

# Study on the Relationship Between Myocardial Microcirculation Perfusion and Electrocardiogram ST Segment Depression in Patients With Hypertrophic Cardiomyopathy

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## Research

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# Abstract

**Objective:** To investigate the correlation between myocardial microcirculation perfusion status and the ST-segment depression (STD) in patients with hypertrophic cardiomyopathy (HCM)

**Method:** Myocardial microcirculation perfusion of 32 patients with HCM (HCM group) and 28 healthy volunteers (control group) were examined using MCE, and the parameters including peak intensity (PI), area under the curve (AUC), rising slope (RS), and the time to peak (TTP) were analyzed. All subjects were examined by electrocardiogram, and the amplitude of downward movement of ST segment was measured. Then patients were divided into 3 groups according to the degree of downward movement of ST segment: ST1 group ( $0 < ST \leq 0.1$  MV); ST2 group ( $0.1 \text{ MV} < ST \leq 0.2$  MV); ST3 group ( $0.2 < ST \leq 0.3$  MV). At last, the relationship between myocardial microcirculation disorder and the degree of ST segment depression was explored.

**Results:** Patients with HCM exhibit lower PI and AUC than their healthy counterparts ( $P < 0.001$ ). No significant difference was found in RS and TTP between two groups ( $P > 0.05$ ). ST depression was found in all the patients in the HCM group ( $P < 0.001$ ). There was no significant linear correlation between PI and the degree of ST segment depression ( $r = -0.348$ ). Then PI value was compared among ST1, ST2, ST3 and control group. The results showed that the PI value in both ST1 group and ST2 group differs from ST3 group ( $P < 0.01$ ), while there was no significant difference between ST1 and ST2 group ( $P < 0.05$ ).

**Conclusion:** When ST depressed more than 0.20 mV, the STD is related to the decrease of microcirculation perfusion in hypertrophic myocardium.

## Background

STD (ST segment depression, STD) is an indicator of abnormal ventricular repolarization on ECG. It has been well elucidated that the STD is associated with the risk of cardiovascular events<sup>[1-2]</sup>. Peter M. Okin and his colleague demonstrates that the absolute deviation more than 0.05mV of ST-segment in any ECG lead can predict cardiovascular and all-cause mortality<sup>[3]</sup>.

In patients with hypertrophic cardiomyopathy (HCM) without obvious coronary angiographic lesions, ECG can show ST segment depression like myocardial ischemia, and myocardial microvascular perfusion decreased can be found<sup>[4]</sup>. Microvascular dysfunction has been proved to be common in HCM, and worsens with the aggravation of myocardial hypertrophy or fibrosis. Some studies claimed that the decrease of myocardial microcirculation is an independent predictor of deterioration and death in HCM<sup>[5-6]</sup>. Studies have confirmed that<sup>[10]</sup> the early manifestation of HCM will appear abnormal ECG. Although, the importance of ECG examination has been emphasized in the 2014 ESC guidelines for the diagnosis and treatment of HCM, we are unable to evaluate cardiac histology based on ECG results.

Intravenous administration of myocardial contrast agent may also be valuable in defining the microcirculatory integrity and reserve in patients following SEA and its potential role in septal remodeling. In addition, MCE is beneficial in making the diagnosis of HCM, especially in patients who have inadequate transthoracic echo windows or in patients who have uncommon forms of HCM [21].

Previous study have illustrated the changes of ST segment in HCM, or the correlation between MCE and microcirculation perfusion. However, few studies focused on the relationship between ST segment depression (especially in patients with HCM) and microcirculation perfusion. Considering that both STD and MCE could reflect myocardial microcirculation perfusion, in present study, we want to explore if there is any correlation between these two approaches when reflecting HCM.

## Materials And Methods

Patients diagnosed with HCM in the first affiliated Hospital of Xinjiang Medical University from January 2016 to October 2019 were enrolled. The HCM patients underwent ECG, left ventriculography and coronary angiography. Among these patients, 32 without coronary artery stenosis were included in the HCM group (20 males and 12 females). The average age of these patients was  $44.69 \pm 10.63$  years (ranged from 26 to 67 years). Twenty-eight patients, which included 18 males and 10 females, and age ranged from 30 to 72 years, with an average of  $(44.68 \pm 10.31)$  years, with negative ECG, left ventriculography and coronary angiography were selected as control.

Patients with HCM diagnosis were enrolled, and underwent examination by electrocardiogram, cardiac contrast ECG and coronary angiography at the same time. Patients with negative coronary angiography with a hypertrophic thickness of  $(19.00 \pm 3.45)$  mm were included. The degree of downward shift of ST segment is between 0.04mV and 0.3mV, and the degree of T wave flattening or inverted downward shift is between 0.1mV and 1.5mV. 28 in patients with negative ECG, cardiac contrast echocardiography and coronary angiography were selected as the control group. The myocardial thickness was about  $0.00 \pm 0.00$ mm in cm, ST segment and  $0 \pm 0.00$ mV during the T wave.

The inclusion criteria of HCM: All patients should meet the diagnostic criteria of HCM in adults according to the 2014 European College of Cardiology's guidelines for the diagnosis and Management of Hypertrophic Cardiomyopathy<sup>9</sup>; the hypertrophic site involves interventricular septum with a thickness of  $\geq 15$ mm, which is not only caused by abnormal cardiac load but also by myocardial hypertrophy of a class of cardiomyopathy. All patients have signed the informed consent form.

The exclusion criteria of HCM patients were as follows: patients with hypertrophic ventricular wall caused by hypertension, coronary heart disease, valvular disease, congenital heart disease and metabolic disease were excluded by examining the medical history, echocardiography, ECG and physical examination. Patients with obstructive HCM had left ventricular outflow tract pressure gradient of  $\geq 30$  mm Hg at rest. HCM patients who received surgical treatment and other ventricular wall hypertrophies caused by

hypertension, coronary heart disease, valvular disease, congenital heart disease, Myocardial Bridge patient, metabolic disease and so on were excluded.

## **1.2 Instruments and methods.**

### **1.2.1 ECG examination:**

The subjects were placed in supine position, and a routine 12-lead ECG examination was conducted at rest. The paper speed was 25 mm/s, voltage 1 MV = 10 mm. The ECG was read by two clinically experienced attending physicians.

Measuring method:

According to the recommendations of the updated global practice guidelines for remote health and arrhythmia monitoring during and after the HRS/EHRA/APHRS/LAHRS/ACC/AHA pandemic<sup>[12]</sup>, the starting point of the QRS wave or the horizontal line at the beginning of the QRS wave (usually the PR segment) should be considered as the baseline, and the lowest depression amplitude should be selected for measurement.

The results were as follows:

If the ST segment moved downwards when compared to the baseline, and the duration was more than 0.12s, then the degree of ST depression was divided into different groups ST1, ST2 and ST3 according to different cut off values (0.1mV  $\leq$  0.2mV  $\leq$  0.3mV).

(in which  $0 < ST \leq 0.1\text{mv}$  is the ST1 group;  $0.1\text{mv} < ST \leq 0.2\text{mv}$  is the ST2 group; and  $0.2\text{mv} < ST \leq 0.3\text{mv}$  is the ST3 group)

### **1.2.2 Instruments and contrast agents.**

The images were analyzed offline using Philips EPIQ7C ultrasonic instrument, with S5mur1 phased array probe and QLab software at a frequency of 3.5mur5.0MHz. Ultrasound contrast agent Sonowei (produced by Boleko, Italy) with SF6 gas of 59 mg, and freeze-dried powder 25 mg was used. Before its use, 5 ml normal saline (0.9%Nacl) was mixed with the agent, followed by shaking hard to form a milky liquid.

### **1.2.3 Contrast-enhanced ultrasound:**

A synchronous ECG was connected to the established venous access. The patient was placed on left lying position, followed by adjusting the machine, optimizing the image, routinely measuring and evaluating the size and function of the heart, and then switching to LVO imaging mode (TIS 0.7 ~ MI 1.4). According to the imaging situation, an intravenous injection of contrast medium after well shaking, a 1mL extract was injected through the left elbow vein. Within 2 minutes of injection, 1 ml saline was used to flush, observe and acquire the image. The dynamic images included apical four-chamber view, apical

two-chamber view, apical three-chamber view, left ventricular long-axis view, mitral valve, papillary muscle and apical horizontal view of the left ventricle for 5 consecutive cardiac cycles. After that, switch to MCE mode (TIS 0.8, flash MI 1.5), the 1mL extract was quickly injected through the left elbow vein, then rinsed with 1ml saline, and acquired the images. The flash key was pressed (8 frames, MI = 0.9), in which a high energy pulse was produced to destroy the myocardial contrast microbubbles, and observe the process of myocardial microbubbles filling again. Five consecutive cardiac cycles were recorded before "flash", and 10 consecutive cardiac cycles were recorded after "flash". The process was completed by two experienced doctors and a nurse, and all the retained images were saved and analyzed.

#### **1.2.4 Ultrasonic image analysis.**

The stored images were transferred to a QLAB workstation, started the analysis software, and placed the region of interest of size and shape (5 mm × 5 mm) in the centre of the hypertrophic myocardium, avoiding the hyperechoic area as far as possible (considering the abnormally high value of variant or compensatory hyperplastic vessels that affects the results of the analysis). Proofread the position of the interesting region frame by frame, delete the frame with excessive displacement, ensure that it is located in the hypertrophic part and dynamically track each region of interest in the whole image analysis, and select all images of 10 cardiac cycles after flickering to establish the time-intensity curve. Similar method was used in the control group to select the central region of the interventricular septum. Finally, the ultrasonic perfusion parameters including the peak intensity (PI), area under the curve (AUC), rising slope (RS), and time to peak (TTP) were analyzed. PI is the maximum value of the curve, which indicated the maximum volume of the blood and the area under the curve (AUC). This meant that the blood in the selected unit time showed positive correlation with the total blood volume. PI and AUC are related to blood volume. The RS represents the rising slope of the fitting curve, and the time to peak (TTP) represents the time it takes for the curve to reach the highest point. Measurement of electrocardiogram and ultrasonic perfusion parameters in hypertrophy group and control group (figure 1).

#### **1.3 Statistical methods.**

SPSS 19.0 software was used to analyze the data. The measurement data were expressed as means±standard deviation. The data in accordance with normality and homogeneity of variance were compared by t-test, and the data that was not in accordance with normality and homogeneity of variance were compared by rank sum-test. The counting data were compared by  $\chi^2$  test, and comparison among the three groups was done by single-factor analysis of variance and LSD method was used for pairwise comparison. Pearson correlation analysis was used to analyze the correlation. The test standard  $\alpha = 0.05$  ( $P < 0.05$ ) was considered to be statistically significant. Bland-Altman plots were used to analyze the repeatability of ultrasound perfusion parameters measured twice by different observers. By observing the intra-group correlation coefficient (intraclass correlation coefficient, ICC), the ICC >0.75 represents good repeatability, the 0.4 < ICC < 0.75 represents good repeatability, and the ICC < 0.4 represents poor repeatability.

# Results

## 2.1 Clinical characteristic

As shown in Table 1, no significant differences in age, height, weight, heart rate, systolic blood pressure and diastolic blood pressure were observed between two groups.

## 2.2 Comparison of observation indexes between HCM group and control group.

As presented in Table 2. HCM patients exhibit thicker ventricular wall than control (□□□□vs□□□□  $P < 0.001$ ). Moreover, the ST segment of HCM patients was significantly reduced ( $P < 0.001$ ), (Table 2).

The myocardial perfusion analysis was performed to calculate myocardial perfusion parameters in control group and HCM group. As shown in Table 4, the PI value of HCM patients was significantly lower than that of control group ( $t = 12.53, p < 0.001$ ). In addition, HCM group presents lower AUC compared to control group ( $t = 11.134, p < 0.001$ ). No significant difference in RS and TTP was found between two groups (Table 2).

## 2.3 Correlation between ST segment depression and PI.

The correlation between PI and ST segment depression was analyzed, and the results showed a correlation coefficient of  $r = -0.348$ , indicates a weak correlation between PI and ST depression (figure 2).

## 2.4 Relationship between the degree of STD and the MCE parameters.

To explore the relationship between the degree of STD and myocardial microcirculation disturbances. Firstly, HCM patients were divided into 3 subgroups according to the degree of STD, and then the PI value was compared among these three groups and control group. As shown in Table 3, Table 4 and figure 3, our results showed that PI of all 3 subgroups were significantly differs form control group (mean difference was 9.887, 10.647, 15.085,  $P = 0.000$ ). Moreover, significant differences of PI were also observed between ST1 and ST3, ST2 and ST3 groups (mean difference was 5.198, 4.438, 0.01, 0.023). There was no statistical difference between ST1 and ST2 groups (with a mean differences of 0.760 and 0.622).

## 2.5 Repeatability test

The Bland-Altman plots were used to analyze the repeatability of PI and AUC. The perfusion parameters recorded in 32 HCM patients (HCM group) and 28 controls were compared with those of another ultrasound doctor who received similar training (using double blind principle and same image reading method). The data obtained from the same batch of images was analyzed, repeatability test was performed, and the Bland-Altman diagram was drawn as shown in Fig. 4. For PI, the difference between the measurements obtained from the two observers was  $-0.173$  (95% CI  $-0.7483$ - $0.4016$ ), coefficient of variation was 5.5365, and the ICC between different observers was 0.952, showing no statistically significant differences between the two measurements after statistical test ( $t = 0.133, P = 0.894$ ). For

AUC, the average difference between the measurement results of the two observers were 0.787 (95% CI -0.2692-1.8432), the coefficient of variation was 1.558, and the ICC between different observers was 0.99, showing no statistically significant differences between the two measurements after statistical tests ( $t = -0.059$ ,  $P = 0.953$ ). So, these results suggest that the repeatability of PI and AUC remained good. (□□□□□□□□□□ □□)

## Discussion

### 3.1 Changes of STD in electrocardiogram of patients with HCM.

Our study found that there were varying degrees of STD in the HCM group, which was consistent with the results of previous studies [13-15]. When the endocardium was damaged, the ST vector deviates from the epicardial surface and points to the endocardium, which makes the ST segment of the lead on the epicardial ECG move downward. Besides, the hypertrophic myocardial fibers are abnormally thick and disordered, which prolongs the activation time of the left ventricular wall. Because the excitement does not reach the epicardium, the endocardium has begun to repolarization, affecting the change of repolarization, resulting in secondary changes of ST-T [16].

### 3.2 Evaluation of microcirculatory perfusion characteristics of HCM by MCE.

Our study showed that the microcirculatory perfusion of hypertrophic myocardium was significantly decreased in HCM, which was manifested by decreased PI and AUC. Previous study revealed that PI and AUC are related to blood volume and abnormal intimal hyperplasia in hypertrophic myocardium of HCM [17]. Therefore, it leads to the decrease of myocardial microcirculation perfusion in different degrees in patients with HCM, which is consistent with other literature reports.

### 3.3 Relationship between microcirculation perfusion and STD in patients with HCM.

Although the value of PI in patients with HCM was decreased, there was no significant linear correlation between PI and the degree of STD. In order to further analyze the relationship between myocardial perfusion and STD, the changes of STD were divided into three different groups according to the degree. Our results indicate that was related to the decrease of myocardial microcirculation perfusion in hypertrophic myocardium when the depression of ST segment was greater than 0.20mV. It has been established that the more sever the ventricular hypertrophy is, the STD may became more obvious, and the activation time of left ventricular wall is prolonged and the degree of ST downward shift is more obvious, the correlation with the decrease of microcirculation is more obvious [20].

### 3.4 Conclusion.

To sum up, When the degree of downward shift of ST segment is greater than 0.20mV, it is related to the decrease of myocardial microcirculatory perfusion in HCM group.

This paper is just a preliminary study on the correlation between microcirculation perfusion and STD of HCM patients, with larger sample and longer follow-up needed to further demonstrate more abundant conclusions.

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## Tables

Table 1  
Comparison of general clinical data between HCM group and control group

Observation index	HCM group(n = 32)	control group(n = 28)	t value	P value
Age (years)	47.2 ± 10.8	46.3 ± 12.3	0.241	0.811
Height (cm)	169.9 ± 8.3	169.7 ± 7.2	0.044	0.966
Weight (kg)	75.4 ± 11.7	73.0 ± 9.3	0.638	0.528
Heart rate (beats / min)	71.7 ± 5.3	70.0 ± 5.8	0.087	0.931
Systolic blood pressure (mmHg)	117.9 ± 6.9	115.1 ± 7.2	0.776	0.443
Diastolic pressure (mmHg)	74.8 ± 5.8	72.2 ± 4.3	1.389	0.174

Table 2  
Comparison of observation indexes between HCM group and control group

Observation indicator (unit)	HCM group	control group	t value	P value
Myocardial thickness (mm)	19.00 ± 3.45	9.29 ± 0.76	14.595	<0.001
STD(mV)	0.16 ± 0.08	0 ± 0.00	10.40	<0.001
PI(dB)	34.16 ± 3.3	22.96 ± 4.63	10.606	<0.001
AUC(dB·s)	226.64 ± 21.01	153.99 ± 22.21	12.958	<0.001
RS(dB/s)	15.94 ± 15.91	11.39 ± 11.04	1.303	0.145
TTP(s)	1.92 ± 2.44	1.85 ± 2.33	0.110	0.973

Table 3  
comparison of ultrasonic parameters PI among four groups

Group	n	Mean	Standard deviation	95% CI		F	P
				Lower limit	Upper limit		
control group	28	34.16	3.341	32.86	35.45	43.668	0.001
ST1	12	24.27	5.171	20.98	27.56		
ST2	14	23.51	4.046	21.17	25.85		
ST3	6	19.07	2.864	16.07	22.08		

Table 4

Results of multiple comparison of PI of ultrasonic parameters in four groups

	<b>Control group and ST1 group</b>	<b>Control group and ST2 group</b>	<b>Control group and ST3group</b>	<b>ST1 group and ST3 group</b>	<b>ST2 group and ST3 group</b>	<b>ST1 group and ST2 group</b>
Mean difference	9.887	10.647	15.085	5.198	4.438	0.760
P	0.000	0.000	0.000	0.010	0.023	0.622

## Figures

Figures 1-4 are not available with this version.