

Evaluation of the longitudinal deformation of the left ventricular myocardium in subjects with impaired fasting glucose with and without increased glycated hemoglobin

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ABSTRACT

Objective: Prediabetes comprises a heterogeneous group because of the poor concordance of its definition. The aim of our study was to evaluate the longitudinal deformation of the left ventricular (LV) myocardium at the two opposite ends of the prediabetes spectrum as defined by fasting blood sugar and glycated hemoglobin (HbA1c).

Methods: Eighty consecutive subjects in a cross-sectional single-center study with impaired fasting glucose (IFG) (100–126 mg/dL) and without significant epicardial coronary artery stenosis seen on selective coronary angiography were included in our study and were divided into two groups based on their HbA1c levels (<5.7% and 5.7%–6.4%). The longitudinal deformation of the LV myocardium was compared between the two groups using two-dimensional speckle-tracking echocardiography (2DSTE).

Results: The Student t-test, Mann–Whitney U test, or χ^2 test was used for data analysis, whichever was appropriate. The systolic strain ($-16.1\% \pm 2.0$ vs. $-16.8\% \pm 2.4$; $p=0.214$), systolic strain rate (-1.3 ± 0.2 s $^{-1}$ vs. -1.4 ± 0.2 s $^{-1}$; $p=0.403$), and early and late-diastolic strain rates (1.4 ± 0.3 s $^{-1}$ vs. 1.5 ± 0.3 s $^{-1}$; $p=0.456$ and 0.9 ± 0.1 s $^{-1}$ vs. 1.0 ± 0.2 s $^{-1}$; $p=0.684$, respectively) of the LV myocardium were not statistically different between the IFG subjects with and without increased HbA1c as detected using 2DSTE.

Conclusion: The longitudinal deformation of the LV myocardium as detected using 2DSTE in the subjects without significant epicardial coronary artery stenosis was not statistically significantly different between the IFG subjects with and without increased HbA1c.

Keywords: prediabetes, two-dimensional speckle-tracking echocardiography, left ventricle (*Anatol J Cardiol* 2018; 19: 160-7)

Introduction

Prediabetes is a hyperglycemic state that has been defined by the American Diabetes Association as fasting blood sugar (FBS) >100 mg/dL but <126 mg/dL known as impaired fasting glucose (IFG), blood glucose after 75 mg of oral glucose load between 140 mg/dL and 199 mg/dL, or glycated hemoglobin (HbA1c) between 5.7% and 6.4% (1). It is estimated that approximately one-third of the general population is affected by prediabetes (2). Prediabetes is associated with cardiovascular events (3) and complications such as nephropathy, (4) retinopathy, (5) and neuropathy (6). In addition, there is an increased risk of conversion to diabetes (7). The effects of prediabetes on myocardial function in different cardiac chambers have been shown in some studies (8-10).

According to the definition by the American Diabetes Association, prediabetes encompasses a heterogeneous group owing to the poor concordance of test results that draw upon the definition of this condition (11). With respect to FBS and HbA1c, there are three different groups in the prediabetes spectrum: IFG

with normal HbA1c, IFG with increased HbA1c (5.7%–6.4%), and normal fasting glucose with increased HbA1c (5.7%–6.4%), all of which have different pathophysiologic mechanisms such as hepatic insulin resistance in IFG and hepatic and peripheral insulin resistance in the case of increased HbA1c (12). HbA1c is an index of integrated averaged blood glucose during the preceding 2–3 months, and FBS is a marker of the glucose level at a certain time point (13). Consequently, in the prediabetic spectrum, IFG subjects with normal HbA1c and those with increased HbA1c (5.7%–6.4%) are at the two opposite ends of this spectrum: IFG with and without increased HbA1c. It has been shown that in nondiabetic patients, the incidence of heart failure is increased with a rise in the HbA1c level (14). According to clinical data, among subgroups of prediabetic subjects, the hazard ratio for overall cardiovascular diseases, major ischemic heart diseases, and percutaneous coronary intervention rises only in subjects with increased HbA1c compared with euglycemic subjects (15). Moreover, in nondiabetic subjects, HbA1c is stronger than FBS is correlated to coronary heart diseases (16). From a cardiologist's point of view, it is important to know whether or not left

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ventricular (LV) myocardial deformation is affected by different dysglycemic states in the prediabetes spectrum.

Two-dimensional speckle-tracking echocardiography (2DSTE) is a reliable and feasible method to evaluate myocardial function; it is independent of angle and free of significant noise compared with tissue Doppler imaging (17). Having hypothesized that different glycemic perturbation milieus among prediabetes subjects have different effects on the LV myocardial function, we sought to evaluate the longitudinal deformation of the LV myocardium at the two opposite ends of the prediabetes spectrum (i.e., IFG with and without increased HbA1c) using 2DSTE.

Methods

Study population

Eighty consecutive patients who were admitted to our hospital for selective coronary angiography electively because of positive noninvasive tests or high-risk profiles for the presence of significant coronary artery disease according to their attending physicians' opinions were included in our cross-sectional single-center study from October to November 2016. During this period, a total of 1,273 selective coronary angiographic procedures were performed. Approximately, 421 patients had <50% stenosis in the epicardial coronary artery. In total, 348 patients were excluded from the study and 94 were included. Our inclusion criteria comprised normal sinus rhythm, FBS between 100 mg/dL and 125 mg/dL, normal LV mass (<95 g/m² in women and <115 g/m² in men), and LV ejection fraction >50% as detected using transthoracic echocardiography. The exclusion criteria comprised the presence of >50% stenosis in the epicardial coronary artery; any degree of valvular stenosis; moderate and more than moderate valvular regurgitation; any history of myocardial infarction, myocarditis, cardiac surgery or percutaneous coronary intervention, cardiac pacing, inflammatory diseases, cancer, cardiomyopathies, and pericardial diseases; and poor echocardiographic views.

Venous sampling after 12 h of fasting was done in our hospital laboratory for cell blood count and biochemical analysis during a 1-week period before admission for angiography. The laboratory staff was blinded to our inclusion criteria or echocardiography data. On the morning after coronary angiography, our study subjects were selected through history taking and review of their records. After taking their history, including drug history and systolic and diastolic blood pressures, venous sampling was done to evaluate the patients' HbA1c levels. HbA1c was analyzed using a commercial kit (Roche, Mannheim, Germany) and Cobas Integra 400 plus AutoAnalyzer (Roche). Diabetic patients were excluded from the study if they had history of insulin or antidiabetic agent usage, elevated HbA1c (>6.4%), or FBS >125 mg/dL or if they were known cases of diabetes on diet based on a review of their previous medical documents or any suspicion of the presence of diabetes according to their history, such as reporting increased FBS without presenting laboratory data. In

total, 40 subjects had increased HbA1c levels and the others had normal HbA1c levels. Informed written consent was obtained before venous sampling. The study protocol was approved by our institutional review board.

According to a study by Tadic et al. (8) and considering an equivalent sample size in both groups, a sample size of 33 subjects was required to demonstrate a difference of approximately 1.4% in longitudinal systolic strain with an effect size of 0.9 and a level of significance of 0.05 ($\alpha=0.05$) for a two-way test and a study power of at least 95%.

Standard echocardiography

All the echocardiographic examinations were performed on the morning following admission and before discharge by the same echocardiologist, who was blinded to the laboratory results. These echocardiographic examinations were performed in a commercial setting (EKO 7, Samsung Madison, Seoul, South Korea; 2–4 MHz probe) in the left lateral decubitus position with one-lead ECG monitoring. The LV end-systolic and end-diastolic diameters, LV septal and posterior wall thickness in the parasternal long-axis view, biplane LV volumes at end-systole and end-diastole, and biplane left atrial volumes were measured. The peak flow velocity wave of the mitral valve at early and late diastole (E and A, respectively) and the deceleration time of the E wave were obtained and measured using pulsed-wave tissue Doppler imaging. The myocardial velocities in the septal and lateral mitral annuli in systole (s'), early diastole (e'), and late diastole (a') were obtained using pulsed-wave tissue Doppler imaging, and their peak velocity was measured. The mean of the septal and lateral e' was used to compute the E/e' ratio. These measurements, together with that of the LV mass, were done according to the recommendations of the American Society of Echocardiography (18, 19).

2DSTE

For 2DSTE, three consecutive cardiac cycles were obtained in expiration at a frame rate of 60–80 frames/s and stored in an echocardiography setting for further analysis. At end-systole, automatically determined by software, the endocardial border of LV was traced via the point-and-click method and then the epicardial border of LV was traced by software automatically. The traced endocardial and epicardial borders were subsequently adjusted by the echocardiologist with the virtual borders. After confirmation, it was checked whether the traced borders followed the virtual borders during the cardiac cycle, and if the virtual borders were not followed, the abovementioned stages were repeated. Each wall of LV was automatically divided into three equal parts by the software. The strain curves of LV had one negative systolic peak, and the strain rate curves had one negative peak in systole and one positive peak at early and late diastole (Fig. 1). The values of these peaks were measured for each myocardial part, and their mean was presented as the global systolic strain, global systolic strain rate, global early diastolic

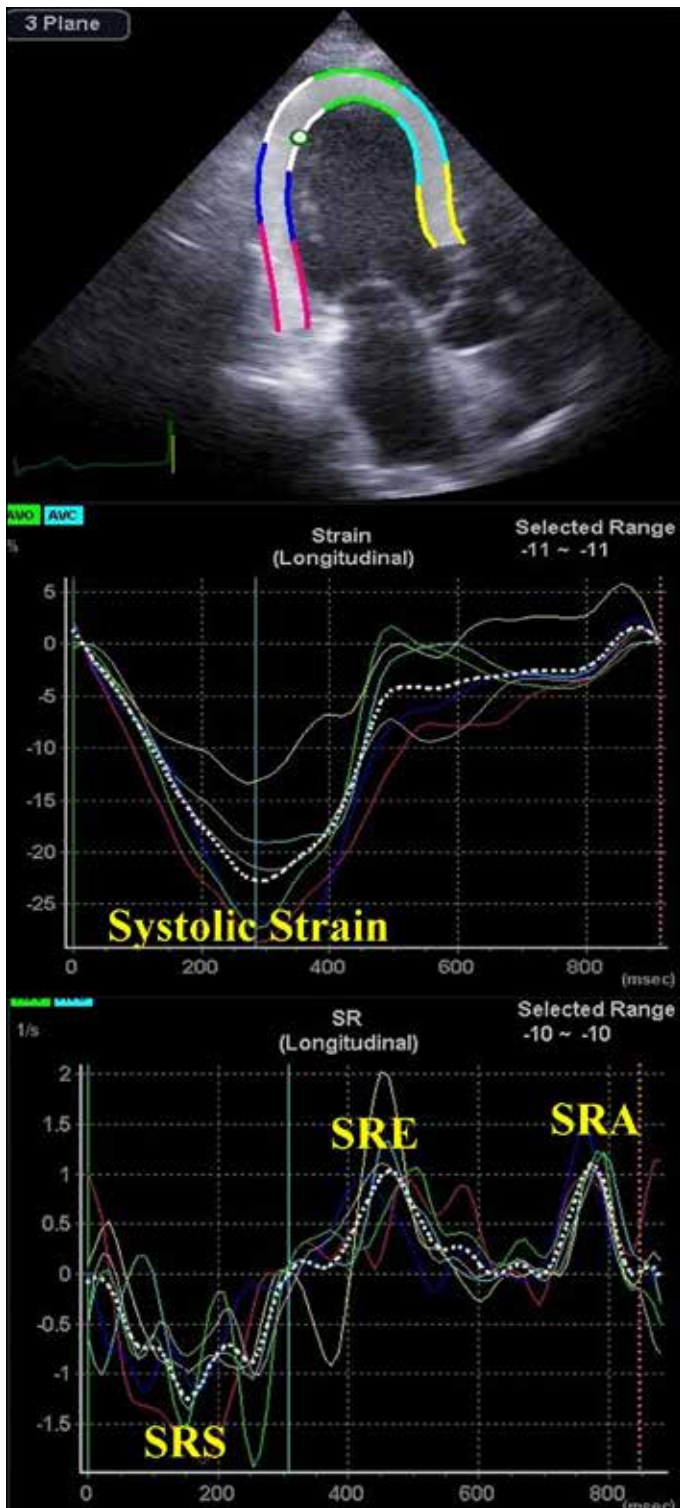


Figure 1. Longitudinal deformation of the left ventricular myocardium in the three-chamber view as evaluated using two-dimensional speckle-tracking echocardiography. (a) Strain curves and (b) strain rate curves

strain rate, and global late-diastolic strain rate. If there were noisy signals after several trials, those myocardial parts were excluded from computation. In addition, the presence of more than three unanalyzable parts was a criterion for the exclusion of

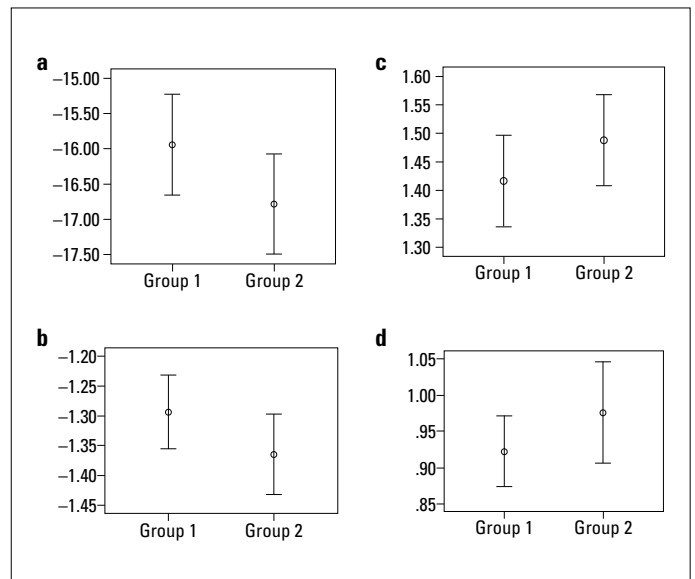


Figure 2. Comparison of the longitudinal deformations of the left ventricular myocardium between the subjects with impaired fasting blood sugar with and without increased glycated hemoglobin (group 1 and group 2, respectively). (a) Systolic strain, (b) systolic strain rate, (c) early diastolic strain rate, and (d) late diastolic strain rate

the patient from the study. In total, nine patients were excluded because of poor echocardiographic views or poor signals and 1,406 (97.6%) myocardial parts were analyzed. Inter- and intraobserver variabilities were independently checked by two echocardiologists. One month after the termination of the study, the images of 12 randomly selected patients were evaluated.

Statistical analysis

The categorical variables were presented as frequencies and percentages and compared using the χ^2 test. The continuous variables were presented as means and standard deviations and compared using the Student t-test, if normally distributed; otherwise, they were presented as medians and interquartile ranges and compared using the Mann-Whitney U test. Multiple variable linear regression models were utilized to explore the correlation between the dysglycemic group and the 2DSTE-derived indices of the LV myocardial deformation adjusted for potential confounders, including age, sex, systolic blood pressure, history of hypertension, beta-blocker usage, body mass index, hemoglobin level, LV mass index, and E/e' ratio. Inter- and intraobserver variabilities were demonstrated as coefficient variations. A P value ≥ 0.05 was considered significant. The data analyses were performed using IBM SPSS statistics for Windows, version 23.0 (IBM Corp, Armonk, NY).

Results

The demographic and laboratory data of the study population are depicted in Table 1. The systolic blood pressure at the time of echocardiography was higher in patients with increased

Table 1. Clinical, demographic, and laboratory data of the impaired fasting glucose subjects with and without increased glycated HbA1c

Variables	Impaired fasting glucose without increased HbA1c (n=40)	Impaired fasting glucose with increased HbA1c (n=40)	P
Age, y	53.7±9.8	56.4±9.0	0.194
Male sex, %	23(58)	16(40)	0.117
BMI, kg/m ²	28.6±4.1	30.1±5.1	0.101
BSA, m ²	1.8±0.2	1.8±0.2	0.526
Obesity, %	14(35)	15(38)	0.816
Overweight, %	19(48)	22(55)	0.502
Hypertension, %	14(35)	21(53)	0.115
Smoking, %	6(15)	9(23)	0.390
ACEI/ARB, %	8(20)	11(28)	0.431
Beta-blockers, %	10(25)	17(43)	0.098
Statins, %	7(18)	10(25)	0.412
Heart rate, bpm	67.7±8.3	66.9±9.3	0.704
SBP, mm Hg	119.7±13.1	126.3±15.6	0.043
DBP, mm Hg	77.6±8.4	79.2±10.6	0.464
FBS, mg/dL	107.2±6.5	108.3±5.9	0.420
Urea, mg/dL	29.3±5.9	29.4±9.1	0.970
Creatinine, mg/dL	0.8±0.2	0.9±0.2	0.584
Hb, g/dL	14.9±1.8	14.2±1.9	0.093
Triglyceride, mg/dL	108.0 (92.5–147.3)	155.5 (85.5–203.3)	0.127
Cholesterol, mg/dL	158.0±36.8	167.3±39.7	0.287
HDL, mg/dL	44.6±12.5	45.3±11.1	0.783
LDL, mg/dL	98.8±30.6	101.5±34.4	0.707
HbA1c, %	5.4±0.2	5.9±0.2	<0.001

The categorical variables were compared using the X² test. The continuous variables were compared using the Student t-test, if normally distributed; otherwise, they were compared using the Mann–Whitney U test

ACEI/ARB-angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker; BMI-body mass index; BSA-body surface area; DBP-diastolic blood pressure; FBS-fasting blood sugar; HbA1c-glycated hemoglobin A1c; Hb- hemoglobin; HDL-high-density lipoprotein; LDL-low-density lipoprotein, SBP- systolic blood pressure

HbA1c (p=0.043); however, it was within the normal limit in the two groups. The proportion of obese and overweight patients in both groups was not statistically different (p=0.816 and p=0.506, respectively), but there was a trend toward an increased body mass index in the patients with increased HbA1c (p=0.101). The standard echocardiography data and tissue Doppler echocardiography data are illustrated in Table 2. The measurements by standard echocardiography and tissue Doppler imaging were not statistically different between the two study groups. The 2DSTE data are demonstrated in Table 3. The 2DSTE-derived longitudinal deformation markers, comprising systolic strain (−16.1%±2.0 vs. −16.8%±2.4; p=0.214), systolic strain rate (−1.3±0.2 s^{−1} vs. −1.4±0.2 s^{−1}; p=0.403), early-diastolic strain rate (1.4±0.3 s^{−1} vs. 1.5±0.3 s^{−1}; p=0.456), and late-diastolic strain rate (0.9±0.1 s^{−1} vs. 1.0±0.2 s^{−1}; p=0.684), were not statistically different between the two study

groups (Fig. 2). The multiple variable linear regression models, drawn to detect the correlation between the dysglycemic group and the 2DSTE-derived indices of the LV longitudinal myocardial deformation adjusted for potential confounders such as the body mass index, were not statistically significant (Table 4). The interobserver variabilities for the systolic strain, systolic strain rate, early diastolic strain rate, and late-diastolic strain rate were 5.8%, 6.1%, 6.6%, and 7.0%, respectively, and the intraobserver variabilities for these variables were 8.2%, 8.9%, 9.1%, and 9.5%, respectively.

Discussion

In this study, we evaluated the longitudinal deformation of the LV myocardium using 2DSTE at the two opposite ends of the

Table 2. Echocardiographic data of the impaired fasting glucose subjects with and without increased glycosylated HbA1c

Variables	Impaired fasting glucose without increased HbA1c (n=40)	Impaired fasting glucose with increased HbA1c (n=40)	P
LVEDV index, mL/m ²	48.8±8.3	49.1±8.5	0.873
LVESV index, mL/m ²	17.3±3.3	18.4±4.6	0.246
LVEF, %	64.3±4.3	62.6±6.7	0.178
LA volume index, mL/m ²	25.8±6.0	25.0±7.1	0.593
Posterior wall thickness, mm	7.9±1.1	8.1±0.8	0.486
Interventricular septal thickness, mm	8.2±0.9	8.4±0.9	0.327
LV mass index, g/m ²	67.8±13.4	73.3±14.2	0.074
E, cm/s	59.8±13.9	64.4±16.3	0.178
A, cm/s	62.7±13.7	63.9±14.6	0.706
E/A ratio	1.0±0.3	1.1±0.4	0.393
Deceleration time, ms	228.4±59.3	216±49.1	0.321
Septal s', cm/s	8.2±1.3	7.8±1.1	0.103
Septal e', cm/s	8.5±1.8	7.9±1.9	0.138
Septal a', cm/s	9.3±2.0	9.4±1.7	0.905
Lateral s', cm/s	9.3±2.3	8.8±2.1	0.338
Lateral e', cm/s	10.4±2.7	10.1±3.3	0.739
Lateral a', cm/s	10.8±2.1	10.2±2.3	0.191
E/e' ratio	6.6±2.0	7.4±2.0	0.085

The continuous variables were compared using the Student t-test

HbA1c-glycosylated hemoglobin A1c; LA-left atrium; LV-left ventricle; LVEDV-left ventricular end-diastolic volume; LVEF-left ventricular ejection fraction; LVESV-left ventricular end-systolic volume; SRA-late diastolic strain rate; SRE-early diastolic strain rate; SRS-systolic strain rate

prediabetes spectrum and found no statistically significant differences between the two groups with respect to the 2DSTE-derived markers of the longitudinal deformation of the LV myocardium. The longitudinal deformation of the LV myocardium in prediabetic patients compared with that in euglycemic patients has been previously studied (8, 20). Nevertheless, to the best of our knowledge, the present study is the first of its kind to compare this deformation between two subgroups of prediabetic patients at the two opposite ends of the prediabetes spectrum: IFG with

and without increased HbA1c. There is a dearth of data in the existing literature on the myocardial function in different subgroups of prediabetic patients. There seems to be only one study in which the researchers compared two subgroups of prediabetic subjects: those with isolated IFG and those with IFG and impaired glucose tolerance test (21). The authors found that the systolic strain, systolic strain rate, and early-diastolic strain rate were not different between the two groups, which are consistent with our findings. It is, however, noteworthy that some of their subjects

Table 3. Two-dimensional speckle-tracking echocardiography-derived indices data of the impaired fasting glucose subjects with and without increased glycosylated HbA1c

Variables	Impaired fasting glucose without increased HbA1c (n=40)	Impaired fasting glucose with increased HbA1c (n=40)	P
Systolic strain, %	-16.1±2.6	-16.8±2.4	0.214
SRS, 1/s	-1.3±0.2	-1.4±0.2	0.403
SRE, 1/s	1.4±0.3	1.5±0.3	0.456
SRA, 1/s	0.9±0.1	1.0±0.2	0.684

The continuous variables were compared using the Student t-test.

HbA1c-glycosylated hemoglobin A1c; SRS-systolic strain rate; SRE-early diastolic strain rate; SRA-late diastolic strain rate

Table 4. Adjusted association between the glycated hemoglobin A1c level group and the two-dimensional speckle-tracking echocardiography derived indices

Variables Group	Systolic strain		SRS		SRE		SRA	
	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>
HbA1c group*	-0.112	0.321	-0.112	0.303	0.129	0.269	0.003	0.997

*adjusted for age, sex, systolic blood pressure, history of hypertension, beta-blocker usage, body mass index, hemoglobin level, left ventricular mass index, and E/e' ratio
 HbA1c-glycated hemoglobin A1c; SRS-systolic strain rate; SRE-early diastolic strain rate; SRA-late diastolic strain rate

with isolated IFG had increased HbA1c (5.2%±0.2%) and some of their subjects with IFG and impaired glucose tolerance tests had normal HbA1c (5.7%±0.5%). One of the merits of our study is that we used HbA1c, which has less variability than the oral glucose tolerance test. In the abovementioned study, the authors evaluated the LV longitudinal deformation by color-coded tissue Doppler imaging, which is confounded by angle dependency and noise, and evaluated only the basal and mid-segments of LV. In contrast, we utilized 2DSTE, an angle-independent and significantly noise-free modality, to evaluate all LV myocardial segments. Another salient difference between our studies is that while that study evaluated epicardial coronary artery stenosis using dobutamine stress echocardiography and exercise test and, thus, did not rule out significant epicardial coronary artery stenosis by the gold standard test, we ruled it out by this gold standard. Furthermore, the authors of that study found that the systolic strain, strain rate, and early-diastolic strain rate were not statistically different between the two groups.

There are several studies wherein the researchers have compared the LV longitudinal deformation between prediabetic and euglycemic subjects. Tadic et al. (8) differentiated prediabetic from euglycemic subjects using HbA1c and found that these groups were different from each other in terms of the 2DSTE-derived longitudinal deformation markers of LV. Despite the similarity between that study and ours in the use of HbA1c for the differentiation between the two groups, our studies differ because FBS was within the prediabetic and euglycemic range and coronary artery disease was not excluded in that study. In a study by Wang et al. (22), the inclusion criteria for prediabetic subjects encompassed all subgroups of prediabetes according to the definition by the American Diabetes Association. The authors excluded coronary artery disease only by history and did not present data on FBS and HbA1c. They found that the longitudinal deformation of the LV myocardium was different between their two study groups. Because the prediabetic subjects in that study comprised different subgroups, it is not possible to compare their results with ours. Akçay et al. (23) evaluated the longitudinal function of LV by pulsed-wave tissue Doppler imaging and found that despite differences between the euglycemic subjects and all the subgroups of prediabetes (defined by FBS and glucose tolerance test), there was no difference between the prediabetes subgroups. There is concordance between the results of the aforementioned study and ours; nonetheless, their

subgroup sample size was very small and they obtained only myocardial velocities in the septal and lateral side of the mitral annuli through a method susceptible to error because of angle dependency compared with 2DSTE, which is relatively angle-independent and evaluates the deformation indices in all possible LV segments. In addition, in that study, HbA1c had no role in the definition of prediabetes subgroups and coronary artery disease was excluded by history.

The American Diabetes Association has defined prediabetes with three different methods: FBS, glucose tolerance test, and HbA1c, resulting in the heterogeneity of prediabetes because of the poor concordance of the test results (approximately 10.4%) (11). There are different pathophysiologic mechanisms leading to prediabetes, and these test results can reflect these dissimilar mechanisms. IFG is usually due to hepatic insulin resistance, increased hepatic glucose production, and impaired first-phase insulin secretion. Impaired glucose tolerance is due to insulin resistance of peripheral tissue, such as muscular tissue, and impaired second-phase insulin secretion. Increased HbA1c is usually secondary to a combination of these abovementioned mechanisms (12, 24, 25). Thus, the site of insulin resistance and its consequences are different in prediabetes subgroups. HbA1c is more repeatable than glucose level measurement, does not require fasting, and is not as time-consuming as the glucose tolerance test; it is, however, more expensive than the other two measurements (26, 27).

In light of the results of the present study, it seems that these different sites of insulin resistance (liver vs. liver and peripheral tissue) constitute the two extremes of insulin resistance in prediabetes and do not exert different effects on the myocardial function as expressed using the 2DSTE-derived longitudinal deformation markers. As a result, there seems to be no significant difference in the myocardial function between the two extreme subgroups of prediabetes: subjects with liver insulin resistance and subjects with liver and peripheral tissue insulin resistance. Further, it may be safe to assume that the heterogeneity in the site of insulin resistance plays no significant role in the induction of myocardial dysfunction as evaluated using 2DSTE.

Most of our study subjects were overweight or obese, and there was a trend toward an increased body mass index in comparison to the subjects with increased HbA1c, which is compatible with the findings of a previous study (28). Insulin resistance, which exists in most overweight or obese individuals, plays a

significant role in prediabetes; therefore, it is reasonable to assume that these conditions can occur concomitantly (29).

Study limitations

The current study is a single-center cross-sectional investigation with a limited sample size. In addition, we had no access to magnetic resonance imaging and three-dimensional echocardiography in the evaluation of our patients, and it was not possible for us to conduct a follow-up of the study population. Moreover, our results cannot be generalized to the general population because we selected subjects that needed selective coronary artery angiography. Another limitation is that we measured FBS and HbA1c only once and did not evaluate our study population for factors such as anemia, which could affect the HbA1c level. Furthermore, the HbA1c level is not independent of the body mass index and it may have affected our results. Nonetheless, it is noteworthy that the American Diabetes Association has not recommended the consideration of the body mass index in the definition of prediabetes. Another limitation is that we were unable to measure the insulin level. Finally, if we had included a euglycemic group in our investigation, our study would be more informative.

Conclusion

Our findings demonstrated that although the absolute values of the 2DSTE-derived indices of the longitudinal deformation of the LV myocardium (i.e., systolic strain, strain rate, and early and late diastolic strain rates) in the subjects without significant epicardial coronary artery stenosis but with IFG and increased HbA1c were less than those in the subjects without significant epicardial coronary artery stenosis with IFG and normal HbA1c, these differences were not statistically significant.

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