EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH FIRST ONSET GRAVES DISEASE BY THREE-DIMENSIONAL SPECKLE TRACKING IMAGING

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ABSTRACT

Introduction: *To evaluate the left ventricular function in patients with first onset Graves Disease by three-dimensional speckle tracking Imaging.*

Materials and methods: *A total of 62 untreated Graves' disease patients confirmed in our hospital were selected, including 34 cases in the hyperthyroidism group, 28 cases in the hyperthyroidism heart disease group and 31 cases in the normal control group. The pyramidal three-dimensional model of the left ventricle was obtained by four-chamber apical section. The images were stored and the data were analyzed on the EchoPAC workstation. The overall longitudinal radial and circumferential peak systolic strain (GLS, GRS, GCS) of the left ventricle was measured by three-dimensional speck tracing technique, and the differences among the three groups were compared.*

Results: *Compared with the control group, GLS, GRS and GCS in the hyperthyroidism group and the hyperthyroidism heart disease group were decreased, with statistical significance (P<0.05). Compared with the hyperthyroidism group, the GLS of patients in the hyperthyroidism heart disease group was decreased, and the difference was statistically significant (P<0.05), while there was no significant difference in GRS and GCS between the two groups (P>0.05). ROC curve analysis showed that GLS has a certain predictive value for hyperthyroidism and hyperthyroidism heart disease.*

Conclusion: *When the overall systolic function of the left ventricle was still at the normal level in patients with Graves' disease, the overall deformation capacity of the longitudinal myocardium of the left ventricle began to decline earlier than that of the radial and circumferential myocardium.*

Keywords: *Three dimensional speckle tracking technique, graves disease, left ventricular function.*

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Introduction

Graves' disease, first reported by parry in 1825(1), is a common clinical organ specific autoimmune disease, also known as toxic diffuse goiter. Its clinical manifestations are not limited to thyroid, but a multi system syndrome. Hyperthyroid heart disease refers to a series of heart diseases caused by excessive thyroxine during hyperthyroidism, such as arrhythmia, atrioventricular enlargement, cardiac insufficiency and so on. Hyperthyroid heart disease is a common cause of death in Graves' disease, and its early changes in cardiac structure and function are reversible, so early diagnosis of abnormal cardiac function in patients with Graves' disease is particularly important(2). In recent years, tissue Doppler imaging(3-5) and two-dimensional speckle tracking imaging(6-8) have been widely used internationally to evaluate left ventricular function, but due to its technical limitations, it can not accurately reflect the complex three-dimensional spatial motion of the left ventricle. While three-dimensional speckle tracking imaging (3D-STI) tracks the movement of myocardial spots in three-dimensional space and synchronously measures the myocardial strain in all directions of the left ventricle. There is no "out of plane" situation where the movement of myocardial spots cannot be tracked, so it can more accurately evaluate the overall and local function of the left ventricular myocardium. The purpose of this study was to evaluate left ventricular systolic function in patients with primary Graves' disease using three-dimensional speckle tracking imaging.

Materials and methods

Study objects

A total of 62 untreated Graves' disease patients diagnosed at Harrison international peace hospital from June 2016 to March 2018 were selected, including 19 males and 43 females; The age ranged from 21 to 57 years, with an average of (32.50±7.19) years. According to the diagnostic criteria of Graves' disease and hyperthyroid heart disease, 34 cases were divided into simple hyperthyroidism group (group A) and 28 cases were divided into hyperthyroid heart disease group (group B). The diagnosis of Graves' disease is based on the guidelines for the management of Graves' disease related hyperthyroidism formulated by the European Thyroid Association (ETA)[9, 10]. The specific diagnostic criteria are: the patient has the clinical symptoms and signs of hyperthyroidism, which may be accompanied by exophthalmos, infiltrative ophthalmia, anterior cervical myxedema, etc. in most cases, thyroid palpation and B-ultrasound examination show diffuse goiter of the thyroid gland. The laboratory examination results show that the level of thyroid hormone increases, the level of thyroid stimulating hormone decreases, and may be accompanied by positive thyroid stimulating hormone receptor antibody and thyroid stimulating antibody. The diagnosis of hyperthyroid heart disease is based on the diagnostic criteria formulated by the New York Heart Association (NYHA)[11].

Inclusion criteria:

• The specific diagnostic criteria are: on the basis of the diagnosis of hyperthyroidism, there is one or more arrhythmias or cardiac organic diseases at the same time, except for heart diseases caused by other causes. After the regular treatment of hyperthyroidism, the cardiac symptoms disappear or significantly reduce.

Exclusion criteria:

• Multiple nodular toxic goiter, toxic adenoma or hyperthyroidism caused by other reasons;

• Patients with known history of coronary artery disease, myocardial infarction, congestive heart failure, cerebrovascular disease and peripheral vascular disease. The left ventricular ejection fraction (LVEF) of patients with Graves' disease after routine echocardiography was greater than 50%. There were 31 healthy volunteers in the healthy control group, whose age and sex were matched with those in the above two groups. After a series of laboratory tests, diabetes, hypertension, coronary heart disease and other diseases affecting heart function were excluded. All three groups signed informed consent and were approved by the medical ethics committee of our college (batch number 2019-1-025).

Instruments and methods

GE video E9 ultrasonic diagnostic instrument, equipped with m5S probe (frequency: 1.7~3.3MHz) and 4V probe (frequency: 1.7~3.3MHz, frame rate: 25-40 frames/second), is used to collect two-dimensional images and three-dimensional images. Ask the subject to breathe calmly, take the left lying position, and connect the limb lead ECG at the same time. M5S probe was used to measure the left ventricular end-systolic diameter (LVESd) and left ventricular end-diastolic diameter (LVEDd) from the long axis section of the left ventricle near the sternum. Left ventricular ejection fraction (LVEF) was measured by biplane Simpson method.

Switch the probe to 4V, take the apical four-chamber view, adjust the left ventricle to the center of the image, press the "4D" imaging key after the two-dimensional image is clear, and continuously collect the pyramid shaped three-dimensional dynamic model of the left ventricle for three cardiac cycles. When saving the image, ask the patient to hold his breath at the end of exhalation, and copy the collected three-dimensional image to DVD.

Analyze three-dimensional images: copy the dynamic three-dimensional left ventricular images on echopac workstation for data analysis. The program automatically depicts the left ventricular endocardial and epicardial curves, and manually adjust the curves to make them consistent with the left ventricular wall thickness, so as to ensure that the echo spots are in the myocardium. Three dimensional image data can be obtained: left ventricular global longitudinal peak strain (GLS) The global circumferential systolic peak strain (GCS) of the left ventricle and the global radial systolic peak strain (GRS) of the left ventricle. All collected data shall be measured for 3 times and the average value shall be taken. The same experienced ultrasound doctor shall complete the above operation examination.

Statistical analysis

SPSS 19.0 software was used in this study, and the data were expressed as mean ± SD. The general conditions of patients in the healthy control group, group A and group B, as well as the two-dimensional ultrasound parameters and the three-dimensional parameters of GLS, GCS and GRS of the left ventricle were compared by one-way ANOVA. SNK test was used to compare the two groups, and the difference was statistically significant ($P<0.05$). Draw the receiver operating characteristic curve of three-dimensional strain parameters, namely ROC curve, and determine the ROC curve area and the best cut-off point of three-dimensional strain parameters to evaluate the sensitivity and specificity of left ventricular systolic function.

Results

Comparison of the results of routine echocardiography in three groups of patients

As shown in Table 1-3, compared with the control group, heart rate, thyrotropin receptor antibody (TRAb), free triiodothyronine (FT3), free tetraiodothyronine (FT4) in group A and group B increased significantly ($P<0.01$), while serum thyrotropin (TSH) decreased significantly ($P<0.01$). Compared with group A, there was no significant difference in the values of TSH, FT3 and FT4 in group B ($P>0.05$). Compared with the healthy control group, there was no significant difference in LVEF, LVESD and LVEDd between group A and group B ($P>0.05$). Compared with the control group, the values of fasting blood glucose, body mass index (BMI), blood creatinine, systolic blood pressure, diastolic blood pressure, triglyceride, total cholesterol, alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase in group A and group B had no statistical difference ($P>0.05$).

Group	HR (bpm)	LVEDd (mm)	LVESd (mm)	LVEF (%)	FT3 (pmol/L)	FT4 (pmol/L)	TSH (uIU/ml)
Control group (31)	67.19± 6.17#	46.21± 1.82	26.79± 1.56	59.17± 4.97	4.34± 0.76	11.11± 2.64	2.31± 0.96
Group A (34)	73.22± 7.32#	47.00± 1.68	25.24± 1.97	58.89± 5.21	19.42± 4.71*	47.09± 6.42*	0.18± 0.07*
Group B (28)	119.51± 12.45*	47.32± 1.92	26.12± 2.11	57.25± 4.86	20.53± 5.48*	45.97± 7.27*	0.16± 0.06*

Table 1: Comparison of echocardiographic parameters in each group ($\bar{x}$±s).
*Note: Compared with the control group, *P<0.05; Compared with group B, #P<0.05.*

Group	TRAb (IU/L)	Fasting blood sugar (mmol/L)	BMI (kg/m²)	Creatinine (umol/L)	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Control group (31)	0.89± 0.21	6.46± 1.23	22.65± 1.74	55.14± 10.87	112.67± 10.25	77.94± 7.23
Group A (34)	0.02± 0.02*	6.57± 1.39	22.71± 1.89	56.21± 11.76	110.96± 9.45	76.52± 6.91
Group B (28)	0.02± 0.01*	6.61± 1.42	22.59± 1.67	54.87± 10.28	111.32± 9.98	76.73± 6.47

Table 2: Comparison of general data in each group ($\bar{x}$±s).
*Note: Compared with the control group, *P<0.05; Compared with group B, #P<0.05.*

Group	Triglyceride (mmol/L)	Total cholesterol (mmol/L)	Glutamic pyruvic transferase (U/L)	Cereal grass transferase (U/L)	Alkaline phosphatase (U/L)
Control group (31)	1.24±0.49	4.11±1.02	26.15±7.97	21.56±6.76	72.69±19.97
Group A (34)	1.31±0.55	4.15±0.96	27.21±8.35	19.42±6.32	73.34±20.09
Group B (28)	1.29±0.52	4.23±1.08	26.87±8.28	20.53±6.59	73.85±20.32

Table 3: Comparison of general data in each group ($\bar{x}$±s).
*Note: Compared with the control group, *P<0.05; Compared with group B, #P<0.05.*

Comparison of 3D-STI parameters among groups

The comparison of three-dimensional parameters between group A, group B and the control group is shown in Table 4. The left ventricular GLS curves of group A, group B and healthy control group are shown in Figure 1. Compared with the control group, the left ventricular GLS, GCS and GRS values of patients with Graves' disease in the two groups decreased, with statistical difference ($P<0.05$). Compared with group A, GLS in group B decreased with statistical difference ($P<0.05$), and there was no statistical difference between the other two strains (GCS, GRS) in the two groups ($P>0.05$).

Sensitivity and specificity of three-dimensional ultrasound parameters in evaluating left ventricular systolic dysfunction

ROC curve analysis shows that left ventricular GLS has a good differential diagnostic value for simple hyperthyroidism and normal people (AUC=0.713, respectively, $P<0.001$). The best cut-off value of left ventricular GLS is -22.8%, lower than -22.8%, which tends to normal people, on the contrary, it tends to patients with simple hyperthyroidism, and its sensitivity and specificity are 55.9% and 80.6% respectively (Figure 2A).

ROC curve analysis showed that left ventricular GLS had good differential diagnostic value for patients with simple hyperthyroidism and hyperthyroid heart disease (auc=0.917, respectively, $P<0.001$). The best cut-off value of left ventricular

GLS was -18.6%, lower than -18.6%, which tended to patients with simple hyperthyroidism, on the contrary, it tended to patients with hyperthyroid heart disease, and its sensitivity and specificity were 89.3% and 82.4% respectively (Figure 2B).

Group	GLS (%)	GCS (%)	GRS (%)
Control group (31)	-25.25±1.98#	-17.17±2.97#	47.15±9.72#
Group A (34)	-22.37±2.54*#	-14.25±3.12*	40.24±10.06*
Group B (28)	-16.13±1.76*	-14.12±2.64*	40.19±7.15*

Table 4: Comparison of 3D-STI parameters among groups ($\bar{x}\pm s$).
*Note: Compared with the control group, *P<0.05; Compared with group B, #P<0.05.*

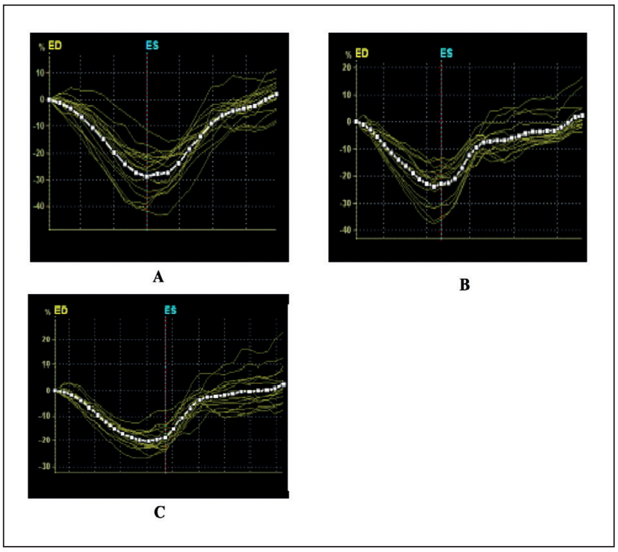

Figure 1: Comparison of 3D-STI parameters among groups.
A. Global longitudinal peak systolic strain curve of the healthy control group; B. Global longitudinal peak systolic strain curve of the left ventricle in the hyperthyroidism group; C. Global longitudinal peak systolic strain curve of the left ventricle in the hyperthyroid heart disease group.

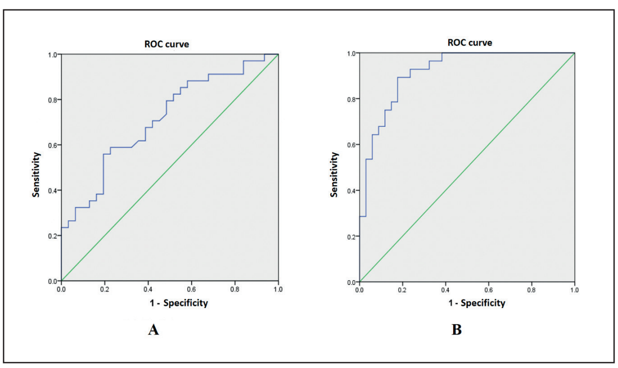

Figure 2: ROC curve of left ventricular GLS.
A. ROC curve of left ventricular GLS with diagnostic value in simple hyperthyroidism and normal subjects; B. ROC curve of left ventricular GLS with diagnostic value for simple hyperthyroidism and hyperthyroid heart disease.

Discussion

Graves' disease can increase the level of thyroid hormone in the blood. The increased thyroid hormone can act on almost all systems of the body, and the cardiovascular system is one of its important target organs[12-14]. Clinically, when Graves' disease patients meet the diagnostic criteria of hyperthyroid heart disease, the heart often has irreversible changes such as malignant arrhythmia, cardiac enlargement and cardiac insufficiency. Therefore, it is particularly important to explore the indicators for early prediction of hyperthyroid heart disease and early clinical intervention. Conventional two-dimensional ultrasound can not reflect the abnormality of cardiac function in patients with primary Graves' disease, while 3D-STI technology is based on two-dimensional speckle tracking imaging combined with real-time three-dimensional echocardiography technology to realize the quantitative evaluation of myocardial function through the tracking of cardiac muscle spots in three-dimensional space, which has high clinical application value[15, 16].

In this study, 3D-STI technology was used to preliminarily analyze left ventricular remodeling in patients with primary Graves' disease. Compared with the control group, GLS, GCS and GRS in groups A and B decreased, indicating that the overall strain capacity of left ventricular myocardium in patients with Graves' disease was lower than normal, and myocardial remodeling and cardiac function were impaired. The reason is that left ventricular remodeling in patients with Graves' disease is related to the effect of large doses of thyroid hormones on cardiomyocytes. The increased thyroid hormone in the blood can directly act on cardiomyocytes, activate renin-angiotensin system and cause the expression of various growth factors, thus promoting the growth of cardiomyocytes, increasing the oxygen consumption of cardiomyocytes, and causing myocardial hypoxia, apoptosis and decreased contractility[17, 18]. In this case, myocardial remodeling occurs to maintain the steady state of the cardiovascular system

In this study, the GLS level in group B was significantly lower than that in group A, and there was no significant difference in the two strain indicators (GCS, GRS) between the other two groups, indicating that patients with Graves' disease were mainly GLS decreased. It is related to the unique anatomical structure of the left ventricle. The left ventricular myocardium is composed of three layers of muscle fibers: longitudinal endocardial layer, annular intermediate layer and oblique epicardial layer. Its anatomical structure determines the complex three-dimensional spatial motion (mainly including longitudinal motion in the long axis direction and radial and circular motion in the short axis direction), rather than simple myocardial shortening. Therefore, when the left ventricular ejection fraction has not decreased, the change of strain value in one direction alone cannot affect the overall systolic function of the left ventricle.

The elevated thyroid hormone in the body makes the heart in a high hemodynamic state through various mechanisms. Under the influence of rapid blood flow, the longitudinal myocardial fibers under the left ventricular endocardium are the most vulnerable, and finally lead to the decrease of myocardial strain in the long axis direction. It shows that patients with Graves' disease are vulnerable to changes in GLS(19). From the results of ROC curve analysis of three-dimensional strain parameters in this study, the sensitivity and specificity of GLS to evaluate the decrease of left ventricular systolic function caused by hyperthyroidism were 55.9 and 80.6%, respectively. The sensitivity and specificity of GLS in evaluating the decrease of left ventricular systolic function caused by hyperthyroid heart disease were 89.3 and 82.4%, respectively. It also shows that the change of GLS in patients with Graves' disease can sensitively reflect the change of left ventricular systolic function, so GLS can be used as an early sensitive indicator of left ventricular myocardial damage. To sum up, when the overall left ventricular systolic function in patients with Graves' disease is still at a normal level, the overall deformation capacity of the left ventricular longitudinal myocardium has begun to decline, and is earlier than the overall deformation capacity of the myocardium in the radial and circumferential directions. Therefore, three-dimensional speckle tracking technology can accurately evaluate the left ventricular function, so as to provide a basis for early clinical intervention.

Limitations:

- 3D-STI technology has high requirements for measurement, and some images need to manually fine tune the region of interest, which can cause a certain measurement error;
- The effect of the duration of disease on cardiac function has not been studied;
- The selected sample size is small, so the sample size can be further increased to observe the overall systolic function of the left ventricle.

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