Speckle-Tracking Echocardiography for Detecting Subclinical Left Ventricular Dysfunction in Patients With Familial Hypercholesterolemia

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Myocardial ischemia and left ventricular dysfunction have been documented in young adults with familial hypercholesterolemia. We investigated whether speckle-tracking echocardiography can be used to detect subclinically impaired global and regional myocardial function in patients with this lipid disorder.

This single-center study included 47 patients with familial hypercholesterolemia and 37 healthy control subjects who underwent transthoracic Doppler echocardiography and speckle-tracking echocardiography from January 2003 through December 2016. Conventional echocardiographic and strain parameters in the 2 groups were analyzed and compared.

Left ventricular dimensions were significantly larger at end-diastole (P=0.02) and end-systole (P=0.013), left ventricular walls were significantly thicker (P <0.0001), and the early transmitral/early diastolic mitral annular velocity ratio was significantly higher (P=0.006) in the patient group than in the control group. In the patient group, global longitudinal and circumferential strain values were significantly lower (P <0.0001) and global radial strain values significantly higher (P=0.006); all segmental longitudinal strain (P <0.04) and most segmental circumferential strain values (P ≤0.01) were significantly lower; and some segmental radial strains, especially at the apex, were significantly higher (P ≤0.04). However, average longitudinal, circumferential, and radial strains in the different segments of the 3 main coronary artery territories were significantly lower in the patient group (P <0.01). Global longitudinal strain (r=0.561; P=0.001) and global circumferential strain (r=0.565; P <0.0001) were inversely correlated with low-density-lipoprotein cholesterol levels.

We conclude that speckle-tracking echocardiography can be used to detect subclinical global and regional systolic abnormalities in patients with familial hypercholesterolemia.

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Speckle-tracking echocardiography (STE) is a technique for detecting myocardial deformation. It enables clinicians to track myocardial tissue movement and to detect early signs of global and regional myocardial dysfunction in patients with subclinical...
disease by measuring longitudinal, radial, and circumferential strains. The technique has already been used to detect early changes in myocardial deformation in isolated cases of hypercholesterolemia in obese children and adolescents. Few studies, however, have specifically isolated cases of hypercholesterolemia in obese children to detect early changes in myocardial deformation in FH patients. In a previous study, we found significantly reduced longitudinal and circumferential strains in asymptomatic patients with FH, leading us to conclude that impaired LV function can be detected before a decrease in LV ejection fraction (LVEF). Changes in segmental myocardial function in patients with FH are less well studied. Therefore, we conducted another study of FH patients to determine whether STE can be used to detect subclinical impairment of regional myocardial function.

**Patients and Methods**

From January 2003 through December 2016, 47 patients with FH (27 males, 20 females; mean age, 21.7 ± 14.2 yr; range, 4–49 yr) were seen at the lipid clinic of Anzhen Hospital in Beijing (Table I). All had been diagnosed with homozygous FH at the clinic. Familial hypercholesterolemia was diagnosed if a patient met at least 2 of the following criteria: an LDL cholesterol (LDL-C) level above the 95th percentile, adjusted for age and sex; premature coronary artery disease in a first-degree relative <60 years old; and tendon xanthomata in the index patient, a first-degree relative, or a pediatric relative with an LDL-C level above the 95th percentile, adjusted for age and sex. All patients included in the study were normotensive and had normal ventricular wall motion and ejection fraction (EF) on echocardiograms. Patients with a history of smoking and known vascular disease were excluded.

Of the 47 patients with FH, 37 had age-matched healthy siblings (21 male, 16 female; mean age, 21.8 ± 13.4 yr; range, 2–46 yr) who had normal physical examination, electrocardiographic, and echocardiographic findings and no history of heart disease. These siblings were enrolled as the control group.

All study-related procedures were performed in accordance with the Declaration of Helsinki. The Beijing Anzhen Hospital Institutional Review Board approved this study, and informed consent was obtained from each study participant or an authorized representative.

**Clinical Assessment**

On the day of study, resting blood pressure was measured consecutively 3 times with an automatic oscillometric cuff device, after the participant had been sitting for ≥5 min. A fasting lipid profile was obtained to establish the levels of total cholesterol (TC), triglycerides, high-density-lipoprotein cholesterol (HDL-C), and LDL-C.

**Conventional Echocardiography**

All conventional transthoracic echocardiographic measurements were acquired with use of a Vivid 7 ultrasound cardiovascular system (GE Healthcare) and a 3-S phased-array transducer (transmission frequency, 1.7–3.4 MHz). Left ventricular diameter and wall thickness were measured from 2-dimensional (2D) guided M-mode tracings obtained from parasternal long-axis views. Left ventricular ejection fraction was calculated from the apical 2- and 4-chamber views by using the biplane modified Simpson method. Early diastolic mitral inflow velocity (E), late diastolic mitral inflow velocity (A), E/A ratio, and E-wave deceleration time (E-DT) were measured from transmitral recordings in the apical 4-chamber view by means of pulsed-wave Doppler imaging. The peak velocity at the lateral annulus during early diastole (e') was measured in the apical 4-chamber view by means of tissue Doppler imaging. The ratio of peak transmitral early velocity to early diastolic mitral annular velocity (E/e') was calculated.

**Two-Dimensional Speckle-Tracking Echocardiography and Strain Analysis**

Two-dimensional echocardiographic images of 3 cardiac cycles were obtained from the apical 2-, 3-, and 4-chamber views and parasternal short-axis views at the levels of the mitral valve, papillary muscles, and apex. The frame rate ranged from 40 to 80 frames per second. The 2D images were digitally stored in cine-loop format for offline myocardial strain analysis with EchoPAC PC version 7.0 (GE Healthcare) software.

Global and segmental strains were measured. Each echocardiographic view was divided into a 6-segment.

**TABLE I. Clinical Characteristics**

| Variable          | FH Group (n=47) | Control Group (n=37) | P Value |
|-------------------|-----------------|----------------------|--------|
| Age (yr)          | 21.7 ± 14.2     | 21.8 ± 13.4          | 0.96   |
|                   | (4–49)          | (2–46)               |        |
| Male              | 27 (58.3)       | 21 (56.7)            | 0.93   |
| TC (mmol/L)       | 13.47 ± 5.06    | 5.32 ± 1.05          | <0.0001|
| LDL-C (mmol/L)    | 10.84 ± 4.76    | 3.27 ± 0.77          | <0.0001|
| TG (mmol/L)       | 1.66 ± 0.63     | 1.41 ± 0.36          | 0.32   |
| HDL-C (mmol/L)    | 1.53 ± 0.74     | 1.64 ± 0.67          | 0.49   |
| SBP (mmHg)        | 108.85 ± 16.81  | 108.11 ± 9.83        | 0.81   |
| DBP (mmHg)        | 64.94 ± 9.99    | 64.97 ± 5.74         | 0.95   |
| HR (beats/min)    | 79.38 ± 14.42   | 79.97 ± 9.49         | 0.88   |

DBP = diastolic blood pressure; FH = familial hypercholesterolemia; HDL-C = high-density-lipoprotein cholesterol; HR = heart rate; LDL-C = low-density-lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides

Data are presented as mean ± SD (range), as number and percentage, or as mean ± SD. P <0.05 was considered statistically significant.
model. Segmental longitudinal strain (LS), circumferential strain (CS), and radial strain (RS) on the LV were calculated as previously described. Longitudinal strain was analyzed in 2-, 3-, and 4-chamber views; CS and RS were analyzed in basal, medial, and apical short-axis views (Fig. 1). Global strain was then obtained by averaging the 6 regional strain curves from each view. Peak global longitudinal strain (GLS) was the average of the peak average for GLS obtained in long-axis views. Similarly, peak global circumferential strain (GCS) and global radial strain (GRS) were calculated from images taken in short-axis views. Regional LS, CS, and RS values in different LV segments were obtained in the 3 major coronary artery territories: the left anterior descending (LAD), the left circumflex (LCx), and the right coronary artery (RCA). Territorial strains were calculated by averaging strain values in segments assigned to each of the 3 major coronary arteries, according to standard practice. Specially trained echocardiographers obtained and processed the data offline, and one reader who had no information on the participants’ clinical status evaluated the data.

**Reproducibility**

The strain measurements based on 2D STE images from 10 patients with FH were randomly assigned for analysis of intraobserver and interobserver variability.

**Statistical Analysis**

Data were analyzed with SPSS version 19.0 (SPSS, an IBM company). Continuous variables were expressed as mean ± SD. Univariate analysis of continuous variables was performed by using unpaired Student t tests for normally distributed data and Mann-Whitney U tests for non-normally distributed data. Linear regression analysis was performed to determine the relationship of LDL-C to GLS, GCS, and GRS. P values <0.05 were considered statistically significant.

**Results**

**Clinical Characteristics**

The FH and control groups were comparable in age, sex, blood pressure, and heart rate (Table I). Both groups also had comparable levels of HDL-C (P=0.49) and triglycerides (P=0.32). The FH group, however, had significantly higher levels of total cholesterol (13.47 ± 5.06 vs 5.32 ± 1.05 mmol/L [to convert to mg/dL, divide by 0.0259]; P<0.0001) and LDL-C (10.84 ± 4.76 vs 3.27 ± 0.77 mmol/L; P<0.0001).

**Conventional Echocardiographic Characteristics**

In comparison with the control group, the FH group had significantly thicker LV walls (P<0.0001) and larger LV dimensions at end-diastole (P=0.02) and end-systole (P=0.013) (Table II). However, global systolic function, expressed in terms of LVEF, was similar in both groups (P=0.87). Diastolic function in both groups was similar in regard to E, A, and E/A. In contrast, the FH group had significantly higher values for E-DT (183 ± 45 vs 170 ± 40 ms; P=0.001) and E/e′ (7.80 ± 2.30 vs 5.20 ± 1.90 ms; P=0.006) (Table II).

**Strain Analysis**

**Global Strain.** Global longitudinal strain and GCS values were significantly lower (P <0.0001) and GRS values significantly higher (P=0.006) in the FH group than in the control group (Table III).

**Regional Strain.** All segmental LS values were significantly lower in the FH group than in the control group (Table IV). Most segmental CS values were also significantly lower in the FH group (Table V); however, values...
in the anterior, lateral, posterior, and inferior walls at the apex and the posterior wall at the papillary muscle level were similar between groups (Table V). In addition, some segmental RS values, especially at the apex, were significantly higher in the FH group (Table VI). In the analysis of territorial strains, the average LS, CS, and RS values in the basal, middle, and apical segments of the 3 main coronary artery territories were significantly lower in the FH group (Table VII).

### Linear Correlation Between Global Strains and LDL-C
Global longitudinal strain \( r=0.561; P=0.001 \) (Fig. 2A) and GCS \( r=0.565; P<0.0001 \) (Fig. 2B) correlated inversely with LDL-C, whereas GRS \( r=0.563; P=0.003 \) (Fig. 2C) correlated positively with LDL-C.

#### TABLE III. Global Strain

| Variable | FH Group \( \bar{n}=47 \) | Control Group \( \bar{n}=37 \) | \( P \) Value |
|----------|--------------------------|--------------------------|-------------|
| GLS \( \% \) | \(-19.86 \pm 4.76\) | \(-24.44 \pm 1.73\) | <0.0001 |
| GCS \( \% \) | \(-20.95 \pm 5.21\) | \(-25.92 \pm 2.78\) | <0.0001 |
| GRS \( \% \) | \(52.64 \pm 14.85\) | \(41.76 \pm 14.82\) | 0.006 |

FH = familial hypercholesterolemia; GCS = global circumferential strain; GLS = global longitudinal strain; GRS = global radial strain

Data are presented as mean \( \pm \) SD. \( P<0.05 \) was considered statistically significant.

#### Reproducibility
The reproducibility of global LS, CS, and RS measurements was good. Analysis of intraobserver variability yielded significant intraclass correlation coefficients of

#### TABLE IV. Regional Longitudinal Strain in the 3 Main Coronary Artery Territories

| Variable | FH Group \( \bar{n}=47 \) | Control Group \( \bar{n}=37 \) | \( P \) Value |
|----------|--------------------------|--------------------------|-------------|
| LAD      |                          |                          |             |
| A3C septal Basal | \(-17.83 \pm 6.74\) | \(-23.85 \pm 3.76\) | <0.0001 |
| A3C septal Mid          | \(-18.97 \pm 7.58\) | \(-24.49 \pm 4.11\) | <0.0001 |
| A4C lateral Basal       | \(-17.82 \pm 6.73\) | \(-23.84 \pm 3.75\) | <0.0001 |
| A4C lateral Mid         | \(-18.96 \pm 7.57\) | \(-24.48 \pm 4.19\) | <0.0001 |
| RCA      |                          |                          |             |
| A3C posterior Basal     | \(-17.63 \pm 6.74\) | \(-23.85 \pm 3.76\) | <0.0001 |
| A3C posterior Mid       | \(-18.97 \pm 7.58\) | \(-24.49 \pm 4.11\) | <0.0001 |
| A4C septal Basal        | \(-17.63 \pm 6.73\) | \(-23.84 \pm 3.75\) | <0.0001 |
| A4C septal Mid          | \(-18.96 \pm 7.57\) | \(-24.48 \pm 4.19\) | <0.0001 |

A2C = apical 2-chamber; A3C = apical 3-chamber; A4C = apical 4-chamber; FH = familial hypercholesterolemia; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery

Data are presented as mean \( \pm \) SD. \( P<0.05 \) was considered statistically significant.
0.901 (P<0.001; 95% CI, 0.653–0.974) for LS, 0.953 (P<0.001; 95% CI, 0.868–0.983) for CS, and 0.821 (P<0.001; 95% CI, 0.559–0.930) for RS. Analysis of interobserver variability also yielded significant intraclass correlation coefficients: 0.939 (P<0.001; 95% CI, 0.857–0.980) for LS, 0.844 (P<0.001; 95% CI, 0.508–0.956) for CS, and 0.799 (P<0.001; 95% CI, 0.501–0.903) for RS.

**TABLE V. Regional Circumferential Strain in the 3 Main Coronary Artery Territories**

| Variable* | FH Group (n=47) | Control Group (n=37) | P Value |
|-----------|----------------|---------------------|---------|
| **LAD**   |                |                     |         |
| MV level  |                |                     |         |
| Anteroseptal | −27.11 ± 8.22 | −33.53 ± 5.14 | <0.0001 |
| Anterior   | −16.85 ± 5.76 | −22.57 ± 5.58 | <0.0001 |
| PM level  |                |                     |         |
| Anteroseptal | −27.29 ± 7.31 | −33.62 ± 6.13 | 0.001   |
| Anterior   | −20.14 ± 8.75 | −25.46 ± 6.67 | 0.002   |
| AP level  |                |                     |         |
| Anteroseptal | −25.38 ± 6.29 | −31.41 ± 5.52 | 0.002   |
| Anterior   | −24.33 ± 7.54 | −26.55 ± 6.76 | 0.17    |
| Lateral   | −22.87 ± 9.78 | −24.19 ± 8.41 | 0.52    |
| Posterior | −22.92 ± 7.93 | −24.84 ± 8.45 | 0.29    |
| Inferior  | −23.96 ± 7.17 | −26.98 ± 8.39 | 0.08    |
| Septal    | −25.21 ± 8.27 | −34.13 ± 6.14 | <0.0001 |
| **LCx**   |                |                     |         |
| MV level  |                |                     |         |
| Lateral   | −18.25 ± 7.66 | −24.37 ± 7.68 | <0.0001 |
| Posterior | −21.19 ± 8.12 | −26.36 ± 8.23 | 0.002   |
| PM level  |                |                     |         |
| Lateral   | −22.35 ± 8.26 | −26.87 ± 7.58 | 0.009   |
| Posterior | −23.29 ± 8.21 | −26.62 ± 8.53 | 0.06    |
| **RCA**   |                |                     |         |
| MV level  |                |                     |         |
| Inferior  | −16.54 ± 7.95 | −20.66 ± 6.47 | 0.01    |
| Septal    | −27.88 ± 7.19 | −30.11 ± 5.52 | <0.0001 |
| PM level  |                |                     |         |
| Inferior  | −19.13 ± 7.34 | −23.25 ± 5.66 | 0.004   |
| Septal    | −28.78 ± 8.58 | −33.19 ± 6.31 | <0.0001 |

AP = apical; FH = familial hypercholesterolemia; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MV = mitral valve; PM = papillary muscle; RCA = right coronary artery

*Parasternal short-axis view at all levels

Data are presented as mean ± SD. P<0.05 was considered statistically significant.

**Discussion**

Using conventional transthoracic Doppler echocardiography, we observed normal LVEF and mild diastolic dysfunction in patients with FH. Using STE, we were then able to detect subclinical systolic abnormalities. Three key findings support the usefulness of STE in patients with FH. First, global and most segmental...
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Longitudinal and circumferential systolic functions in the LV were significantly reduced in the FH group, whereas global and partial segmental radial functions were preserved. Second, the average strains in the basal, middle, and apical segments of the LAD, LCx, and RCA territories were significantly decreased. Third, there was a significant inverse correlation between LDL-C and both GLS and GCS.

Diastolic Dysfunction

Previous investigators have reported that hyperlipidemia is independently associated with impaired LV diastolic function and that impaired diastolic function diminishes exercise capacity in patients with congestive heart failure and normal systolic LV function. The E/e’ ratio estimated by using tissue Doppler imaging is a noninvasively determined surrogate for LV diastolic function. Left ventricular elastic recoil and diastolic pressure directly affect mitral E-wave velocity and E-DT. In the current study, FH was associated with prolonged E-DT and increased E/e’ ratio, which in turn revealed impaired diastolic function. Such deterioration in LV diastolic function may represent underlying myocardial ischemia resulting from hyperlipidemia or a direct effect of hyperlipidemia on the myocardium.

Systolic Dysfunction

Left ventricular ejection fraction is not considered a sensitive indicator of subclinical systolic dysfunction. However, using STE to assess LV function and to detect subclinical systolic abnormalities in our patients with FH and normal LVEF, we found that global strain and most segmental LS and CS values were significantly decreased, whereas RS was increased. The impaired regional LV systolic function evidenced by these findings suggests that LVEF may not reflect regional depression in contractile function, which can be offset to varying degrees by compensatory hypercontractile segments. The increase we observed in RS may have been related to increased radial wall thickness, which could have helped to maintain LVEF even though long-axis shortening was already markedly impaired.

In our study, we included territorial strain in analyzing regional function. Territorial strain reflects the average peak systolic strain in segments assigned to different coronary distribution areas. Consequently, we found that myocardial function was widely impaired in our FH group and that territorial strain in the basal, middle, and apical segments of the LAD, LCx, and RCA territories were significantly decreased. Third, there was a significant inverse correlation between LDL-C and both GLS and GCS.

Table VII. Average Territorial Strains for the 3 Main Coronary Arteries

| Variable | FH Group (n=47) | Control Group (n=37) | P Value |
|----------|----------------|----------------------|---------|
| LAD      |                |                      |         |
| Basal    | −16.19 (−36.23, 77.89) | −20.32 (−39.78, 68.30) | <0.0001 |
| Mid      | −17.87 (−37.52, 80.22) | −23.56 (−41.07, 76.06) | <0.0001 |
| Apical   | −19.39 (−36.22, 77.25) | −24.31 (−40.74, 64.62) | <0.0001 |
| Average  | −17.15 (−38.12, 72.14) | −22.97 (−40.35, 69.12) |         |
| LCx      |                |                      |         |
| Basal    | −8.98 (−26.98, 80.64)  | −15.84 (−31.71, 81.31) | <0.0001 |
| Mid      | −10.39 (−27.75, 75.55) | −16.82 (−31.49, 81.64) | <0.0001 |
| Average  | −10.41 (−29.41, 75.9)  | −16.13 (−31.44, 81.12) |         |
| RCA      |                |                      |         |
| Basal    | −16.05 (−36.06, 89.91) | −19.80 (−41.36, 71.61) | 0.001   |
| Mid      | −17.96 (−37.1, 76.9)   | −22.38 (−42.61, 84.50) | 0.006   |
| Average  | −17.39 (−36.22, 77.25) | −20.91 (−41.45, 76.63) |         |

FH = familial hypercholesterolemia; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery

Data are presented as median and interquartile range. The upper and lower limits of reference intervals were calculated as percentiles (2.5th and 97.5th). P <0.05 was considered statistically significant.
in which most atherosclerotic plaques in a population of asymptomatic adult patients with FH were located in the proximal and mid segments of the coronary arteries. Another recent case-control study comprising 45 patients with FH and 45 control subjects also had similar results, although that study focused only on pediatric patients with heterozygous FH. In contrast, we included both pediatric and adult patients with homozygous and heterozygous FH. This ensured that our study’s findings would add to the current literature and help confirm the diagnostic value of STE in assessing myocardial function.

Regional myocardial dysfunction with FH is likely multifactorial and related in part to cumulative exposure to various atherosclerotic and nonatherosclerotic risk factors, leading to diverse intermediate disease processes. As LDL-C levels increase, the global longitudinal and circumferential strains decrease. High LDL-C levels are the most characteristic feature of FH and the most important determinant of the disease phenotype. Lowering plasma LDL-C levels is therefore the most important therapeutic target in FH. We hypothesize that the abnormalities we observed in our FH group were an early sign of hypercholesterolemia-induced myocardial dysfunction, in agreement with findings from experimental studies.

The precise mechanism linking cholesterol level to impaired myocardial function cannot be determined from our study results. However, several proposed mechanisms may help explain hypercholesterolemia-induced LV dysfunction: increased cardiac oxidative stress, alteration of myocardial energy metabolism, changes in myosin heavy-chain isoform expression patterns, downregulation and redistribution of connexin-43 expression in myocardium, and impaired activation of myocardial adenosine triphosphate–sensitive potassium channels. These mechanisms may in turn provide the basis for a hypercholesterolemic cardiomyopathy.

**Study Limitations**

This single-center study has several limitations. First, we did not distinguish between homozygous FH and heterozygous FH, and some patients did not undergo genetic testing. Second, because our study participants were Chinese, we did not apply any popular criteria designed for diagnosing FH in Western countries (for example, the Dutch Lipid Clinic Network criteria). Third, none of our study participants had undergone computed tomographic angiography despite its value in understanding mechanisms of cardiac impairment; none had indications of acute coronary syndrome or other obvious cardiovascular diseases. Finally, the study sample size was small and lacked a sufficiently large matched control group. Thus, comparisons between the FH and control groups included no adjustments other than the confounding factors already discussed.
than for sex and age. These limitations need to be addressed in future studies that adjust for different confounding factors, include more subjects, and use more powerful statistical tests.

Conclusion

In this study, STE was useful for detecting subclinical systolic dysfunction in patients with FH. Increased LDL-C in those patients resulted in significantly decreased average strains in the 3 main coronary artery territories, preserved global and partial segmental radial function, and decreased longitudinal and circumferential function.

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