher in patients without VC (7.15 ± 1.52 vs. 6.26 ± 0.35 cm/s, $p < 0.05$), suggesting a better LV systolic function. 2D-STE also showed that LV longitudinal systolic function was better assessed by GLS in patients without VC (-0.25 ± 0.04 vs. -0.18 ± 0.03 , $p < 0.01$ vs. VC group). No statistically significant difference was found in GCS between the 2 groups. Representative figures of echocardiography are shown in Figure 1.

Discussion

This study has demonstrated that LVH and cardiac dysfunction were more obvious in long-term hemodialysis patients with cardiac VC compared to those without VC. LVH is a strong predictor of adverse cardiovascular outcome in patients undergoing chronic hemodialysis treatment. LVH, mainly the concentric type, was found in both of the study groups; however, patients in the VC group had thicker hearts when compared to the group without

Table 3. Echocardiographic parameters of left ventricular diastolic function in patients with and without VC

Characteristics	VC	Without VC	<i>p</i>
E/A	0.77±0.21	0.88±0.32	0.172
DT, ms	231.1±20.9	228.3±33.4	0.820
S/D	1.62±0.27	1.54±0.36	0.577
LAV, mL	51.5±16.6	49.8±13.2	0.784
PASP, mm Hg	32.0±8.8	30.8±9.5	0.739
PVa, cm/s	26.2±2.8	25.2±4.4	0.584
E/E', cm/s			
Septal	16.7±4.1	12.3±4.4	0.006
Lateral	12.2±3.0	11.2±5.0	0.594

Data are presented as mean ± standard deviation. VC, valve calcification; E, peak early diastolic velocity; A, peak atrial systolic velocity; DT, E wave deceleration time; S/D, pulmonary vein flow S velocity and D velocity ratio; LAV, left atrium volume; PASP, pulmonary artery systolic pressure; PVa, pulmonary vein atrial reversal flow velocity; E', average peak early diastolic velocity.

Table 4. Echocardiographic parameters of left ventricular systolic function in patients with and without VC

Characteristics	VC	Without VC	<i>p</i>
LVEF2D, %	66.7±4.7	69.0±4.9	0.116
FS, %	37.2±3.7	38.9±4.0	0.146
LVEF3D, %	64.4±7.6	62.0±5.6	0.394
SV, mL	44.8±13.6	47.2±16.6	0.732
GLS	−0.18±0.03	−0.25±0.04	<0.001
GCS	−0.25±0.04	−0.26±0.05	0.602
S', cm/s			
Septal	6.26±0.35	7.15±1.52	0.039
Lateral	8.15±2.06	8.35±1.75	0.800

Data are presented as mean ± standard deviation. VC, valve calcification; LVEF, left ventricular ejection fraction; FS, left ventricular fractional shortening; SV, single volume; GLS, left ventricular longitudinal global strain; GCS, left ventricular global circumferential strain; S', systolic velocity of mitral valve annulus.

Fig. 1. Representative echocardiography figures of 2 patients on hemodialysis in two groups: without valve calcification (VC) (a–d) and with VC (e–h). **a, e** Two-dimensional echocardiography. **b, f** Tissue doppler imaging. **c, g** Real-time three-dimensional echocardiographic imaging. **d, h** Two-dimensional speckle-tracking echocardiography for left ventricular longitudinal global strain (GLS). GLS (white dotted line) is the mean of the six segments of the myocardium of the left ventricle (i.e., yellow basal septum, light blue mid septum, green apical septum, red basal lateral, dark blue mid lateral, purple apical lateral). GLS can be seen to be significantly lower in the VC group.

(For figure see next page.)

VC, suggesting the possibility of VC being used as a predictor of worse prognosis in hemodialysis patients. This study is similar to a prior study [12, 13] which showed that cardiac VC is strongly interrelated with LVH in chronic hemodialysis patients, and the underlying mechanism might partly be the valve resistance to LV outflow in aortic VC patients.

Patients with VC had worse LV diastolic function with higher mitral annular E/E' value by TDI. To evaluate LV systolic function, we measured LVEF, SV, and S'. LVEF and SV were within normal range in all the patients and were not significantly different between the 2 groups. However, we found a lower S' at the septal side in the VC group, suggesting a further decline in systolic function compared to those without VC.

Compared with LVEF, GLS is a more sensitive, objective, and reproducible modality for assessing cardiac functions, even among heart failure patients with preserved LVEF. GLS is the ratio of the maximal change in myocardial longitudinal length in systole to the original length, which can assess LV function accurately. During systole, LV myocardium in the longitudinal direction shortens, and GLS is represented by a negative value. The more negative value of GLS, the better the LV function. Less negative GLS is predictive of poor prognosis among stable hemodialysis patients with preserved LVEF [14–18]. In our study, 2D-STE revealed a statistically significant decline in GLS in patients on hemodialysis with VC compared with patients without VC, while circumferential function was not different. Systolic dysfunction may be initially apparent in the longitudinal direction, because subendocardial fibers more vulnerable to myocardial ischemia and fibrosis are longitudinally oriented [6]. LV concentric hypertrophy is mainly caused by hypertrophic response in the mid-myocardial layers, which are mainly more circumferentially oriented. This compensates for the reduction in longitudinal function and can explain the preserved EF. LV diastolic and systolic function appeared to be better in patients without VC than those with VC, indicating more severe myocardial damage in hemodialysis patients with cardiac VC.

Previous studies have shown that VC is accelerated by advanced age, systemic hypertension, hyperlipidemia, diabetes, and conditions that increase annular stress like mitral valve prolapse. Autopsy studies have confirmed an association between coronary artery calcification and cardiac VC, suggesting that VC is a marker of atherosclerosis [3]. The pathophysiology of VC is also an active process akin to atherosclerosis and involves initiating factors, endothelial dysfunction, inflammatory responses, oxidative stress leading to remodeling and mineralization of valves [19, 20]. However, the molecular and cellular processes that contribute to VC are not fully characterized. There are complex interrelationships between lipid retention, inflammation, phosphate signalling, and osteogenic pathways [21, 22]. A recent article identified a specific gene that makes patients more predisposed to developing VC [23]. VC is also considered to be a part of the later stages of the atherosclerosis process, as its relation is strongest with calcified plaque, less with mixed plaque, and nonsignificant with noncalcified plaque [24]. Therefore, cardiac VC often indicates more severe atherosclerosis and coronary lesions. Finding VC on echocardiography will help identify those persons who might be at a high risk of having an underlying coronary artery disease and thus make them amenable to earlier treatment [25]. Besides, VC was clearly related to an elevated calcium × phosphate product due to hyperparathyroidism and hyperphosphatemia in dialysis patients [26]. Meta-static calcification not only affects the valve cusps or ring but also the myocardium, producing cardiac failure or complete heart block. Energy subtraction radiography can measure increased myocardial calcium content which is not detectable by echocardiography [27]. VC can be a proxy for myocardial calcification. Duration of dialysis is also an independent predictor of VC. An increased cardiac output (due to anemia or arteriovenous fistula) will increase the mechanical stress on the valve cusps and predispose to premature calcification.

In hemodialysis patients, echocardiography can easily and noninvasively identify cardiac VC, which indicates more severe myocardial and coronary calcification. Relatively speaking,

the assessment of myocardial and coronary calcification is not that convenient. VC can be a marker for identifying cardiovascular calcification and high-risk population. It also indicates more severe LVH and worse heart function, suggesting a poor prognosis. If dialysis patients with a normal LVEF are suffering from heart failure symptoms, TDI and GLS will be useful, as they can detect the subtle change of heart function in the early stage of LV dysfunction.

Study Limitations

The major limitation of this study is the small sample size. Although we observed statistically significant differences in LV geometry and early heart function between patients with and without VC, the sample size was small. The univariate analysis with results was not corrected for age, BP, diabetes, and cholesterol levels also because of the small sample size.

Larger studies are needed to determine whether our findings can be replicated. Long-term follow-up is also needed to determine the clinical relevance of the observed changes in strain. Whether detection of this early subclinical dysfunction has long-term implications needs to be evaluated in future studies.

Statement of Ethics

This work complies with ethical standards.

Disclosure Statement

All the authors have no conflicts of interest.

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