Role of Exercise Stress Echocardiography in the Detection of Subclinical Diastolic Dysfunction in Asymptomatic Diabetics

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Abstract

Background: **Subclinical left ventricular dysfunction is not uncommon and is a predictor of heart failure. Diabetes commonly presents with exertional dyspnea and reduced exercise tolerance, which is due to diastolic dysfunction. Diastolic exercise echocardiography is a relatively novel modality to detect latent diastolic dysfunction.** ***Aim:*** **We aimed to evaluate the different parameters that affect raised filling pressure during exercise in asymptomatic diabetics using exercise stress echocardiography.** ***Subjects and Methods:*** **This is a case-control study that included 70 persons (35 diabetics and 35 normal volunteers age and sex-matched) who had exertional dyspnea but were asymptomatic at rest. They had a normal systolic and diastolic functions at rest. They did treadmill exercise stress ECG. Post-peak stress images were obtained as quickly as possible after the patient transferred from the treadmill to the imaging table measuring the E/e' ratio.** ***Results:*** **Filling pressure raised dramatically in the diabetic group compared to non-diabetics. Using linear regression analysis, HbA1c as a continuous variable, duration of DM, and waist circumference showed a positive linear significant association with E/e' during exercise.** ***Conclusion:*** **HbA1c level, duration of DM, waist circumference, and eGFR are related to subclinical diastolic dysfunction in asymptomatic diabetics during exercise.**

Keywords: Diastolic dysfunction, Heart failure, Stress echocardiography.

Introduction

Diabetes Mellitus (DM) is a common disease as more than 5% of adults have this disease, with a prevalence of 1% in the youth increasing in older than 60 years to 13%[1]. Diabetes commonly presents with exertional dyspnea and reduced exercise tolerance, which is due to diastolic dysfunction in the vast majority of them[2-4]. Diastolic dysfunction in diabetics usually is not detected early. Diabetics also may be overweight and have trouble losing extra weight. Another factor is that many physicians do not routinely assess levels of physical activity or signs and symptoms of diastolic dysfunction, such as progressive exertional dyspnea or exercise intolerance. That's why more sensitive imaging modalities are required for the early detection of diastolic dysfunction[5]. Subclinical left ventricle diastolic dysfunction (LVDD) is not uncommon[6] and is an important predictor of heart failure[7] and long-term mortality[8]

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Recent heart failure guidelines focus more on the early detection of asymptomatic changes in left ventricle diastolic function by using diastolic stress echocardiography[9].

Subject and Methods

This is a case-control study to evaluate the role of exercise stress echocardiography in the detection of sub-clinical diastolic dysfunction in asymptomatic (no cardiac symptoms) diabetics. We evaluated 70 participants: 35 diabetics with a disease duration of at least 5 years since the time of diagnosis and 35 normal volunteers age and sex-matched (proven by either random or fasting blood sugar + HbA1c levels) who don't have cardiac symptoms. After excluding other confounders by resting echo (structural heart disease, LV dysfunction, or ischemia), ECG (exclude resting ischemia). All of them had a normal systolic and diastolic functions at rest. They did exercise stress ECG using a treadmill. Post-peak stress images were obtained as quickly as possible after the patient transferred from the treadmill to the imaging table measuring the E/e' ratio.

Statistical analysis

The data was collected using Microsoft EXCEL and analysis was performed using Statistical Package for Social Sciences (SPSS) version 23.0. Statistical significance tests will be used and probability value (P value) of less than or equal (0.05) will be considered statistically significant (At 95% level of confidence). Descriptive statistics will be presented as (Means ± Standard Deviation) for quantitative variables and as (Percent) for qualitative variables. Quantitative variables were compared using unpaired t-test between the two groups. Qualitative variables were compared using Chi-Square test/Fisher's exact test. Pearson correlation coefficient was used to find out the association of E/e′ with various parameters.

Personal, clinical and imaging data will be collected and relationship between different factors will be done then the results of management will be represented in tables and graphs.

Ethical Considerations

Written consent was taken from every case sharing in the study. All the steps of the test in fullest possible information were explained to any patient who is considered to take part in this research, presented in terms and a form that they could fully understand. The study was approved by the ethical committee council of Suez Canal University.

Results

The study included 70 participants: 35 diabetics and 35 non-diabetic (proven by blood sugar and HbA1c levels) controls with matched age and gender. All participants have normal LV systolic function (ejection fraction above >55%) and with normal LV geometry including wall thickness and internal LV dimensions. Table 1 showed the baseline characteristics of the study population. It was noted that the waist circumference, BMI, HbA1c, creatinine level and smoking were statistically significantly different between the two studied groups while other variables were similarly distributed between both groups. Out of these 70 subjects; thirty-six (51.1%) were females. Total numbers of smokers were 27 (18.9%). On the other hand, about 53 (75%) subjects were dyslipidemic. More than half of the diabetic group (51%) were smokers (P value 0.024) and more than two third of them (68.6%) were dyslipidemic (P Value 0.132).

Table 1: Baseline characteristics of the study population			
Parameters	**Diabetic (n=35)**	**Non-Diabetic (n=35)**	**Pvalue***
Age (years)	49.4 ± 4.8	50 ± 5.9	0.640
Waist circumference (cm)	109.3 ± 5.6	102.7 ± 6.8	<0.001*
LDL level (mg/dl)	124.8 ± 20.7	127.4 ± 16.0	0.776
BMI (kg/m²)	32.2 ± 2.6	29.3 ± 3.1	<0.001*
HbA1c (%)	8.0 ± 1.3	5.3 ± 0.4	<0.001*
Creatinine Level(mg/dl)	1.2 ± 0.2	0.9 ± 0.1	<0.001*
Male, n (%)	20 (58.8%)	14 (41.2%)	0.116
Smoker, n (%)	18 (51.4%)	9 (25.7%)	0.024*
Dyslipidemic, n (%)	24 (68.6%)	29 (82.9 %)	0.132

LDL: Low Density Lipoprotein, BMI: Body Mass Index, HbA1c: hemoglobin A1C

About 58.8% of the diabetic group were males with a mean age (49 ± 5years) and 58.3% of the control group were female with a mean age (50 ± 6years). Ninety one percent (91.4%) out of 35 diabetic patients had the disease for 5-10 years duration. Mean diabetes disease duration in the study group was (6.43±1.989) years. Table 2 showed that different echocardiographic parameters were statistically significantly different between both groups, both at baseline and at peak exercise (p value <0.05). Although both groups had favorable filling pressure at baseline (7.4 vs 7.1 respectively), it was statistically significant different (p =0.03).

Table 2. Different echocardiographic parameters at baseline and peak exercise between the two studied groups				
		Diabetic Group (n=35) Mean ± SD	**Non-Diabetic Group (n=35) Mean ± SD**	**p- value***
Baseline	**E**	53.4 ± 4.2	57.0 ± 3.6	<0.001
	A	48.6 ± 2.1	50.6 ± 2.7	0.002
	E/A	1.1 ± 0.1	1.0 ± 0.1	0.022
	e '	7.2±0.6	8.1 ±0.7	<0.001
	E / e '	7.41 ± 0.7	7.1 ± 0.1	0.034
Exercise	**E**	64.5 ± 3.7	67.0 ± 3.0	0.003
	e '	5.7 ± 1.5	7.7 ± 1.9	<0.001
	E/ e '	11.9 ± 2.8	9.3 ± 2.7	<0.001

**P value <0.05 is considered statistically significant*
E: Early mitral inflow diastolic velocity by pulsed wave Doppler.
e': average Septal and lateral mitral annulus e wave velocity by tissue Doppler. E/e': : Ratio of early mitral inflow diastolic velocity by PW-derived and average mitral annuli e' velocities by TDI.

Also, filling pressure raised dramatically with exercise to intermediate range in both groups (from 7.4 to 11.9 for diabetics, and from 7.1 to 9.1 for non-diabetics), and the statistical significance was maintained at P=<0.001. Figure 1 showed that there was a statistically significant different between pre and post exercise test in each group. However, there is more rise in the filling pressure in the diabetic group. It shows that within each group, obese patients had higher elevations in filling pressure with exercise. Using linear regression analysis, HbA1c showed a positive linear significant association with raised LV filling pressure during exercise (P<0.001, figure 2A). Similarly, the duration of DM was associated with a positive similar correlation (P<0.001, figure 2B). The relation between BMI and raised filling pressure was not significant (P= 0.07, Figure 2C). However, there was a trend of positive correlation. Also, the waist circumference was associated with a positive similar correlation (P<0.001, figure 2D).

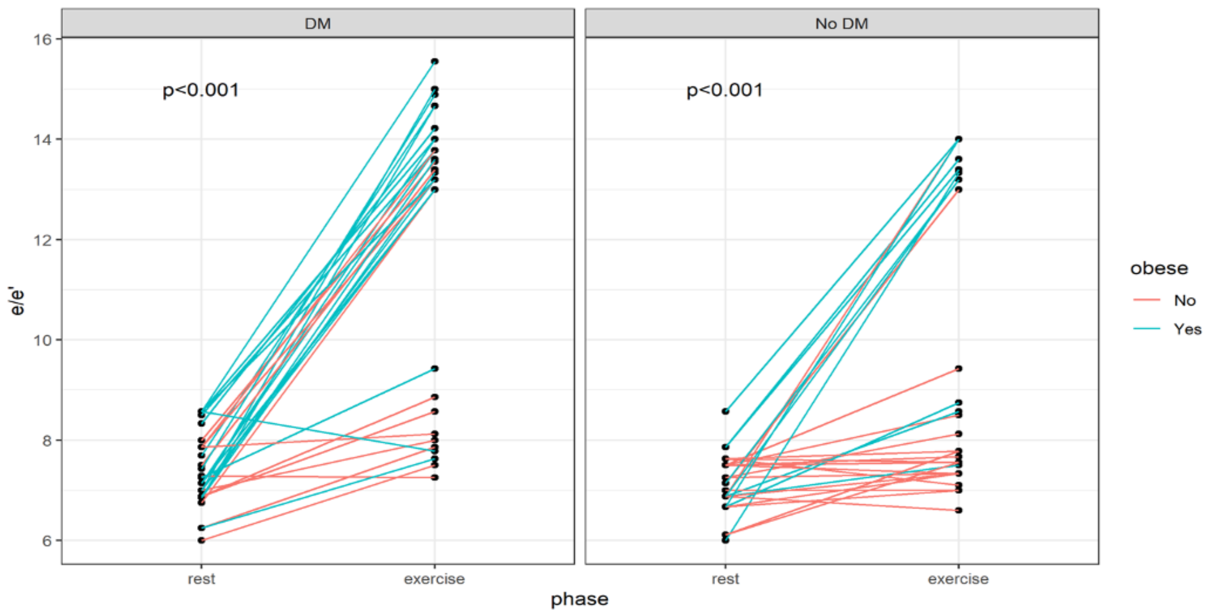

Figure 1. Pre and post exercise E/e' between the diabetic and non-diabetic groups

Discussion

This study provides evidence of the role of exercise echo to detect early diastolic dysfunction in asymptomatic diabetics and determines different predictors affecting sub clinical diastolic dysfunction. This study showed statistically significant positive correlation, between duration of DM and E/e' during exercise in all patients (P < 0.001). A study by kamil Ashour [10] also found a direct relation between diabetes mellitus duration and presence of preclinical diastolic dysfunction with occurrence of significant diastolic dysfunction after more than 5 years from the diabetes onset. This is attributed to hyperglycemia per se which can lead to alteration in substrate supply and utilization by cardiac myocytes that represent the primary injury in the pathogenesis of diastolic function impairment. In a study by Mishra et al.[11], duration of diabetes correlated well with diastolic dysfunction. However, in a study by Raev[12], diastolic dysfunction was present even in patients of 6 months duration of diabetes. This indicates that pre-clinical cardiomyopathy in diabetes has different pathogenesis not related to the duration of DM or glycemic control. This is of great interest and has given rise to many hypothetical mechanisms such as autonomic neuropathy. We found statistically significant positive correlation between the level of HbA1c and raised filling pressure during exercise in all patients (P < 0.001). This is in accordance with the study conducted by kamil Ashour who found that poor glycemic control and HbA1c level were correlated to diastolic dysfunction in diabetics. It was found that each 1% increase in HbA1c level is associated with an 8% increase in the risk of heart failure[13-16], and HbA1c> 8 is associated with diastolic dysfunction[17], but diastolic dysfunction was not reversed by glycemic control but may show some improvement and careful glycemic control may decrease the risk of progression to overt heart failure[18,19].

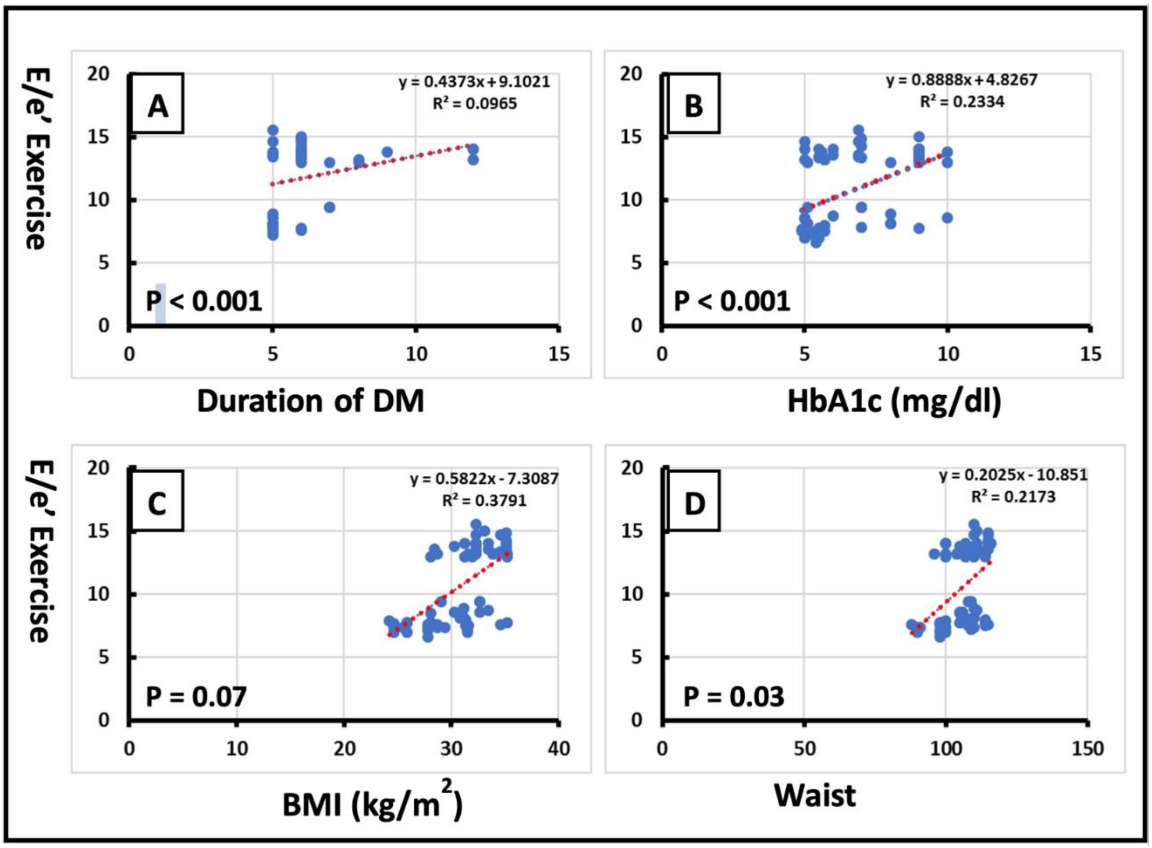

Figure: 2 Correlation between different parameters and exercise filling pressure (E/e') for diabetic group.

We also found that waist circumference was significantly different between patients who had raised filling pressure and those who didn't. Many substances are believed to play a role in this including angiotensin 2, leptin, resistin, and adiponectin, which are secreted by adipocytes and affect myocardium either directly or indirectly, and predispose to LV diastolic dysfunction[20]. Adiponectin deficiency in obesity contributes to myocyte apoptosis, precipitating abnormal relaxation, and can lead to adiposity-related DD[21]. Also, angiotensin 2 and leptin have a fibrotic effect on the intercellular matrix leading to DD[22].

Russo et al.[23] reported that increased BMI was associated with worse LV diastolic function independent of LV mass and other associated risk factors. Also, there is independent association between diastolic function and obesity[24], especially with abdominal obesity[25] and visceral fat mass[26]. Insulin resistance can be one of the important pathophysiological links involved in this association[27,28]. Several studies have suggested that LVDD is one of the earliest signs of myocardial involvement in type 2 diabetes mellitus (T2DM)[29], being a key component of diabetic cardiomyopathy[30].

Study Limitation

The study was a single center study, which may reduce its generalizability. Some confounders in diabetic group may affect generalization of our results (Obesity, BMI, waist circumference, smoking). This is a cross-sectional study, so we did not follow-up of the progression LV diastolic function which may have added important information to congestive diastolic heart failure in theses diabetic patients. Although the correlations were positive and statistically significant; it was weak correlations due to the small sample size.

Conclusion

Exercise echocardiography reliably detects subclinical diastolic dysfunction among asymptomatic diabetics which was more prevalent compared to non-diabetic controls. Also, HbA1c level, duration of DM, and waist circumference are related to subclinical diastolic dysfunction in asymptomatic diabetics during exercise.

Disclaimer: None

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