Early Impairment of Right Ventricular Systolic Function in Patients with Prediabetes and Type 2 Diabetes Mellitus: An Analysis of Two-dimensional Speckle Tracking Echocardiography

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Research Article

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Abstract

Diabetes mellitus is a risk factor for adverse cardiovascular events, and it can raise the risk of heart failure. The right ventricle makes an important contribution to overall cardiac function, and right ventricular(RV) dysfunction will affect the course and outcome of the disease, therefore, early

identification of right ventricular myocardial systolic dysfunction is of great clinical importance. We sought to apply two-dimensional speckle-tracking echocardiography (2D-STE) techniques to determine whether right ventricular global longitudinal strain (RVGLS) and right ventricular free wall strain (RV-FWLS) are altered in patients with prediabetes and diabetes mellitus. This cross-sectional study included 43 patients with prediabetes, 52 patients with type 2 diabetes mellitus (T2DM), and 49 age- and sex-matched healthy volunteers were included as controls. Conventional echocardiography measured tricuspid annular systolic excursion (TAPSE), tricuspid valve systolic velocity (RV-S'), and right ventricular fractional change (RV-FAC), and 2D-STE measured left ventricular longitudinal strain (LVGLS), RVGLS, and RV-FWLS. The results showed that TAPSE was not significantly different between the prediabetes group and the control and diabetic groups and RV-S' velocity was not significantly different among the three groups. RV-FAC showed no statistically significant difference between the prediabetes and diabetic groups, RVGLS were significantly impaired and significantly different in the three groups ($P=0.000$). RVGLS modestly correlated with glycosylated hemoglobin A1c (HbA1c) ($r=-0.576, P=0.000$), and weakly with RVFAC ($r=0.398, P=0.000$), LVGLS ($r=0.416, P=0.000$), sex ($r=-0.205, P=0.014$), BMI ($r=0.195, P=0.019$), heart rate ($r=-0.216, P=0.009$), Triglycerides ($r=-0.198, P=0.025$), interventricular septal thickness ($r=-0.208, P=0.012$), LV end-diastolic diameter ($r=0.210, P=0.012$), septum strain ($r=0.438, P=0.000$). Further regression analysis we found that HbA1c ($B=-0.440, P=.000$), septum strain ($B=0.301, P=0.000$), LV end-diastolic diameter ($B=0.226, P=0.001$), sex ($B=-0.134, P=.043$) were independently associated with RVGLS in the whole study population. RVGLS was the best diagnostic indicator for prediabetes and diabetes (AUC values of 0.689 and 0.731, respectively), and a cut-off value of RVGLS $\leq 18.95\%$ had 85% sensitivity and 61% specificity for the diagnosis of prediabetes and $\leq 17.55\%$ had 82% sensitivity and 58% specificity for the diagnosis of diabetes. Therefore, we believe that abnormally elevated hyperglycemia negatively affects the myocardial function of the right ventricle, The decrease of right ventricular systolic function may be related to left ventricular remodeling and myocardial strain. two-dimensional speckle tracking echocardiography can detect subtle changes in impaired right ventricular systolic function. HbA1c, septum strain, LV end-diastolic diameter, the sex were independent risk factors for RVGLS.

1 Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder that can lead to diabetic cardiomyopathy (DCM)[1]. Diabetes is a risk factor for cardiovascular adverse events, which can increase the risk of heart failure. The risk of new heart failure in patients with diabetes is 2-5 times higher than that in the control group [2], and the risk of young patients is even as high as 4-8 times, diabetes can also increase the risk of death in patients with heart failure by 2-4 times. Studies have found that prediabetes

also causes significant cardiovascular risks, such as left ventricular hypertrophy (LVH), increased carotid intima-media thickness, and reduced coronary reserve flow[3]. For many years, the right ventricle has been considered as a volume channel, but its importance in cardiac hemodynamics has been ignored. Recently, researchers have found that the right ventricle makes an important contribution to the overall cardiac function. Right ventricular dysfunction may affect left ventricular function not only by limiting left ventricular preload but also by affecting the systolic and diastolic interference of the interventricular septum and pericardium[4]. Right ventricular dysfunction will also affect the course and prognosis of the disease[5].

The data on the involvement of the right ventricle in type 2 diabetes is limited. At present, the known mechanisms of left ventricular damage caused by type 2 diabetes will affect the changes of many organs in the whole body, so it may also damage the myocardial function of the right ventricle (RV). Although several animal studies have confirmed right ventricular systolic dysfunction in Zucker diabetic fatty rats[6], overall, the mechanisms of diabetic right ventricular dysfunction are not clear, and experimental data applying pulsed and tissue Doppler to the assessment of diabetic right ventricular function have been inconsistent over the past few years, with some researchers finding reduced right ventricular systolic function [4,6], while others have not find any differences [7,8]. During the last two decades, two-dimensional speckle tracking echocardiography (2DSTE) has been a well-established technique and gradually applied to clinical diagnosis, which uses conventional two-dimensional digital echocardiographic image processing algorithms to identify small and stable myocardial footprints or speckles produced by ultrasound-myocardial tissue interactions within a defined region of interest, track the distance between speckles or their temporal displacement frame by frame during the cardiac cycle and provide non-Doppler information about overall and segmental myocardial deformation[9].

Therefore, this study applied a two-dimensional speckle tracking technique in an attempt to determine (1) whether progressive deterioration with glycemic status is accompanied by changes in right ventricular systolic function. (2) The value of clinical application of RV strain variables in assessing subtle changes in right ventricular systolic function in prediabetic and diabetic patients. (3) To determine the risk factors affecting RV systolic function in diabetic patients.

2 Results

2.1 Baseline clinical characteristic

The age and gender distribution, as well as heart rates, smoking prevalence, and blood pressures, were similar among the three groups (Table 1). TC and serum creatinine levels were not statistically significantly different among the three groups. Body mass index (BMI) and triglyceride increased in the patients with diabetes compared with the controls—however, patients with prediabetes did not differ from the controls group and the patients with diabetes (Table 1). HbA1c gradually increased from the controls group, through patients with prediabetes, to patients with diabetes (Table 1).

2.2 LV Parameters

There was no statistically significant difference in LV diameters and LV ejection fractions among the three groups, whereas interventricular septal thickness was significantly higher than those in the control and prediabetic groups (Table 2). LVGLS gradually decreased from controls, through the patients with prediabetes, to the patients with diabetes (Table 2).

2.3 RV and RA Parameters

RV and RA diameters did not differ among the three groups (Table 2). RVFAC was progressively reduced in the diabetic group compared with the prediabetic and control groups, but was not statistically different in the prediabetic and diabetic groups, Tricuspid annular plane systolic excursion (TAPSE) differed only between the controls and patients with diabetes and RV-S' velocity was not significantly different among the three groups (Table 2).

RVGLS gradually decreased from the controls, through patients with prediabetes, to those with diabetes, RVFW-LS in the controls were higher than in patients with prediabetes and diabetes. There was no difference in RVFW-LS between the prediabetes and diabetic groups. On the other hand, RV LS of the interventricular septum (IVS-LS) differed only between the controls and patients with diabetes (Table 2).

2.4 Correlation and Multivariate Regression Analysis

Among the echocardiographic and clinical parameters, RVGLS modestly correlated with HbA1c ($r=0.576, P=0.000$), and weakly with RVFAC ($r=0.398, P=0.000$), sex ($r=-0.205, P=0.014$), BMI ($r=0.195, P=0.019$), heart rate ($r=0.216, P=0.009$), Triglycerides ($r=0.198, P=0.025$), interventricular septal thickness ($r=0.208, P=0.012$), LV end-diastolic diameter ($r=0.210, P=0.012$), LVGLS ($r=0.416, P=0.000$), septum strain ($r=0.438, P=0.000$). The multivariate regression analysis that included age, sex, BMI, heart rate, HbA1c, Triglycerides, interventricular septal thickness, LV end-diastolic diameter, LVGLS, septum strain demonstrated that HbA1c ($B=0.440, P=.000$), septum strain ($B=0.310, P=0.000$), LV end-diastolic diameter ($B=0.226, P=0.001$), sex ($B=-0.134, P=.043$) were independently associated with RVGLS in the whole study population (Table 3).

RVGLS, conventional RV function indices, and clinical parameters were entered into ROC analysis to evaluate the prediabetes and diabetes mellitus, and $AUC > 0.5$ was considered to have diagnostic value.

The area in the ROC curve of the ultrasound diagnostic index of right ventricular systolic function in prediabetes ranged from 0.689 (RVGLS), 0.671 (RV-FWLS), 0.539 (TAPSE), 0.510 (RV-S') to 0.640 (RVFAC) (Fig. 2, Table 4). A cut-off value of $RVGLS \leq 18.95\%$ had 85% sensitivity and 61% specificity for diagnosis of prediabetes. The area in the ROC curve of the ultrasound diagnostic index of right ventricular systolic function in diabetes ranged from 0.731 (RVGLS), 0.687 (RV-FWLS), 0.623 (TAPSE), 0.574 (RV-S') to 0.575 (RVFAC). A cut-off value of $RVGLS \leq 17.55\%$ had 82% sensitivity and 58% specificity for diagnosis of diabetes mellitus. (Fig. 3, Table 5).

3 Materials And Methods

Study population

This is a cross-sectional study performed between July 1, 2020, and July 31, 2021, including 52 patients with type 2 diabetes, 43 patients with prediabetes, and 49 age- and sex-matched healthy volunteers. All subjects had blood pressure $\leq 140/90$ mm Hg and left ventricular ejection fraction $\geq 50\%$. The diagnosis of prediabetes and diabetes was based on the 2020 guidelines of the American Diabetes Association and the World Health Organization[10]. The groups were as follows: HbA1c $\geq 6.5\%$ for diabetes, 5.7%-6.4% for pre-diabetes, and ≤ 5.7 for the control group. Patients with coronary artery disease, arterial hypertension, Pulmonary artery systolic pressure (PASP) ≥ 40 mmHg, congenital heart disease, cardiomyopathy, serious renal dysfunction defined as glomerular filtration rate ≤ 30 mL/min/1.73m² were excluded in this study. The present study protocol is consistent with the Declaration of Helsinki, and was approved by the local ethics committee (the Second Affiliated Hospital of Nanchang University), All participants signed informed consent.

Conventional echocardiography measurements

Resting conventional 2D transthoracic echocardiography was performed using a GE Vivid E95 (GE Vingmed, Horten, Norway). Measurements of RV systolic function, including TAPSE, RV-S', and RV-FAC were obtained according to consensus guidelines[11,12,13].

RV-FAC represents the RV global contractile function, It correlates well with the RV ejection fraction (RVEF) measured by cardiac magnetic resonance (CMR)[14]. RV-FAC is calculated as $(RV \text{ end-diastolic area} - RV \text{ end systolic area}) / RV \text{ end-diastolic area} \times 100\%$. abnormal values $< 35\%$ indicates decreased right ventricular systolic function.

TAPSE refers to the distance of the maximum systolic displacement of the tricuspid annulus in the lateral wall of the right ventricle, which represents the longitudinal systolic function of the right ventricle. According to the M-shape curve of tricuspid annulus in apical four-chamber view, the displacement distance of tricuspid annulus from end-diastole to end-systole was measured, which was considered abnormal when its value is < 17 mm.

Doppler tissue imaging (DTI) S' wave reflects the global systolic function of the right ventricle. DTI S' was evaluated by using pulsed tissue Doppler mode to measure the velocity of the tricuspid annulus in the lateral wall of RV. When its value was < 9 mm/s, it was considered to be a decrease in RV systolic function.

Two-dimensional strain imaging by speckle tracking

The probe was placed in the apical region and stored apical four-chamber, three-chamber, and two-chamber images for three consecutive cardiac cycles at a controlled frame rate of 50-70 frames per second. Imported the image into the analysis software (EchoPAC110.1.2 version, GE Vingmed Ultrasound AS), select the apical four-chamber section, opened automated functional imaging (AFI), and placed the recording points on the intima of the tricuspid annulus of the free wall of the right ventricle, the apex of the right ventricle and the tricuspid annulus on the side of the interventricular septum. The software

automatically tracked the region of interest after myocardial motion and manually adjusted the region of interest, and the system automatically generated the strain curves and strain values for each segment. The dynamic maps of apical four-chamber, three-chamber, and two-chamber sections of the left ventricle were analyzed in turn by the same method, and the data of each segment could be obtained in accordance with the analysis standard. The STE index obtained by the above method was RVGLS, LVGLS. RVGLS is the average of six segments of the interventricular septum (IVS) and the right ventricular free wall (RVFW), and the longitudinal strain of the right ventricular free wall (RVFW-LS) is the average of three segments of the right ventricular free wall (RVFW)(Fig. 1). Since strain is a measure of the shortening of the myocardium and normal strain is negative, the absolute value of strain is taken in this paper.

Other clinical and laboratory examinations

Data were collected from all subjects—including HbA1c, serum total cholesterol levels (TC), serum triglyceride levels (TG), and serum creatinine. Concentrations for biochemical analysis were measured using conventional methods.

Statistical analysis

Data were analyzed using SPSS version 21 (SPSS, Inc, Chicago, IL). All parameters were tested for normal distribution using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean $\pm$ SD. One-way ANOVA with the Bonferroni post hoc analysis tests was used for group comparisons, and χ^2 was used for categorical variables. Correlations were determined using Pearson's bivariate two-tailed correlation test. Independent variables predicting RVGLS were selected using stepwise multivariate analysis. Receiver operating characteristic (ROC) curves were constructed to determine the best cut-off value of right ventricular longitudinal strain in the diagnosis of right ventricular systolic dysfunction among normal people, prediabetes patients, and diabetic patients. A p-value of <0.05 was considered to be statistically significant.

4 Discussion

The present study has the following findings: (1) regional and Global longitudinal strain of right ventricle decreased in patients with prediabetes and type 2 diabetes with normal left ventricular ejection fraction in comparison with the controls. (2) RVGLS are more sensitive than other conventional echocardiographic variables in detecting subtle changes of right ventricular systolic function in patients with abnormal glucose metabolism, a cut-off value of RVGLS $\leq 18.95\%$ had 85% sensitivity and 61% specificity for the diagnosis of prediabetes and $\leq 17.55\%$ had 82% sensitivity and 58% specificity for the diagnosis of diabetes. (3) The decrease in right ventricular systolic function is associated with a decrease in left ventricular myocardial strain and left ventricular remodeling. (4) HbA1c, septum strain, LV end-diastolic diameter, sex were independent risk factors for RVGLS.

The right ventricular wall is mainly composed of the superficial muscle layer and the deep muscle layer, superficial muscle fibers arranged roughly in a circular pattern and the deep muscle fibers are arranged longitudinally from the base to the apical segment, and 80% of the contractile function of the right ventricle is responsible for the deep muscle fibers. The longitudinal strain of the right ventricle is a good indicator of right ventricular systolic function. Longitudinal strain can be measured by Doppler tissue imaging (DTI) and 2DSTE, but the speckle tracking technique makes the measurement more accurate without some drawbacks of angle dependence and noise interference[15]. Some studies have confirmed that the two-dimensional right ventricular strain is moderately correlated with the RVEF measured by magnetic resonance (Pearson correlation coefficient = 0.54 to 0.86), and the study also confirmed low inter-and intraobserver variability and good feasibility and reproducibility[16,17]. In the past, speckle tracking techniques have often been used to evaluate the regional and global function of the left ventricle, and several studies have now demonstrated the feasibility of speckle tracking techniques in assessing right ventricular systolic function[18]. In particular, right ventricular strain, as an objective indicator of RV systolic function, has been included in the latest echocardiographic guidelines[19]. In this study, the RVGLS and RVFW-LS in the diabetic group were significantly lower than those in the control group, and the triglyceride in the diabetic group was significantly higher than that in the control group. There was a negative correlation between RVGLS and triglyceride in the whole population, which indicated that the abnormal increase of blood glucose and blood lipid levels affected the systolic function of right ventricular myocardium. Several possible mechanisms could be responsible for right ventricular myocardial damage in patients with diabetes. First of all, Hyperglycemia causes reactive oxygen species to increase oxidative stress, which directly damages proteins, DNA and induces apoptosis in cardiac myocytes to cause cardiac dysfunction [20]. Hyperglycemia can also activate DNA repair enzymes and affect glycolytic pathways, thereby inducing cellular damage, such as through protein kinase C activation, as well as increasing levels of advanced glycosylation end products, which can lead to myocardial damage[21]. Hyperglycemia is often accompanied by hyperlipidemia, especially the excessive deposition of triglycerides in cardiomyocytes leads to the production of toxic lipid intermediates, such as diacylglycerol and ceramide, both of which can promote oxidative stress and cardiomyocyte apoptosis[22].

Previous studies have confirmed that LVGLS is significantly reduced in patients with prediabetes and T2DM, and the same conclusion had been drawn in this study. However, was there a relationship between reduced right ventricular strain and left ventricular strain in patients with abnormal glucose metabolism or T2DM? In the present study, RVGLS was found to be associated with septal thickness, LV end-diastolic diameter, LVGLS, and septal strain, and further regression analysis revealed that septal strain and LV end-diastolic diameter were independent risk factors for RVGLS, so the present study concluded that right ventricular myocardial strain was associated with LV remodeling and strain in prediabetic and diabetic patients. Dibble[23] et al also reported an independent correlation between septal function and right ventricular systolic function, This suggests that the decrease of right ventricular systolic function may be related to the left ventricular remodeling and myocardial strain. The reason may be the interweaving of subintimal fibers in the interventricular septum between the right ventricle and the left ventricle[24], as a

result, the process of diffuse fibrosis in cardiomyocytes with abnormal glucose metabolism may affect the function of both ventricles at the same time.

In this study, compared with prediabetes and control group, the RVFAC of diabetic group decreased gradually, but there was no statistical difference between prediabetic group and diabetic group. Tricuspid annular systole (TAPSE) was only different between control group and diabetic group. There was no significant difference in RV-S' velocity among the three groups, but there were significant differences in RVGLS and RV-FWLS among the three groups. The results showed that right ventricular strain parameters could detect subtle changes in right ventricular systolic function in patients with abnormal glucose metabolism with normal ejection fraction, which confirmed the clinical role of speckle tracking technique in detecting subclinical systolic function of right ventricle. When we further evaluated the diagnostic value of various ultrasonic indexes in the diagnosis of right ventricular systolic function by ROC curve, we found that the area under RVGLS and RV-FWLS curve was the largest, which once again verified the advantage of right ventricular strain in the diagnosis of right ventricular systolic function. Although the guidelines and some studies believe that RV-FWLS can be used as a good index for ultrasonic diagnosis of right ventricular systolic function [19,25,26], in this paper, we found that the area under the curve of RVGLS was larger than that of RV-FWLS, and the cutoff values ≤ 18.95 , ≤ 17.55 respectively are more sensitive and specific for the diagnosis of prediabetic and diabetic right ventricular systolic function. The reason may be that the effect of elevated blood glucose on the heart is global and synchronous. Similar conclusions were reached in the MT study[27].

This study also found that HbA1c was independently associated with RVGLS in the whole study population, which was consistent with the results of Tadic Marijana's study[28]. Wong AK et al[29] found that a 1% increase in HbA1c levels was associated with an 8% increase in the risk of heart failure, On the contrary, a 1% decrease in HbA1c levels was associated with a 16% lower risk of heart failure and adverse outcomes. These findings may suggest that controlling glucose levels is important for improving right heart function. This paper also confirms that gender is also an independent risk factor for global right ventricular strain in prediabetes and diabetes and that gender has a significant impact in right ventricular structural and functional risk stratification. In a study by the World Federation of Societies of Echocardiography (WASE) attempting to investigate whether there are differences in RV systolic parameters by age, gender and ethnicity, it was found that stratification by gender showed that compared with males, females had smaller absolute and indexed RV areas, absolute RV dimensions and higher magnitude FAC, RV-FWLS and GLS[30], therefore, the researchers believe that gender is an important factor in determining right ventricular size and systolic function measured by two-dimensional echocardiography.

Limitations

the current investigation has several limitations. First of all, the number of patients in the study sample is relatively small, so it is necessary to do further research on a larger population. Second, there is a lack of a large number of reference values of right ventricular myocardial mechanics in patients with diabetes. In

our research, we used vendor-specific software that was designed for LV strain but not specifically designed for RV strain. Third, there was no comparative study with the gold standard of cardiovascular magnetic resonance imaging (MRI).

5 Conclusion

Our research shows that abnormal hyperglycemia has a wide range of effects on the myocardial function of the left and right ventricles, not only as a decrease in global left ventricular longitudinal strain but also as damage to the right ventricular myocardial function. The impairment of right ventricular function is an integral part of the phenotype of diabetic cardiomyopathy. Glycosylated hemoglobin is an independent risk factor for RVGLS, so glycosylated hemoglobin is an important monitoring index for the treatment and prognosis of diabetes mellitus. Subtle changes of right ventricular systolic function can be detected by two-dimensional speckle tracking echocardiography.

Declarations

Financial support and sponsorship

Nil.

Conflict of interest

The authors have no conflicts of interest to declare.

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Tables

Tables are available in the Supplementary Files Section.

Figures

Figure 1

Caption not included with this version.

Figure 2

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Figure 3

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