Original Article

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Internal Medicine Section

Effect of Treadmill Test According to Bruce Protocol Stage 1 on Left Ventricular Diastolic Function in Patients with Exertional Dyspnea and Normal Left Ventricular Function

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ABSTRACT

Introduction: Diastolic dysfunction, detected commonly by echocardiography is the fore-runner of Heart Failure (HF) with preserved Ejection Fraction (HFpEF) in future. Exercise stress by Treadmill Test (TMT) followed by echocardiography can unmask sub-clinical diastolic dysfunction.

Aim: To estimate the proportion of patients with unexplained exertional dyspnea that had sub-clinical diastolic dysfunction and to find out the factors associated with it.

Materials and Methods: This institution-based cross-sectional study, included participants with history of unexplained exertional dyspnea having normal baseline electrocardiogram and echocardiogram (N=106). Patients having serious co-morbidities like azotemia, decompensated liver disease, malignancy and also individuals who did not give consent were excluded. Included individuals were subjected to exercise stress by TMT Bruce protocol stage 1. Postexercise echocardiography was done to find out proportion of patients showing diastolic dysfunction in postexercise echocardiogram. Factors associated with unmasking of sub-clinical diastolic dysfunction were assessed by logistic regression analysis.

Results: Postexercise echocardiography revealed diastolic dysfunction in 33 individuals (31.13%). On multivariate analysis, diabetes and hypothyroidism were significant predictors of exercise-induced diastolic dysfunction. The appearance of diastolic dysfunction was due to changes in mitral inflow E/A ratio and pulmonary vein systolic flow/diastolic flow (S/D) ratio in postexercise echocardiogram.

Conclusion: Exercise stress can unmask sub-clinical diastolic dysfunction in significant number of patients.

Keywords: Diastolic dysfunction, Diastolic stress test, Ejection fraction, Heart failure

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) constitutes a large proportion of HF patients and leads to significant morbidity and mortality. The pathophysiology revolves around abnormal diastolic relaxation of Left Ventricle (LV), reduced LV compliance, LV remodeling and raised Left Atrial (LA) pressure. This subgroup poses a diagnostic dilemma to the treating physician. Incidence of HFpEF is on the rise and prognosis remains guarded [1].

The criteria for defining HFpEF have also faced continued controversy over the last decade. Currently, European Society of Cardiology (ESC) has led down criteria to diagnose HFpEF [2]. It is frequently associated with hypertension, obesity, lung diseases, anaemia or atrial fibrillation. Preclinical Diastolic Dysfunction (PDD), defined as diastolic dysfunction without symptoms of HF, resides in stage B according to the American College of Cardiology/American Heart Association (ACC/AHA) scheme. Even after controlling for co-morbidities, PDD is associated with development of HF in future and it predicts all-cause mortality [3,4]. Diastolic dysfunction is demonstrated by several echocardiographic criteria [5].

Recently, it has been proposed that diastolic function at rest may differ significantly from diastolic function during exercise. In other words, an exercise stress may unmask sub-clinical diastolic dysfunction [6-8]. One of the simplest and readily available tools to measure such exercise-induced diastolic dysfunction is TMT [9,10].

With this idea, the present study was undertaken in the cardiology department of a tertiary care hospital in eastern India. The objectives were to assess the effect of TMT according to Bruce protocol stage 1 on LV diastolic function on symptomatic patients with exertional dyspnea and baseline normal echocardiography attending the Out-Patient Department (OPD) and to determine the effect of different factors on the degree of LV diastolic dysfunction induced by TMT [11].

MATERIALS AND METHODS

This institution based cross-sectional study was conducted among patients with history of exertional dyspnea attending the OPD of the Department of Cardiology; within the study period of six months from May 2018 to October 2018. Ethical clearance was obtained from Institutional Ethics Committee (Letter No MC/Kol/IEC/NON-SPON/521/03/2018, dated 22/03/2018).

Sample size calculation was done using the formula:

$(z_\alpha)2pq/L_2$, where z_α=1.96, p=expected proportion of abnormal postexercise echocardiogram, q=100-p, L=relative precision. Taking p as 50%, L as 20% of p, i.e., 10, the estimated minimum sample size came to be roughly 96. (p was taken as 50% by default as no study from this geographical region on this particular topic was available at the time of this study and studies in other parts of the world came up with variable results).

All patients with unexplained exertional dyspnea up to New York Heart Association (NYHA) class I/II/III, aged between 40-70 years with normal baseline electrocardiogram and echocardiographic left ventricular systolic (EF greater than 50%) and diastolic function, without structural heart disease or established coronary artery disease, presenting within the stipulated study period and giving informed consent were included. Patients were mostly referred from other Departments like Medicine and Chest. Individuals with definite alternate reasons for dyspnea like established lung disease, anaemia, morbid obesity or rhythm disturbances, presence of serious co-morbidities like azotemia, decompensated liver disease, malignancy and also individuals who did not give consent were excluded from the study. Patients with joint problems involving lower limbs, non-ambulatory patients, patients complaining of dyspnea at rest and haemodynamically unstable patients were also excluded.

Final sample size was 106. The parameters studied were clinical profile of the patients, symptoms reported, routine laboratory parameters like complete haemogram, fasting and post-prandial blood sugar, free Thyroxine (T4), Thyroid Stimulating Hormone (TSH), liver function tests, renal function tests, resting Electrocardiography (ECG) and Echocardiography with Doppler.

The echocardiographic evaluation was done according to the American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) guidelines on diastolic function assessment (2016) and cardiac chamber quantification (2015) [5,12]. The participants underwent TMT according to Bruce protocol stage 1 and postexercise echocardiography was done. Echo parameters studied in the postexercise echocardiogram were Left Ventricular Ejection Fraction (LVEF), wall-motion abnormality and Doppler including tissue doppler study for mitral inflow pattern (E and A velocity) and septal mitral leaflet E' and A'.

STATISTICAL ANALYSIS

The data were recorded in predesigned, semi-structured proforma. All the data was initially entered to Microsoft Excel and later these spread sheets were used for analysis. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 20.0. Descriptive statistics were calculated as frequency, percentage, mean and standard deviation. For inferential statistics, various tests of significance were used according to the type of variables dealt with. Firstly, a univariate analysis was done to ascertain the relationship with other variables. Then, the variables found to be significant in univariate analysis were also entered into a multiple logistic regression model. For all the statistical tests of significance, p-value of <0.05 was considered to reject the null hypothesis.

RESULTS

Among 106 patients studied, 56 (52.83%) were males and 50 (47.17%) were females. Mean age in the study population was 55.28 (±8.58), range 42-70 years. Mean age of males was 54.63 (±8.33) and mean age of females was 56.02 (±8.88). Median age was 55 years. Mean EF (Simpson's method) in the baseline echocardiography was 62.54±3.97 (range 55% to 75%). Postexercise mean EF was 61.09±2.86 (range 54% to 72%). The difference was not statistically significant.

Postexercise diastolic dysfunction was present in 33 individuals (31.13%). Out of these, 24 had grade 1 diastolic dysfunction (Impaired relaxation) and 9 had grade 2 (pseudo-normalisation) [Table/Fig-1] [13].

[Table/Fig-1] also shows the relation between different clinical parameters and presence of postexercise diastolic dysfunction. It was noted that on univariate analysis, hypertension, diabetes, hypothyroidism and NYHA class of dyspnea were found to be predictors of postexercise diastolic dysfunction. However, on logistic regression analysis using ENTER method, only diabetes and hypothyroidism were significantly associated. Nagelkerke R square was 0.403 indicating good model fitness.

It was also noticed that as number of risk factors increased, the chances of having postexercise diastolic dysfunction increased linearly [Table/Fig-2]. Significant changes in echo parameters like mitral inflow E/A and pulmonary venous flow S/D ratio occurred in postexercise echo compared to baseline echo [Table/Fig-3].

DISCUSSION

This study showed that an exercise stress can unmask incipient diastolic dysfunction. The chance of developing postexercise diastolic dysfunction was increased by presence of diabetes and hypothyroidism. The chance of developing postexercise diastolic dysfunction also increased linearly as number of risk factors increased. Most of the change in postexercise echo parameters was noted in mitral E/A and pulmonary venous S/D ratio.

Multiple studies have been conducted to unmask preclinical diastolic dysfunction. Grewal J et al., found out an inverse relation between diastolic dysfunction and exercise capacity assessed by TMT in terms of Metabolic Equivalents (METS) [14]. Wan SH et al., commented that left ventricular function measured at rest was not the only determinant of exercise intolerance and HF severity [15]. Recently, it has been suggested that diastolic function during exercise differs from rest measurements and may be a better

Parameter	No. of patients (Percentage)	No. of patients with postexercise DD (33 (31.13%)	Odd ratio (95% CI)	Adjusted odd ratio (95% CI)
Age (in years)				
<55	45 (42.45)	13	1	
55 or more	61 (57.56)	20	1.20 (0.52-2.77)	
Gender				
Male	56 (52.83)	17	1	
Female	50 (47.17)	16	1.08 (0.474-2.46)	
BMI (kg/m^2)				
<23	48 (45.28)	15	1	
23 or more	58 (54.72)	18	0.99 (0.43-2.26)	
Hypertension				
Absent	64 (60.38)	15	1	1
Present	42 (39.62)	18	2.45 (1.06-5.68)	2.05 (0.98-10.32)
Diabetes				
Absent	63 (59.43)	7	1	1
Present	43 (40.57)	26	12.24 (4.52-33.11)	6.56 (2.93-10.55)
Hypothyroidism				
Absent	68 (64.15)	12	1	1
Present	38 (35.85)	21	5.76 (2.36-14.08)	3.41 (1.86-9.53)
Class of dyspnea				
NYHA Class I/II	79 (74.53)	20	1	1
NYHA Class III	27 (25.47)	13	2.74 (1.10-6.80)	2.15 (0.92-7.64)

[Table/Fig-1]: Association of various clinical parameters with development of postexercise diastolic dysfunction (n=106) [13].
Diabetes defined as FBS ≥126 mg/dL, or PPBS ≥200 mg/dL, or HbA1c ≥6.5%, or undergoing treatment for diabetes; Hypertension defined as SBP ≥140 mmHg, or DBP ≥90 mmHg, or on antihypertensive drugs; Hypothyroidism defined as TSH ≥ 4mIU/mL [13], or on levothyroxine supplementation; DD: Diastolic dysfunction

No. of risk factors present	Postexercise diastolic dysfunction present	Postexercise diastolic dysfunction absent	Chi-Square test for linear trend
0	0	18	χ^2= 34.67 p<0.0001 df=3
1	11	52	
2	12	3	
3	10	0	
Total	33	73	

[Table/Fig-2]: Analysis of postexercise diastolic dysfunction in study population based on total number of risk factors (n=106).

Variables before and after TMT	Z value based on positive rank	p-value
E/A ratio	-5.69	<0.001
E/e' ratio	-1.01	0.311
Pulmonary vein S/D ratio	-4.79	<0.001

[Table/Fig-3]: Difference of echo parameters before and after exercise according to Wilcoxon signed rank test (n=106).
E/A: Mitral inflow; E/e: Mitral annulus velocity

predictor of HF severity [6-8]. In the PREDICTOR study from Italy, comprising a study population of 1720, all aged above 65 years, it was observed that 35.4% had subclinical diastolic dysfunction [16]. Very recently, prognostication of patients has been done based on a Diastolic Stress Test (DST) which involves pre and postexercise stress echocardiography [17]. Obokata M et al., opined that exercise echocardiography may help in ruling out HFpEF [18]. Oh JK and Kane JC, may have correctly pointed out that diastolic stress echocardiography should be incorporated in day to day clinical practice [19].

Limitation(s)

The limitations of the present study are its cross-sectional nature. Hence, it was not possible to follow-up the study subjects in order to find out whether they develop diastolic dysfunction at rest or HFpEF in future.

CONCLUSION(S)

The present study suggested that diabetes and hypothyroidism may be predictors for postexercise diastolic dysfunction. Further studies with larger sample size are required to find out all possible predictors and the long term implications of postexercise diastolic dysfunction.

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