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Original Article

Left ventricular diastolic reserve by exercise stress echocardiography in prediabetes

*Abdulameer Jasim Jawad Al-Gburi**

Department of Medicine, College of Medicine, Al-Mustansiriyah University, Baghdad, Iraq

Abstract

Objectives: The objective of this study was to evaluate if the diastolic reserve is different in prediabetes versus control during exercise. **Materials and Methods:** During the resting stage and graded supine bicycling exertion (25 W, 3 min increment), the mitral inflow and septal mitral annular velocities were determined in 50 patients with prediabetes (21 females, mean age 48 ± 16 years) and 50 gender- and age-matched controls. None demonstrated rest or inducible cardiac ischemia on echocardiography. **Results:** Between the two study groups, the velocities of the mitral inflow (E) and septal mitral annulus (E′) at rest are not significantly different. E′ during exercise, on the other hand, was significantly lower in individuals with prediabetes than in controls (8.57 ± 2.46 vs. 9.82 ± 2.42 cm/s at 25 W, $P = 0.012$; 9.42 ± 1.93 vs. 11.15±2.97 cm/s at 50 W, $P = 0.001$). E/E′ behaves oppositely during exercise with a value that is significantly higher in patients with prediabetes. **Conclusion:** The diastolic reserve of the left ventricle, as determined by the change in E′ and E/E′ throughout exercise, is abnormal in individuals with prediabetes who do not have overt cardiac disease. Using exercise stress echocardiography may be helpful for the early recognition of subclinical diastolic dysfunction in prediabetics which may have clinical repercussions in the future.

Keywords: *Diastolic dysfunction, Exercise stress echocardiography, Impaired fasting glucose, Insulin resistance*

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Introduction

Cardiovascular disease, specifically ischemic heart disease, is a significant cause of decreased quality of life and death in individuals with diabetes mellitus [1]. Patients with diabetes are at risk to develop heart failure, have poorer prognosis with heart failure, and may develop cardiomyopathy without other risk factors. The diabetic heart disease spectrum is characterized by a continuum from normal heart function to subclinical dysfunction of the left ventricle (LV), followed by clinical heart failure.

There seems to be a progressive increase in the risk of cardiovascular disease with increasing glucose intolerance levels before the diagnosis of diabetes mellitus [2-5]. Notably, diastolic dysfunction is frequent in prediabetes [6], and the diagnosis of diastolic dysfunction may give a way for identifying at-risk people, which may be a candidate for early and more aggressive intervention to avoid heart failure [7]. Although LV diastolic dysfunction can be clearly diagnosed by traditional testing methods, such as echocardiography, the earliest phase of LV dysfunction may be compensated by numerous mechanisms [8]. Impaired myocardial function in people with prediabetes had been previously investigated in the resting state [6,9].

A physiological and helpful approach to measure ventricular function involves monitoring circulatory changes during exercise. Diastolic reserve is the capability of the LV to enhance diastolic function to keep normal filling pressures during exercise. Similar to the decreased systolic reserve found in concealed LV systolic dysfunction, a reduced diastolic reserve may be detected earlier in diabetic cardiomyopathy. Early diastolic mitral annular velocity (E′) rises with an increasing transmitral pressure gradient in animals without diastolic dysfunction but remains constant in those with diastolic dysfunction, as previously demonstrated in a canine model [10]. Studies in rats [11] and humans [12]

Address for correspondence: Dr. Abdulameer Jasim Jawad Al-Gburi, Department of Medicine, College of Medicine, Al-Mustansiriyah University, Baghdad, Iraq.
E-mail: abdulamerjasim@gmail.com

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have demonstrated comparable findings. No prior research has been conducted on the response of diastolic parameters to exercise in individuals with prediabetes. We expected that the increase of LV relaxation during exercise would be flattened in prediabetics. Thus, the goal of the current research was to investigate the LV diastolic function at rest and diastolic reserve with exercise in participants with prediabetes using Doppler echocardiography.

Materials and Methods

Study participants

During the resting stage and graded supine bicycling exertion (25 Watts, 3 min increments), the velocities of the mitral inflow and septal mitral annulus were determined in a consecutively enrolled 50 patients with prediabetes and 50 gender- and age-matched controls. The study was done in a private specialized cardiac clinic in Baghdad, Iraq, between January 2021 and April 2022. The weight and height of the subjects were determined. The body mass index (BMI) was determined as the weight divided by height squared. Blood pressures were determined in both arms using a calibrated and automated blood pressure instrument (Contec ABPM50, Contec Medical Systems Co., Ltd) with the participant seated. After an overnight fast of 8 h, a venous blood sample was taken. The total cholesterol, triglycerides, and glucose levels in the plasma were determined using conventional enzymatic techniques. Hemoglobin level was measured because it may affect glycated hemoglobin level.

Prediabetes is characterized by fasting blood glucose (FBG) levels from 100 to 125 mg/dL and/or glycated hemoglobin from 5.7% to 6.4% [13]. Prediabetics did not exhibit any evidence of cardiac disease, or chronic kidney disease, were asymptomatic, had a normal resting electrocardiogram in sinus rhythm, and did not use any antidiabetic, antihypertensive, or lipid-lowering drugs. Subjects with hypertension, significant arrhythmia (atrial fibrillation, ventricular and supraventricular arrhythmias, and frequent ectopics), more than mild valvular disease, prior myocardial infarction, significant coronary heart disease, any regional wall motion abnormality, ejection fraction <50%, pericardial disease, and inability to exercise were excluded. Control participants were at low risk of ischemic heart disease, asymptomatic, have normal exercise stress echocardiography, and without hypertension or chronic kidney disease. All processes were carried out in accordance with ethical standards, were approved by the Local Ethics Committee in al-Mustansiriyah University – College of Medicine (REG0701/2021), and adhered to the 1964 Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from all participants in this study.

Diastolic exercise stress echocardiography

With the participant lying supine in the left lateral position, standard two-dimensional measures (LV dimensions, left atrial volume index [LAVI], and interventricular septal thickness) were acquired. The Simpson methodology was used to determine the ejection fraction [14]. The resting stage images from the conventional apical and long-axis and short-axis parasternal views were acquired first. Then, a multiple level supine bicycling exercise test using a variable load bicycle ergometer was undertaken (Ebike, GE Healthcare, Milwaukee, USA) [15]. Subjects pedaled at a steady pace beginning with a 25 W workload and increasing by 25 W every 3 min [16]. Echocardiography was done using a Philips HD11xe ultrasound system equipped with a 2.5 MHz-phased array transducer during rest, exercise stages, and recovery [17]. A 1–2 mm pulsed-wave Doppler sample volume was positioned at the tip of the mitral valve from the apical window, and flow velocities were monitored for five heart cycles. These velocities were tracked to determine the early (E) and late (A) peak filling velocities, as well as the E wave deceleration time (DT). Using continuous-wave Doppler, the jet velocity of the tricuspid regurgitation (TR) was determined to calculate the pulmonary artery systolic pressure. Tissue Doppler mode was used to determine the mitral annular velocity. The filter was tuned to reject signals over a certain frequency, and the Nyquist limit was set to 20 cm/s. Sample volume and gain were kept to a minimum to ensure that the tissue signal was as clear as possible with the least amount of background noise. The mitral annular early diastolic (E′) velocities were determined using a 3 mm sample volume positioned at the mitral annular septal corner from the apical 4-chamber view. Diastolic dysfunction grade at baseline was determined according to the ASE guidelines [17]. These measurements (E and E′ velocities) were made at rest, at each level of exercise, and during recovery in the same order. Each study's data were recorded digitally, and measurements were calculated at the end. Wall motion analysis was performed using digitized images. Abnormal diastolic reserve is defined as the inability to augment mitral annular velocity (E′) proportionally with E velocity with exercise so that E/e′ ratio remains unchanged from resting state to exercise as has been shown previously [12,17,18].

Statistical analysis

The mean and standard deviation of continuous variables were calculated. Categorical variables were expressed as a number and percentage for each group from the total. The Student's *t*-test was used to compare Doppler indices across research groups during rest and exertion stages. Analysis of covariance was used to adjust for covariables. The statistical significance threshold was set at <0.05. All analyses were conducted on Windows using SPSS version 26 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics

The participants were aged between 32 and 68 years with a mean of 48 ± 16 years. Twenty-one (42%) were females. The mean FBG and glycated hemoglobin (HbA1C) for the prediabetes group were 109.7 ± 6.2 mg/dL and 6.05% ± 1.3% versus 84.7 ± 10.3 mg/dL and 5.2% ± 1.5% for the comparison group ($P < 0.05$), respectively. The two groups demonstrated no statistical differences regarding blood pressure readings, BMI, smoking status, and hemoglobin. There was a statistically significant difference in the means of both groups regarding triglycerides ($P = 0.002$), low-density

lipoprotein (LDL) cholesterol ($P < 0.001$), and high-density lipoprotein (HDL) cholesterol ($P = 0.005$) [Table 1].

At rest, there were no significant differences in the dimensions of the LV, LAVI, interventricular wall thickness, or ejection fraction across the groups. Furthermore, no significant differences in tissue Doppler indices (E′ and E/E′), mitral inflow velocities (E, A, E/A, DT), or TR velocity at rest were observed between the two groups [Table 2].

Rest and exercise left ventricular diastolic measures

E′ was comparable between groups during rest (6.96 ± 2.02 vs. 7.4 ± 1.47, $P = 0.222$) and E/E′ was also comparable (10.21 ± 3.88 vs. 8.98 ± 2.92, $P = 0.076$). E′ increased gradually from rest to exercise stages in both groups. However, during exercise, E′ was significantly lower in individuals with prediabetes than in controls (8.57 ± 2.46 vs. 9.42 ± 1.93 cm/s at 25 W, $P = 0.012$; 9.82 ± 2.42 vs. 11.15 ± 2.97 cm/s at 50 W, $P = 0.001$). E/E′ behaves oppositely during exercise with a value that is significantly higher in patients with prediabetes [Table 3]. After adjustment for variables with significant difference at baseline (TG, TC, LDL, and HDL), E/e′ differences between the two groups were as follows: $P = 0.017$ at baseline, $P = 0.413$ at 25 W, and $P < 0.001$ at 50 W.

Table 1: Baseline clinical and laboratory characteristics

	Prediabetes (*n*=50)	Control (*n*=50)	*P*
Age (years)	48±16	48±16	1.000
Sex (female), *n* (%)	21 (42)	21 (42)	1.000
Systolic BP (mmHg)	125.46±8.00	126.22±9.32	0.663
Diastolic BP (mmHg)	79.32±5.38	76.96±6.58	0.052
BMI (kg/m^2)	28.58±4.24	27.08±3.87	0.068
Smoking, *n* (%)	5 (10)	1 (2)	0.094
Hemoglobin (mg/dL)	13.24±0.85	13.27±1.3	0.897
FBG (mg/dL)	109.72±6.27	84.75±10.31	<0.001
HbA_{1c} (%)	6.05±1.32	5.28±1.50	0.007
Total cholesterol (mg/dL)	175.07±42.34	123.19±30.79	<0.001
Triglyceride (mg/dL)	175.42±88.61	132.12±40.99	0.002
LDL (mg/dL)	153.60±29.92	116.46±39.28	<0.001
HDL (mg/dL)	54.68±9.69	59.22±5.68	0.005

BP: Blood pressure, BMI: Body mass index, FBG: Fasting blood glucose, HbA1c: Glycated hemoglobin, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Table 2: Echocardiography findings at baseline

	Prediabetes (*n*=50)	Control (*n*=50)	*P*
LVESD (mm)	31.94±3.24	31.99±4.13	0.947
LVEDD (mm)	47.95±4.66	46.97±5.29	0.327
Ejection fraction (%)	64.31±6.33	65.96±8.45	0.271
IVS (mm)	9.09±1.61	8.86±1.3	0.440
LAVI (mL/m^2)	21.04±4.22	21.34±7.82	0.811
E (m/s)	0.65±0.14	0.62±0.11	0.386
A (m/s)	0.71±0.22	0.65±0.18	0.139
E′ (cm/s)	6.96±2.02	7.40±1.47	0.222
DT (m/s)	191.69±40.47	191.51±32.9	0.981
TR velocity (m/s)	2.33±0.26	2.24±0.32	0.142
E/A	1.01±0.46	1.10±0.40	0.318
E/e′	10.21±3.88	8.98±2.92	0.076
Normal diastolic function, *n* (%)	37 (74.0)	39 (78.0)	0.640
Indeterminate diastolic function, *n* (%)	10 (20.0)	9 (18.0)	0.799
Abnormal diastolic function, *n* (%)	3 (6.0)	2 (4.0)	0.646

A: Peak velocity of the late diastolic filling, E: Peak velocity of early diastolic filling, DT: Deceleration time, LVESD: Left ventricular end-systolic dimension, LVEDD: Left ventricular end-diastolic dimension, IVS: Interventricular septal thickness, LAVI: Left atrial volume index, TR: Tricuspid regurgitation, E′: Early diastolic mitral annular velocity

Discussion

Prediabetes is a term referring to individuals who do not fulfill the criteria for diabetes but have impaired carbohydrate metabolism. A meta-analysis of 20 studies including almost 100,000 patients revealed a curvilinear rise in the cardiovascular risk as glucose intolerance increased [2].

Individuals with asymptomatic LV diastolic dysfunction have poorer exercise capacity compared with those with normal diastolic function indices [19] and are at increased risk for progression to symptomatic heart failure [20-22] and death [23]. The risk of progression is particularly high among individuals with diabetes mellitus. A study of 1760 individuals with diabetes without heart failure found that 36.9% of those with asymptomatic LV diastolic dysfunction developed symptomatic heart failure within 5 years, compared with 16.8% for patients without LV diastolic dysfunction [20].

Diastolic dysfunction has also been observed in prediabetes who do not have any risk factors for heart disease in humans [6,9] and rats [11]. Changes in LV diastolic function had been found to precede the onset of diabetes in another study [24]. It has been proposed that minor cardiac involvement may be caused not only by hyperglycemia but also by insulin resistance, which is the primary component of prediabetes [25]. Participants with prediabetes had greater rates of dyslipidemia across all lipid components when compared to the control group. This is consistent with the independent relationship between LV diastolic dysfunction and dyslipidemia that had been shown previously [26]. Global interest in prediabetes is increasing, particularly given the shortage of research in this region of the world.

The normal ranges of LV parameters in the resting state are broad, frequently overlapping those observed in patients with ventricular dysfunction. This is the rationale for stressing the LV to evaluate its performance. Exercise normally results in a greater relaxation rate because of enhanced sympathetic tone and an exacerbated LV suction action. This will enhance E wave and maintain LV filling volumes in spite of a decreased diastolic filling time without a significant pressure elevation in the left atrium [27]. E′ was shown to be inversely proportional to the isovolumic relaxation time constant (tau [τ]). Enhanced sympathetic drive and subsequent quicker myocardial relaxation may be the major factors underlying the rise in E′ during exercise. In one investigation, E′ remained stable in dogs with diastolic dysfunction despite a higher transmitral gradient, but E′ rose in dogs with normal tau [10]. In humans, a comparable finding has been demonstrated [12]. Although E′ was previously demonstrated to be decreased in individuals with prediabetes at rest, the behavior of E′ and E/E′ to exercise, which may be viewed as a diastolic functional reserve, was not

Table 3: Changes of E′ and E/E′ from rest to exercise

	Prediabetes (*n*=50)	Control (*n*=50)	*P*
E′ (cm/s)			
Baseline	6.96±2.02	7.40±1.47	0.222
25 W	8.57±2.46	9.82±2.42	0.012
50 W	9.42±1.93	11.15±2.97	0.001
E/E′			
Baseline	10.21±3.88	8.98±2.92	0.076
25 W	10.78±2.50	8.42±3.51	<0.001
50 W	11.60±3.05	8.23±3.51	<0.001
E/E′ >8, *n* (%)			
Baseline	32 (64.0)	31 (62.0)	0.836
25 W	42 (84.0)	24 (48.0)	<0.001
50 W	44 (88.0)	28 (56.0)	<0.001
E/E′ ≤8, *n* (%)			
Baseline	18 (36.0)	19 (38.0)	0.836
25 W	8 (16.0)	26 (52.0)	<0.001
50 W	6 (12.0)	22 (44.0)	<0.001

E′: Early diastolic mitral annular velocity, E: Peak velocity of early diastolic filling

investigated. The present study reveals that in individuals with prediabetes, the elevation of E′ during exercise is attenuated and the E/E′ is significantly higher in exercise.

Study limitations

The cross-sectional design of this study ignores the concept of a cause–effect relationship. Furthermore, a bigger sample size is required to validate these findings. In addition, to comply with the WHO recommendations, the oral glucose tolerance test rather than only FBG or HbA1C could be employed to identify individuals with prediabetes. The cause of impaired diastolic reserve in prediabetes may be caused by higher glucose levels alone or may be explained by associated dyslipidemia. Due to the lack of outcome data and the absence of heart failure symptoms in prediabetic patients, the clinical significance of abnormal diastolic reverse in prediabetes remained unclear.

Clinical repercussions

The early diagnosis and management of subclinical LV dysfunction have been proposed as an effective approach for preventing or delaying heart failure. This approach would need an efficient diagnostic strategy. In the newly amended ACC/AHA guidelines [28], no specific guidance addressing how to diagnose subclinical LV dysfunction was published. The new idea of LV diastolic reserve assessment can be utilized to evaluate myocardial function in patients with prediabetes since this population has a high prevalence of subclinical myocardial disease. This may allow for the initiation of therapeutic intervention at an early stage.

Conclusion

The study main and new observation is that LV diastolic reserve, as measured by changes in E′ and E/E′ during exercise, is impaired in individuals with prediabetes who do not have overt cardiac disease. The current study is the first to show impaired LV diastolic reserve during exercise in prediabetic individuals utilizing exercise stress echocardiography.

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Conflicts of interest

There are no conflicts of interest.

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