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References


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Multidirectional myocardial systolic function in hemodialysis patients with preserved left ventricular ejection fraction and different left ventricular geometry

Hong Wang1, Jie Liu2, Xiao-dan Yao1, Juan Li1, Yong Yang2, Tie-sheng Cao2 and Bin Yang1

1Department of Ultrasound Diagnostics, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China, 2Department of Ultrasound Diagnostics, Tangdu Hospital, Fourth Military Medical University, Xi’an, China and 3Research Institute of Nephrology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China

Correspondence and offprint requests to: Bin Yang; E-mail: yb12yx@hotmail.com

Abstract

Background. Multidirectional myocardial strain analysis can provide mechanistic insight into the ventricular systolic function and pathophysiology. The aim of this study was to assess the multidirectional systolic function of the left ventricle (LV) and its relationship to LV geometry in hemodialysis patients with preserved left ventricular ejection fraction (LVEF).

Methods. A total of 98 end-stage renal disease patients (age 46 ± 10 years, 60% men) with preserved LVEF (≥50%) on a maintenance hemodialysis program and 18 healthy volunteers were enrolled. The patients were divided into non-hypertrophic groups (classified as normal LV geometry and concentric remodeling) and hypertrophy groups (classified as eccentric and concentric hypertrophy) according to their LV geometries assessed from LV mass/height2.7 and relative wall thickness in combination. Multidirectional strain analysis was performed by two-dimensional speckle tracking echocardiography.

Results. Myocardial systolic strain (longitudinal and circumferential) and stress-corrected midwall fraction shorting (sc-MWFS) were lower in the hypertrophy groups compared with non-hypertrophic groups. Longitudinal strain and strain rate were even lower in the concentric hypertrophy group than the eccentric hypertrophy group (−15.5 ± 2.2% versus −17.8 ± 2.6%, P = 0.001; −0.7 ± 0.2 versus −0.9 ± 0.2s−1, P = 0.016). Impaired longitudinal strain correlated with higher LV mass index (LVMI), relative wall thickness, pre-dialysis systolic blood pressure (SBP), calcium–phosphate product and lower sc-MWFS (all P < 0.0001) and weakly correlated with higher interdialytic weight gain (P = 0.004). Using multivariate linear regression, the independent predictors of LV longitudinal strain were pre-dialysis SBP, LVMI, relative wall thickness and sc-MWFS. There were no differences in LVEF and myocardial function in radial direction among all groups.

Conclusions. In hemodialysis patients with LV hypertrophy, myocardial function was impaired not only in longitudinal direction but also in circumferential direction despite preserved LVEF. Low longitudinal strain is related to LV hypertrophy, concentric geometry and pre-dialysis blood pressure.
Keywords: echocardiography; hemodialysis; left ventricle; strain; systolic function

Introduction

Cardiac complications are a major cause of death in patients with end-stage renal disease (ESRD). In the dialysis patient population, the high prevalence of left ventricular (LV) hypertrophy is considered an important risk factor for adverse cardiovascular outcomes [1]. Various factors may induce LV geometric changes. The most common cause is overload. With few exceptions, pressure overload results in an increment in ventricular mass with a high relative wall thickness; the earliest change appears to be an increase in relative wall thickness before there is a detectable increase in LV mass. The LV response to the volume overload consists of a progressive chamber enlargement with a characteristic increase in LV mass and normal relative wall thickness, which is defined as eccentric hypertrophy [2]. Accumulating evidence has indicated that LV geometry, in addition to LV mass, may be a determinant of prognosis [3, 4]. Changes in LV hypertrophy were also the major parts of the primary end points in many clinical management or trials to evaluate the effect of reducing cardiovascular morbidity and mortality for ESRD patients [5, 6]. Therefore, it is clinically important to identify myocardial functional consequences of different geometry and to address its underlying mechanisms and determinants in this population. Based on measurements at the endocardial level, left ventricular ejection fraction (LVEF) may be influenced by both intrinsic myocardial function and LV cavity geometry [7]. Thus, there may be subtle decreases in LV systolic function, while LVEF remains normal. Recent work has demonstrated that LV hypertrophy affected LV filling pressure and caused systolic contraction disturbance in patients with chronic kidney disease [8]. The myocardial functional changes underlying LV hypertrophy in ESRD patients have not been identified.

Myocardial strain imaging is highly sensitive to myocardial function changes and can provide comprehensive insight into LV myocardial contractility in three directions (radial, circumferential and longitudinal). Reduced longitudinal systolic function in hemodialysis patients has been quantified by two-dimensional strain analysis [9]. However, the relationship between LV geometry and myocardial function changes in three directions has not been fully examined in ESRD patients. Thus, the present study was designed to detect the subclinical changes of multidirectional systolic function and their related factors in hemodialysis patients with preserved LVEF.

Materials and methods

Study population

Ninety-eight patients who received regular hemodialysis therapy in Jinling Hospital between March and October in 2010 were enrolled in the study. Patients were selected consecutively. Inclusion criteria were patients on maintenance hemodialysis, 4-h sessions thrice weekly, who were prescribed a standard dose of dialysis targeting an equilibrated dose (Kt/V of urea) of ≥1.2. Dry weight was established for each patient on a trial-and-error basis and was defined optimal when the patients had no residual symptoms of orthopnea, dyspnea and edema during the interdialytic period. Exclusion criteria were previous coronary events (myocardial infarction, coronary revascularization), New York Heart Association Class III–IV heart failure, abnormal cardiac rhythm (other than sinus rhythm), low LVEF (<50%) or wall motion abnormality identified by conventional echocardiography, severe valvular stenosis or regurgitation, hypertrophic cardiomyopathy, underlying malignancy, chronic rheumatic heart disease and congenital heart disease. Finally, strain and strain rate data of patients were compared with data obtained from 18 healthy controls, matched for age, gender and body mass index. None of the healthy individuals had known cardiovascular disease, diabetes mellitus or kidney disease, and all had normal 12-lead electrocardiograms and normal thoracoscopic echocardiographic findings. Venous blood samples were taken from the participants in a sitting position for standard hematometry and serum biochemistry tests on the morning before hemodialysis. Pre-dialysis and post-dialysis blood pressure, ultrafiltration volume and interdialytic weight gain results were the mean values for each patient over the latest month before enrollment retrospectively (13 hemodialysis sessions). Changes in systolic blood pressure (ΔSBP) were calculated by sitting post-dialysis SBP minus sitting pre-dialysis SBP at the same dialysis treatment session. The protocol conformed to the ethical guidelines of our institution and informed consent was obtained from each participant.

Echocardiography

Conventional echocardiography was performed using commercially available equipment (Vivid-7, 3.5 MHz transducer; GE Vingmed, Milwaukee, WI). Echocardiographic examinations were performed on the patients within 2 h after completion of hemodialysis while they were at optimal dry weight to avoid an effect of redundant preload on strain imaging. LV dimensions were calculated from the standard M-mode in parasternal long-axis view according to the American Society of Echocardiography guidelines [10]. LV mass was calculated using the formula proposed by Devereux [11] and indexed for height².5. LV hypertrophy was defined as LV mass/height².5 >46.7 g/m².5 in women and >49.2 g/m².5 in men, respectively [12]. Relative wall thickness was calculated from posterior LV wall thickness/LV internal radius ratio at end diastole and considered increased if >0.43 [13]. Concentric hypertrophy was defined as LV hypertrophy with a relative wall thickness >0.43; eccentric hypertrophy as LV hypertrophy with a relative wall thickness ≤0.43; concentric remodeling as a relative wall thickness >0.43 in the absence of LV hypertrophy.

Myocardial systolic properties

LV endocardial systolic function was assessed by biplane Simpson’s ejection fraction (EF) and endocardial fractional shortening (FS) determined from LV systolic and diastolic dimensions. To assess myocardial contractility, midwall fractional shortening (MWFS) and circumferential end-systolic wall stress were assessed [14]. To minimize afterload dependence, stress-corrected MWFS (sc-MWFS) was determined as a percentage of that predicted for any given circumferential end-systolic wall stress using the regression equations derived from the large group of healthy population [15]. sc-MWFS was considered low if <84% in men and <93% in women [15].

Strain imaging

Comprehensive assessment of LV myocardial strain and strain rate was performed using two-dimensional speckle tracking strain imaging. For this purpose, standard two-dimensional gray-scale images of the LV were acquired at parasternal midventricular short-axis view and at apical four-chamber view, with a mean frame rate of 80 ± 5 frames/s. Data were stored in cine-loop format and transferred to a workstation for further off-line analysis. Applying the strain Lagrangian formula (L = L0/L0) [16], the percentage change in myocardial length (L) relative to the initial length (L0) derives myocardial strain (expressed in percentage). The temporal derivation of myocardial strain results in strain rate and is a measure of the rate of deformation. The radial deformation relates to the thickening (positive strain) and thinning (negative strain) of the myocardial wall. The circumferential deformation relates to the shortening (negative strain) and lengthening (positive strain) of the myocardial wall along the curvature of the LV in the short-axis view. Finally, the longitudinal deformation relates to motion from mitral annulus to the LV apex.
in the apical view and results in shortening (negative strain) and lengthening (positive strain). Strain and strain rate were quantified by commercially available software (EchoPAC version 7.0.0; General Electric–Vingmed). Results were reported as the peak value during systole. Peak systolic longitudinal strain and strain rate were calculated by averaging the peak systolic values of the six segments from the apical four-chamber view, whereas peak circumferential and radial strain and strain rate were obtained from the mid-ventricular short-axis view (Figure 1).

All strain and strain rate measurements were exported to a spreadsheet (Microsoft Excel 2002; Microsoft Corporation, Redmond, WA).

Statistical analysis and repeatability
All continuous variables were tested and confirmed to be of Gaussian distribution as determined by the Kolmogorov–Smirnov test and presented as mean ± SD. Categorical variables presented as frequencies and percentages were compared using the chi-square test or the Fisher’s exact test. The independent t-test was used to compare two groups of continuous data, whereas one-way analysis of variance (ANOVA) test was used to evaluate the differences among more than three groups. Post hoc analyses for significant results were performed using Bonferroni correction. Bivariate correlations were evaluated by the Pearson correlation coefficient for normally distributed data. Multiple linear regression analyses were performed to identify clinical and echocardiographic predictors of peak strain using a backward procedure.

Intraobserver reproducibility was determined by repeating the strain and strain rate measurements by one experienced reader in 20 randomly selected patients. A second blinded experienced reader performed the strain analysis in the same 20 patients, providing the interobserver reproducibility data. Intraobserver and interobserver variability were determined by Bland–Altman analysis.

All statistical analyses were performed with SPSS software (version 16.0; SPSS Inc., Chicago, IL). Two tailed P-value <0.05 was considered statistically significant.

Results

Clinical and echocardiographic characteristics

A total of 98 patients were evaluated (mean age 46 ± 10 years, range 25–62 years, 59 males). Clinical characteristics of the study participants are provided in Table 1. The underlying causes for ESRD were chronic glomerulonephritis in 56.1%, hypertensive nephrosclerosis in 15.3%, diabetes mellitus in 12.3%, chronic interstitial nephritis in 9.2% and polycystic kidney in 7.1%. Higher pre-dialysis systolic pressure was present in two hypertrophy groups, while higher calcium–phosphate product (Ca × PO₄) existed in the concentric hypertrophy group.

Table 2 summarizes the echocardiographic characteristics of the patients. LV hypertrophy was present in 74.5% of the patients: 25.5% with eccentric and 49.0% with concentric hypertrophy, respectively. Normal LV geometry was found in 13.3% of patients, and concentric remodeling in 12.2%. There were no significant differences in some indexes of diastolic function, such as E/A ratio, isovolumic relaxation time and deceleration time among the four groups. However, LV hypertrophy groups had significantly decreased mitral annular early diastolic velocity and larger maximal left atrial indexed volume compared with other groups. The higher Tei index was found in the concentric hypertrophy group.

Strain analysis of patients with different LV geometry

Table 3 shows the systolic function and myocardial strain analysis of LV in controls and ESRD patients. EF and FS, which were normal in all patients, showed no difference between controls and ESRD patients. There was a trend for lower MWFS in hypertrophy groups than in other groups (ANOVA, P < 0.001). The post hoc analysis showed that the difference was statistically significant in the concentric hypertrophy group, sc-MWFS was low in 75.5% hemodialysis patients. Comparing with the other
groups, there were significantly more patients with decreased sc-MWFS in the hypertrophy groups.

The systolic function in longitudinal direction and circumferential strain reduced in the two hypertrophy groups compared with non-hypertrophic groups (P < 0.0001, respectively), but the circumferential strain rate as well as the radial strain and strain rate showed no differences between each geometric group and controls, while radial strain was close to statistical significance (P = 0.07). Figure 2 shows the typical curve of longitudinal strain in different LV geometry groups. The concentric hypertrophy group had lower longitudinal strain and strain rate compared with non-hypertrophic groups (P < 0.0001, respectively).

### Table 1. Clinical characteristic in the total population according to LV geometry

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Control (n = 18)</th>
<th>Normal LV geometry (n = 13)</th>
<th>Concentric remodeling (n = 12)</th>
<th>Eccentric hypertrophy (n = 25)</th>
<th>Concentric hypertrophy (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42 ± 12</td>
<td>43 ± 12</td>
<td>45 ± 8</td>
<td>49 ± 11</td>
<td>47 ± 11</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>11/7</td>
<td>8/5</td>
<td>5/7</td>
<td>15/10</td>
<td>31/17</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.9 ± 2.2</td>
<td>21.6 ± 2.1</td>
<td>20.8 ± 1.9</td>
<td>21.5 ± 2.1</td>
<td>21.8 ± 1.8</td>
</tr>
<tr>
<td>Heart rate</td>
<td>73 ± 10</td>
<td>68 ± 12</td>
<td>72 ± 10</td>
<td>67 ± 7</td>
<td>75 ± 10</td>
</tr>
<tr>
<td>Time on dialysis (months)</td>
<td>33.6 ± 15.6</td>
<td>36.2 ± 14.5</td>
<td>32.6 ± 13.1</td>
<td>39.1 ± 10</td>
<td>39.1 ± 10</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.88 ± 0.11*</td>
<td>1.08 ± 1.3</td>
<td>1.04 ± 1.6</td>
<td>1.12 ± 2.1</td>
<td>1.15 ± 1.9</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.6 ± 1.1*</td>
<td>12.1 ± 1.7</td>
<td>11.5 ± 1.8</td>
<td>11.8 ± 1.6</td>
<td>11.4 ± 1.6</td>
</tr>
<tr>
<td>Urea acid (mg/dL)</td>
<td>4.2 ± 1.5*</td>
<td>6.5 ± 1.7</td>
<td>7.1 ± 1.5</td>
<td>6.7 ± 1.8</td>
<td>7.1 ± 1.9</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>145 ± 22</td>
<td>168 ± 28</td>
<td>161 ± 27</td>
<td>171 ± 33</td>
<td>175 ± 29</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>108 ± 58*</td>
<td>145 ± 49</td>
<td>136 ± 55</td>
<td>159 ± 47</td>
<td>157 ± 51</td>
</tr>
<tr>
<td>Session length of dialysis (min)</td>
<td>239 ± 15</td>
<td>235 ± 18</td>
<td>238 ± 21</td>
<td>238 ± 21</td>
<td>242 ± 16</td>
</tr>
<tr>
<td>Interdialytic weight gain (kg)</td>
<td>2.7 ± 0.8</td>
<td>2.9 ± 0.7</td>
<td>3.5 ± 1.0</td>
<td>3.3 ± 1.2</td>
<td>3.3 ± 1.2</td>
</tr>
<tr>
<td>Pre-HD SBP (mmHg)</td>
<td>116 ± 11</td>
<td>132 ± 10</td>
<td>134 ± 7</td>
<td>138 ± 10*</td>
<td>143 ± 9*</td>
</tr>
<tr>
<td>Pre-HD DBP (mmHg)</td>
<td>72 ± 8</td>
<td>73 ± 6</td>
<td>80 ± 7</td>
<td>76 ± 9</td>
<td>79 ± 8</td>
</tr>
<tr>
<td>Post-HD SBP (mmHg)</td>
<td>125 ± 6</td>
<td>126 ± 8</td>
<td>128 ± 8</td>
<td>132 ± 9</td>
<td>132 ± 9</td>
</tr>
<tr>
<td>Post-HD DBP (mmHg)</td>
<td>69 ± 5</td>
<td>70 ± 6</td>
<td>72 ± 9</td>
<td>71 ± 7</td>
<td>71 ± 7</td>
</tr>
<tr>
<td>ΔSBP (mmHg)</td>
<td>−7 ± 3</td>
<td>−8 ± 5</td>
<td>−10 ± 6</td>
<td>−11 ± 6</td>
<td>−11 ± 6</td>
</tr>
<tr>
<td>UF volume (L)</td>
<td>2.8 ± 0.5</td>
<td>3.0 ± 0.7</td>
<td>3.5 ± 0.6</td>
<td>3.4 ± 1.0</td>
<td>3.4 ± 1.0</td>
</tr>
<tr>
<td>Parathormone (pg/mL)</td>
<td>326 ± 167</td>
<td>362 ± 159</td>
<td>356 ± 178</td>
<td>385 ± 196</td>
<td>385 ± 196</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.9 ± 0.2</td>
<td>9.0 ± 0.3</td>
<td>9.2 ± 0.5</td>
<td>9.5 ± 0.4</td>
<td>9.5 ± 0.4</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>4.5 ± 0.6</td>
<td>4.6 ± 0.7</td>
<td>4.8 ± 0.8</td>
<td>5.1 ± 1.1</td>
<td>5.1 ± 1.1</td>
</tr>
<tr>
<td>Ca × PO₄ product</td>
<td>39.2 ± 2.6</td>
<td>41.1 ± 3.5</td>
<td>44.6 ± 3.3</td>
<td>49.1 ± 3.5*</td>
<td>49.1 ± 3.5*</td>
</tr>
<tr>
<td>ACEI/ARB (%)</td>
<td>0</td>
<td>62</td>
<td>58</td>
<td>72</td>
<td>79</td>
</tr>
<tr>
<td>Calcium channel blockers (%)</td>
<td>0</td>
<td>46</td>
<td>42</td>
<td>36</td>
<td>46</td>
</tr>
<tr>
<td>β-blocker (%)</td>
<td>0</td>
<td>23</td>
<td>25</td>
<td>20</td>
<td>46</td>
</tr>
</tbody>
</table>

*aACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor II blocker; DBP, diastolic blood pressure.  
*P < 0.05 versus the other groups.  
‡P < 0.05 versus preceding non-hypertrophic groups.

### Table 2. Echocardiography characteristics in the total population according to LV geometry

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Control (n = 18)</th>
<th>Normal LV geometry (n = 13)</th>
<th>Concentric remodeling (n = 12)</th>
<th>Eccentric hypertrophy (n = 25)</th>
<th>Concentric hypertrophy (n = 48)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic diameter (cm)</td>
<td>4.6 ± 0.6</td>
<td>4.7 ± 0.3</td>
<td>4.6 ± 0.4</td>
<td>5.1 ± 0.4*</td>
<td>4.5 ± 0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Septum thickness (cm)</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.2</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.2</td>
<td>1.3 ± 0.1*</td>
<td>0.01</td>
</tr>
<tr>
<td>Posterior wall thickness (cm)</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>1.0 ± 0.3</td>
<td>1.2 ± 0.2*</td>
<td>0.01</td>
</tr>
<tr>
<td>LVMG (g/m²)</td>
<td>42.3 ± 3.5</td>
<td>43.2 ± 3.5</td>
<td>43.6 ± 2.8</td>
<td>58.0 ± 2.5*</td>
<td>59.9 ± 3.1*</td>
<td>0.001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.35 ± 0.05</td>
<td>0.35 ± 0.03</td>
<td>0.46 ± 0.03*</td>
<td>0.38 ± 0.04</td>
<td>0.57 ± 0.05*</td>
<td>0.001</td>
</tr>
<tr>
<td>Left atrial volume index (mL/m²)</td>
<td>30.1 ± 2.8</td>
<td>31.2 ± 2.3</td>
<td>32.1 ± 3.1</td>
<td>34.6 ± 2.4*</td>
<td>34.8 ± 3.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Mitral E/A ratio</td>
<td>1.3 ± 0.2</td>
<td>1.2 ± 0.3</td>
<td>1.1 ± 0.2</td>
<td>1.2 ± 0.3</td>
<td>1.1 ± 0.3</td>
<td>0.15</td>
</tr>
<tr>
<td>Septal e’ (cm/s)</td>
<td>13 ± 3</td>
<td>10 ± 2</td>
<td>9 ± 2</td>
<td>8 ± 2*</td>
<td>7 ± 2*</td>
<td>0.01</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>81 ± 6</td>
<td>85 ± 18</td>
<td>89 ± 21</td>
<td>93 ± 22</td>
<td>98 ± 26</td>
<td>0.13</td>
</tr>
<tr>
<td>EDT (ms)</td>
<td>172 ± 18</td>
<td>188 ± 22</td>
<td>177 ± 19</td>
<td>191 ± 26</td>
<td>215 ± 33</td>
<td>0.29</td>
</tr>
<tr>
<td>Tei index</td>
<td>0.31 ± 0.12</td>
<td>0.35 ± 0.10</td>
<td>0.38 ± 0.12</td>
<td>0.41 ± 0.09*</td>
<td>0.48 ± 0.15*</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Mitrval E/A, ratio of peak early to late diastolic transmital flow velocity; Septal e’, medial mitral annular early diastolic velocity; IVRT, isovolumic relaxation time; EDT, E-wave deceleration time.

†P < 0.05 versus control group and normal geometry group.

‡P < 0.05 versus preceding three non-hypertrophic groups.

*P < 0.05 versus the other groups.

&0.05 < P < 0.1 versus control group.
Table 3. LV measurements of contractility in the total population according to LV geometry

<table>
<thead>
<tr>
<th></th>
<th>Healthy control (n = 18)</th>
<th>Normal LV geometry (n = 13)</th>
<th>Concentric remodeling (n = 12)</th>
<th>Eccentric hypertrophy (n = 25)</th>
<th>Concentric hypertrophy (n = 48)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>63.5 ± 7.8</td>
<td>62.8 ± 5.3</td>
<td>60.2 ± 7.1</td>
<td>63.7 ± 5.1</td>
<td>61.9 ± 6.4</td>
<td>0.18</td>
</tr>
<tr>
<td>FS (%)</td>
<td>38.8 ± 2.6</td>
<td>34.8 ± 4.1</td>
<td>36.1 ± 6.4</td>
<td>34.3 ± 4.9</td>
<td>32.2 ± 5.8</td>
<td>0.21</td>
</tr>
<tr>
<td>MWFS (%)</td>
<td>20.2 ± 1.9</td>
<td>19.6 ± 2.8</td>
<td>18.5 ± 3.0</td>
<td>17.1 ± 2.9†</td>
<td>15.2 ± 2.6*</td>
<td>0.001</td>
</tr>
<tr>
<td>sc-MWFS (%)</td>
<td>105.2 ± 3.5</td>
<td>101.9 ± 16.4</td>
<td>90.6 ± 8.8</td>
<td>82.8 ± 14.3†</td>
<td>66.9 ± 11.9*</td>
<td>0.001</td>
</tr>
<tr>
<td>Low sc-MWFS (%)</td>
<td>45.5 ± 13.2</td>
<td>45.4 ± 17.2</td>
<td>43.5 ± 14.2</td>
<td>42.6 ± 18.5</td>
<td>40.8 ± 16.4&amp;</td>
<td>0.07</td>
</tr>
<tr>
<td>Radial strain (%)</td>
<td>1.8 ± 0.5</td>
<td>2.1 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>1.9 ± 0.6</td>
<td>1.7 ± 0.8</td>
<td>0.12</td>
</tr>
<tr>
<td>Circumferential strain (%)</td>
<td>-20.8 ± 3.1</td>
<td>-20.6 ± 2.6</td>
<td>-19.8 ± 2.2</td>
<td>-17.6 ± 2.9†</td>
<td>-16.6 ± 2.5‡</td>
<td>0.0001</td>
</tr>
<tr>
<td>Circumferential strain rate (s$^{-1}$)</td>
<td>-1.3 ± 0.2</td>
<td>-1.3 ± 0.2</td>
<td>-1.2 ± 0.1</td>
<td>-1.1 ± 0.2</td>
<td>-1.1 ± 0.2</td>
<td>0.28</td>
</tr>
<tr>
<td>Longitudinal strain (%)</td>
<td>-22.1 ± 2.2</td>
<td>-21.4 ± 2.9</td>
<td>-20.7 ± 3.3</td>
<td>-17.8 ± 2.6‡</td>
<td>-15.5 ± 2.2*</td>
<td>0.0001</td>
</tr>
<tr>
<td>Longitudinal strain rate (s$^{-1}$)</td>
<td>-1.3 ± 0.2</td>
<td>-1.2 ± 0.2</td>
<td>-1.1 ± 0.2&amp;</td>
<td>-0.9 ± 0.2‡</td>
<td>-0.7 ± 0.2*</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

†P < 0.05 versus control group and normal geometry group.
‡P < 0.05 versus preceding three non-hypertrophic groups.
*P < 0.05 versus the other groups.
&0.05 < P < 0.1 versus control group.

Fig. 2. Typical longitudinal strain curve in normal geometry (A), concentric remodeling (B), eccentric hypertrophy (C) and concentric hypertrophy patients (D). The mean peak longitudinal strain in systole was −22.5, −21.7, −18.5 and −15.5%, respectively.
than the eccentric hypertrophy group (−15.5 ± 2.2 versus −17.8 ± 2.6%, P = 0.001; −0.7 ± 0.2 versus −0.9 ± 0.2 s⁻¹, P = 0.016), whereas the post hoc analysis did not show statistical difference in other parameters of strain analysis between the two hypertrophy groups.

**Relationships of strain with LV geometry**

In univariate analyses, lower longitudinal strain correlated with higher LV mass index (LVMi) (r = 0.65, P < 0.0001), higher relative wall thickness (r = 0.64, P < 0.0001) and lower sc-MWFS (r = −0.75, P < 0.0001), higher pre-dialysis SBP (r = 0.45, P < 0.0001), higher Ca × PO₄ product (r = 0.54, P < 0.0001) and weakly correlated with interdialytic weight gain (r = 0.28, P = 0.004). The univariate correlation between longitudinal strain and EF was r = 0.03 (P = 0.78). The other strain parameters were not significantly related to LV geometry and clinical parameters.

Table 4 shows the multiple regression analysis of longitudinal strain, the most significant model (adjusted R² = 0.78, P < 0.0001) generated including relative wall thickness, LVMi, pre-dialysis SBP and sc-MWFS, independent of age, gender, LVEF, left atrial volume index, Ca × PO₄ product and interdialytic weight gain.

**Intraobserver and interobserver reproducibility**

Bland–Altman plots were available as Supplementary data. The Bland–Altman analysis showed small biases, with no significant trend, for all intraobserver and interobserver strain and strain rate measurements.

**Discussion**

The present study demonstrated that there were significant variations in multidirectional myocardial function and contractility related to LV geometry in hemodialysis patients. Subclinical systolic dysfunction was observed in patients with LV hypertrophy despite normal LVEF. Moreover, concentric hypertrophy was associated with lower myocardial systolic function in longitudinal direction than eccentric hypertrophy. These findings highlighted that changes of LV morphology in ESRD patients may represent different myocardial mechanics and pathology. Strain analysis enables early detection of subtle changes in myocardial function in the ESRD population.

Changes in multidirectional myocardial function in hemodialysis patients

Despite the fact that LVEF is the most commonly used surrogate marker of LV systolic function, the presence of myocardial systolic dysfunction may be masked by a normal LVEF, particularly in patients with concentric hypertrophy [17]. In the present study, all patients had a preserved LVEF. However, impaired systolic function did exist particularly in concentric hypertrophy groups. Moreover, this study demonstrated that longitudinal strain was a strong covariate of sc-MWFS and did not relate to LVEF. The result is of practical importance since proper parameters should be chosen to evaluate myocardial systolic function in ESRD patients in clinical management. Multidirectional systolic function that varied with LV geometry disclosed the different pathology mechanisms among geometric groups and may help to explain why LVMi and relative wall thickness represent as the powerful predictors of adverse clinical outcomes [1, 18].

Diastolic dysfunction, which is often prior to the systolic dysfunction, showed the same tendency in hypertrophy groups. Increased left atrial volume and decreased septal mitral annular velocity reflected the duration of elevated filling pressure and impaired LV relaxation in the hypertrophy group. The other parameters related to diastolic function were insensitive in ESRD patients. Tei index representing the global function of the ventricle also showed impaired heart function in the concentric hypertrophy group.

**The mechanism of the relationship between LV geometry and function**

As the LV myocardial fiber architecture is a complex array of longitudinally and circumferentially orientated fibers located predominantly in the epicardium/endocardium and midwall, respectively [19], their functional changes could be quantified by multidirectional myocardial strain analyses. Different causes of LV hypertrophy showed different subclinical myocardial changes detected by speckle tracking imaging [20, 21].

LV hypertrophy induced by hypertension, which is also present in hemodialysis patients for years, has already been studied by strain analysis. The results showed that hypertension predominately affects longitudinal deformation [22, 23], even since pre-hypertension period [24]. Concentric hypertrophy induced by hypertension could result in the deterioration of systolic deformation in three directions [25]. The inverse associations between the LV mass and longitudinal deformation were also observed [23, 26], but the effects of hypertension on radial and circumstantial deformation were inconsistent in some studies [22, 23, 26]. In addition to multidirectional strain analysis, this study focused on the impact of ESRD and hemodialysis process on myocardial strain. Some factors, such as calcium, phosphorus and interdialytic weight gain, did correlate with impaired myocardial deformation. But blood pressure played a more important role as a significant predictor for longitudinal strain.
Aortic stenosis is another common disease inducing LV hypertrophy. Concentric hypertrophy in aortic valve stenosis was also associated with reduced longitudinal function [27]. And with increasing aortic stenosis severity, the myocardial systolic mechanics decreased from longitudinal to circumferential and to radial deformation. Based on that, the myocardial dysfunction was supposed to start in the subendocardium and progress to transmural dysfunction [28]. After the valve replacement, strain and strain rate were improved in all three directions [29]. The ESRD patients in this study showed the impairment in longitudinal and circumferential directions. As it was demonstrated in aortic stenosis, the extent that myocardium deformation was affected may depend on the impact of adverse factors on myocardium. So further longitudinal studies are necessary to verify the accumulated effects of adverse factors in ESRD patients.

LV hypertrophy used to be regarded as an adaptive mechanism of overload. The basic biology underlying LV remodeling and differential load effects indicates that different loads result in distinct phenotype differences. Eccentric hypertrophy caused by preload is more beneficial than concentric hypertrophy caused by afterload which resulted in increased inflammation, fibrosis and cardiomyocyte apoptosis. Preload is associated with Akt activation without fibrosis, little apoptosis, better function and lower mortality [30]. The functional difference of myocardium in this study is consistent with the biological results. The concentric geometry was a significant predictor of myocardial strain.

Furthermore, in addition to overload, more factors are associated with LV remodeling in ESRD patients. For instance, insulin resistance has been proved to play a role in the LV hypertrophy of ESRD patients [31]. Other factors, such as anemia and vitamin D deficiency, also have adverse effect on LV hypertrophy [6, 32]. But this study demonstrated that the clinical determinants of myocardial mechanics are still preload and afterload. Pre-dialysis blood pressure has been associated with afterload. Ca × PO₄ product is a risk factor of artery calcification and contributes to blood pressure. Interdialytic weight gain, also an independent contribution to blood pressure [33], is often regarded as a surrogate marker of fluid overload. And not surprisingly, blood pressure is proved to be the significant predictor of myocardial deformation among them.

Clinical implications

LV hypertrophy was regarded as a valid surrogate end point in observational studies and intervention trials in ESRD patients, but conventional measurement of LV systolic function cannot ascertain the transition from compensatory hypertrophy to subclinical myocardial dysfunction. Myocardial strain is easy to obtain and can reflect the underlying systolic function impairment in hemodialysis patients. As additional information for prognosis and function reversibility was provided by strain analysis in patients with myocardial infarction [34, 35] and aortic stenosis [29, 36], myocardial strain may be expected to be a better monitor marker than endocardial parameters in evaluating the effect of clinical management on myocardial function in ESRD patients. Further longitudinal and intervention studies are required to confirm this speculation.

Study limitations

Hemodialysis may influence the measurement results of strain imaging and LV geometry because of fluctuating cardiac load status. To minimize the influences, all the hemodynamics parameters, in this study, were measured during the same hemodialysis cycle and all patients were asymptomatic and in stable hemodynamic condition at rest. No wall motion abnormalities, the signal of myocardial ischemia during dialysis, were involved in the segments for strain analysis in this study, but the effect of myocardial ischemia cannot be entirely eliminated. Although the post-dialysis period is the proper time when the body fluid distribution is comparable to that of the controls, the effect of body fluid distribution on strain analysis is still unknown.

This study is cross-sectional, so the prognostic significance of the findings is not clear and needs to be verified. Patients with a history of coronary events were excluded to avoid the influence on strain analysis, but on the other hand, patients with a history of cardiovascular disease may get the most benefits from the new method so should be included in further longitudinal studies. The sample size of some groups is limited and more parameters may stand out with a large sample size. And other factors, such as pulse wave velocity of aorta, which is also associated with LV hypertrophy in hemodialysis patients [37], may add significant information to myocardial strain patterns in further study.

In conclusion, despite normal LVEF, LV hypertrophy in hemodialysis patients was associated with subclinical myocardial dysfunction in longitudinal and circumferential directions, which can be detected by strain imaging. Low longitudinal strain is related to high LV mass, concentric geometry and high pre-dialysis blood pressure.

 Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

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