Importance of Exercise Stress Testing in Unmasking Diastolic Dysfunction and Predicting Heart Failure with Preserved Ejection Fraction in Patients with Baseline Normal LV Function and Normal Pulmonary Function Test

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Abstract: ***Introduction**: Echocardiography is most commonly used for detecting diastolic dysfunction which might be a predecessor of heart failure with preserved ejection (HFpEF). Exercise stress testing via treadmill test (TMT) followed by echocardiography can unmask diastolic dysfunction. **Aim**: To detect the prevalence of subclinical diastolic dysfunction in cases of un-explained dyspnoea and the risk factors associated with it. **Materials and method**: This cross-sectional study, done in a single tertiary care hospital, included patients from pulmonology and cardiology out patients' department with complaints of exertional dyspnoea, having normal baseline electrocardiogram, echocardiogram and normal pulmonary function test (N=318). Patients having comorbidities like chronic kidney disease, chronic liver disease, malignancy and individuals who did not give consent, were not included in the study. Included individuals were taken for exercise stress by TMT Bruce protocol stage 1. Post-exercise echocardiography was done to find out the number of patients showing diastolic dysfunction in post-exercise echocardiogram. Factors associated with unmasking of sub-clinical diastolic dysfunction were assessed by logistic regression analysis. **Result**: Post-exercise echocardiography revealed diastolic dysfunction in 99 individuals (31.13%). On further sub-analysis, hypothyroidism, type 2 diabetes mallitus were significant predictors of exercise-induced diastolic dysfunction. The appearance of diastolic dysfunction was assessed via the changes in mitral inflow E/A ratio and pulmonary vein systolic flow/diastolic flow (S/D) ratio in post-exercise echocardiogram.***

Keywords: exercise stress testing, diastolic dysfunction, heart failure with preserved ejection fraction (HFpEF)

1. Introduction

Heart failure is a complex clinical syndrome characterized by a constellation of signs and symptoms involving various organ systems. It is now well-recognized that three semi-discrete forms of heart failure exist; heart failure with reduced ejection fraction (HFrEF) heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF)[1]. With diastole occupying approximately 65% of the cardiac cycle and despite Henderson's remarkably accurate observation 90 years ago, it is surprising that the latter form has only gained attention in the last 20 years. Contrary to initial beliefs, current data support that HFpEF is as common as HFrEF, representing approximately 50% of the world's heart failure population, and carries an almost similar dismal prognosis. In contrast to HFrEF, the prevalence of HFpEF is steadily rising at an alarming rate with little improvement in outcome [Fig. 1]. Therapies of proven benefit in HFrEF have repeatedly been shown to add little if any benefit in HFpEF. With the current increases in global life expectancy and significant advances in diagnosis, treatment and secondary prevention of almost all cardiovascular diseases, HFpEF will likely represent the dominant heart failure phenotype in coming decades.

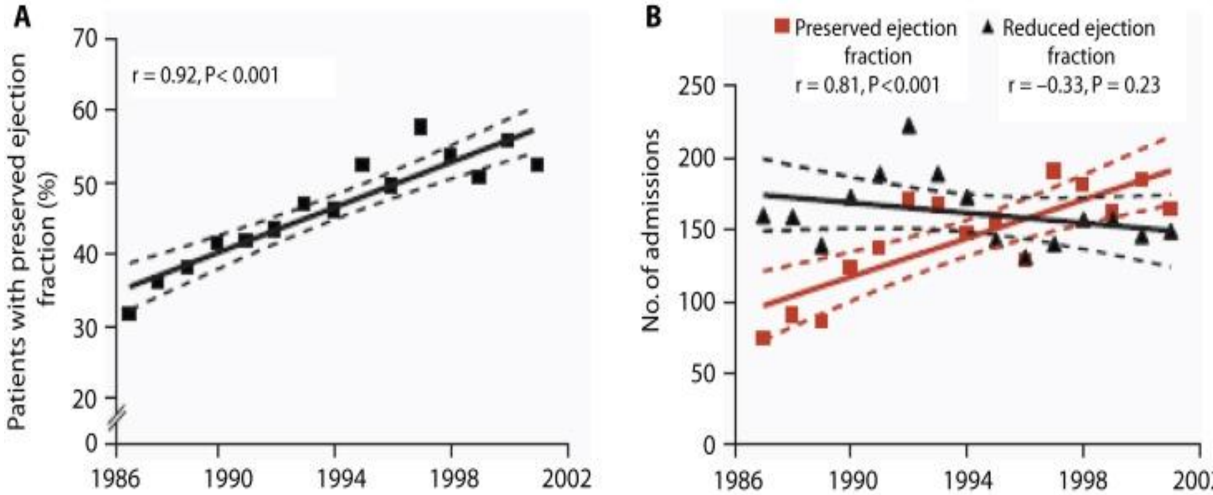

Figure 1: Secular trends in the prevalence of HFpEF. Data collected from the Mayo Clinic for 4596 patients discharged with a diagnosis of heart failure over a 15-year period (1987–2001). Panel A shows a steady increase in the percentage of patients with heart failure who had preserved ejection fraction (>50%) over the study period. Panel B shows the number of admissions for heart failure in patients with preserved ejection fraction (solid red line) and with reduced ejection fraction (solid black line). The dashed lines represent the 95% confidence intervals.

Preclinical diastolic dysfunction (PDD), known as diastolic dysfunction with normal left ventricular systolic function and no symptoms of HF, therefore, resides in stage B according to the ACC/AHA classification. The importance of PDD is evident in that even after controlling for comorbidities, preclinical diastolic dysfunction has been shown to be associated with development of heart failure and is predictive of all-cause mortality[2]. Recently it has been found that cardio-pulmonary exercise via treadmill testing is useful in unmasking pre-clinical diastolic dysfunction [3-5].

This study was undertaken in the cardiology department of a tertiary care hospital with the objective to assess the effect of TMT according to Bruce protocol stage 1 on LV diastolic function on symptomatic patients with exertional dyspnoea and baseline normal echocardiography, pulmonary function test in patients attending the Out-Patient Department (OPD) of cardiology and pulmonary medicine and to determine the effect of different comorbidities on degree of diastolic dysfunction.

2. Materials and Method

Study Area: Medical college and hospital, Kolkata.

Study Population: Patients attending Cardiology and pulmonology outpatient department of Medical College Hospital, Kolkata and fulfilling inclusion criteria.

Study Period: One and half year

Sample Design: Patients with exertional dyspnoea, attending the department of Cardiology and pulmonology, Medical College Hospital, Kolkata, having a normal left ventricular function on baseline echocardiography, normal pulmonary function test and given written informed consent were made part of the study.

Study Variables: All the cases will be studied based on following variables:
History of hypertension, hypothyroidism and diabetes.
Symptoms (exertional dyspnoea)
Echocardiography (assessment of LV function)

Inclusion Criteria:
- Age > 40 years before starting the study.
- Symptom (exertional dyspnea)
- Baseline echocardiography showing normal left ventricular systolic and diastolic function.
- Normal pulmonary function test
- Informed consent giver

Exclusion Criteria:
- Already having proved CAD, structural heart disease.
- Already having left ventricular dysfunction on baseline echocardiography.
- Symptoms at rest.
- Hemodynamically unstable patients.

Sample Size: 318 patients.

Sample Design: Simple Random Selection

Study Design: Hospital based cross-sectional observational study.

Parameters Studied:
1) Symptoms
2) Demographic profile of the patients like age, sex, occupation, address etc.
3) Routine blood investigations like: Complete hemogram, fasting and post-prandial blood sugar, T.S.H., serum alkaline phosphatase.
4) Electrocardiography
5) Pulmonary function test
6) Echocardiography –
   a) 2D and M- mode – LVEF, wall-motion abnormality
   b) Doppler including tissue doppler –
      - Mitral inflow pattern (E and A velocity)
      - Septal mitral leaflet E’
      - Pulmonary venous waves (S, D)

Study Tools

All the cases are studied as per the following: -
1) Questionnaire
2) History and clinical evaluation
3) ECG
4) PFT
5) Echocardiography.

Definition of Outcome

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]. Diastolic dysfunction was diagnosed according to these guidelines.

Statistical Analysis Plan

Firstly, the study got clearance from Institutional Ethics Committee. 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. Descriptive data were represented using various tables, diagrams etc. For inferential statistics, various tests of significance were used according to the type of variables dealt with. For all the statistical tests of significance, p value of <0.05 was considered to reject the null hypothesis. Chi-square test was used to determine the association between categorical variables. For dichotomous outcomes, logistic regression analysis was used. Firstly, a univariate analysis was done to ascertain the relationship with other variables. Then, all the variables found to be significant in univariate analysis were also entered a multiple logistic regression.

3. Result

Age Distribution: Average age was 54.45 years at the time of randomisations.

Sex Distribution

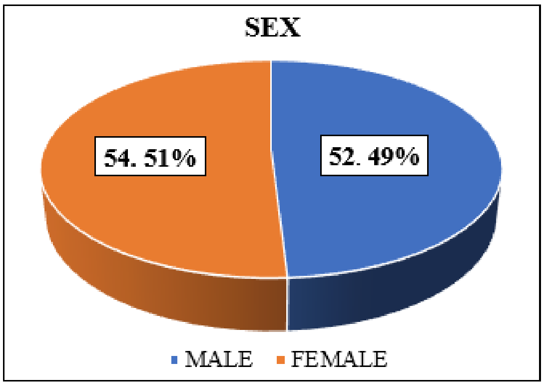

Figure 2: Distribution of male and female sex in study population

Distribution of different risk factors among study population

Table 1: Analysis of male and female sex in study population

		LVDF_Status_Post-EXE		Total	P Value
		Normal	Abnormal		
Sex_	Female	105	51	156	0.734
	male	114	48	162	
Total		219	99	318	

Hypertension

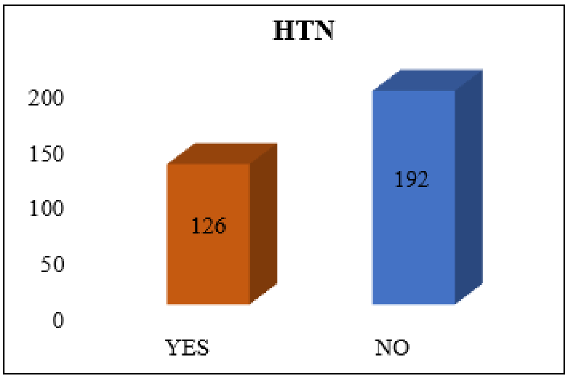

Figure 3: Distribution of hypertension in study population

Table 2: Analysis of hypertension in study population

		LVDF_Status_(Post-EXE)		Total	P value
		Normal	Abnormal		
HTN	Absent	147	45	192	**0.035**
	Present	72	54	126	
Total		219	99	318	

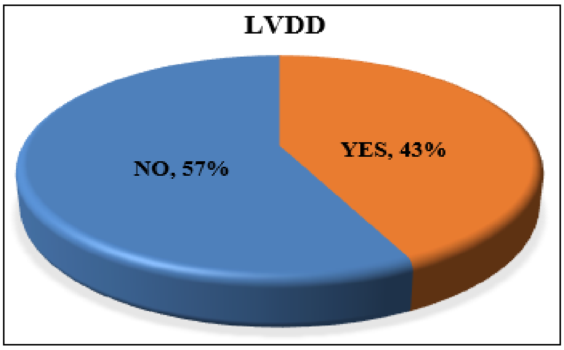

Figure 4: Post exercise LVDD among hypertensive patients

Type II Diabetes Mellitus

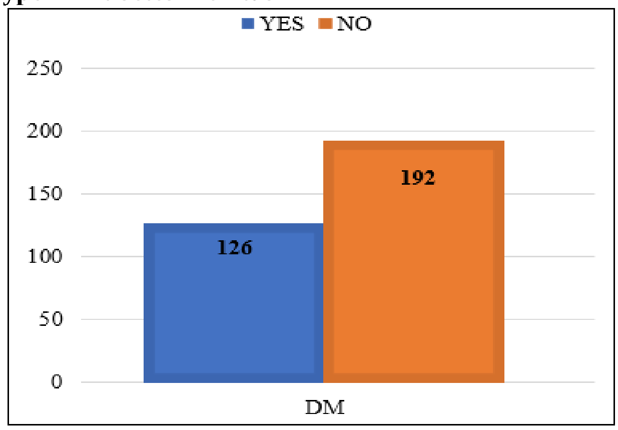

Figure 4: Distribution of diabetes mellitus among study population

Table 3: Analysis of diabetes mellitus in study population

		LVDF_Status_(Post-EXE)		Total	P value
		Normal	Abnormal		
DM_	Absent	168	21	189	**0.000**
	Present	51	78	129	
Total		219	99	318	

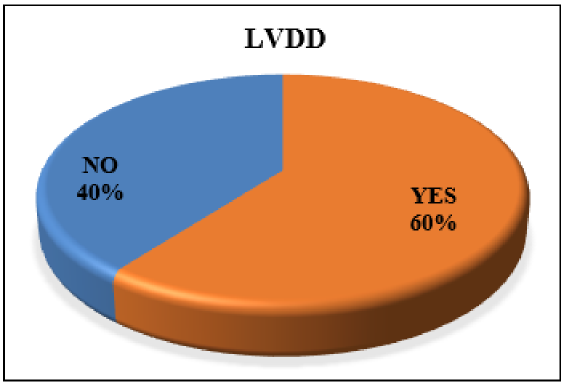

Figure 4: Post exercise LVDD among diabetic patients

Hypothyroidism

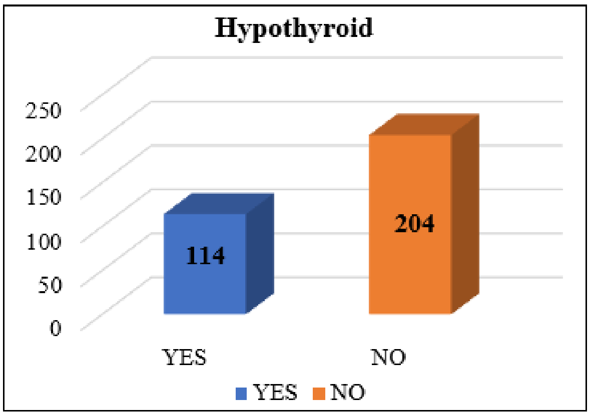

Figure 5: Distribution of hypothyroidism among study population.

Table 4: Analysis of hypothyroidism in study population

		LVDF_Status_ (Post-EXE)		Total	P value
		Normal	Abnormal		
Hypothyroid	Absent	168	36	204	**0.000**
	Present	51	63	114	
Total		219	99	318	

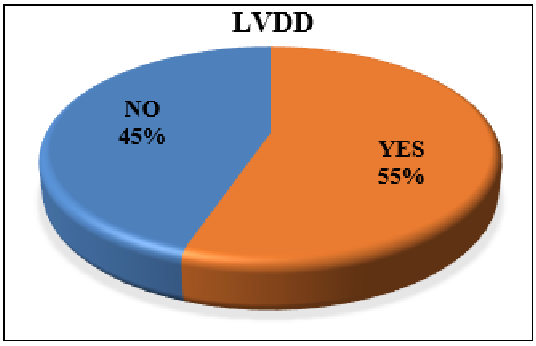

Figure 6: Post exercise LVDD among hypothyroid patients

Assessment of multiple risk factors

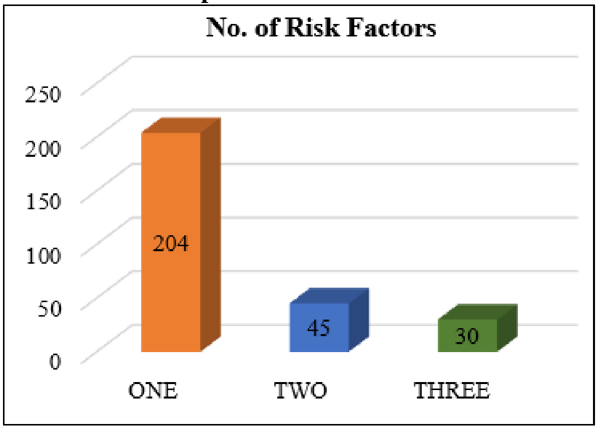

Figure 6: Distribution of total number of risk factors

Table 4: Analysis of LVDD in study population based on total no risk factors

No. of risk factors present	Case	Control	Chi Square test for linear trend
0	0	18	α^2= 34.67 p<0.0001
1	11	52	
2	12	3	
3	10	0	
Total	33	73	

Analysis of different parameters used

Variables before and after TMT	Z value based on positive rank	P value
EA	-5.69	0.000
Ee	-1.01	0.311
SD	-4.79	0.000

Table 5 showing difference of parameters before and after exercise according to wilcoxon signed rank test

Risk Factors as Per Development of Diastolic Dysfunction

	P value	Odds Ratio (OR)	95.0% C.I. for OR	
			Lower	Upper
Sex	0.043	5.816	1.057	32.005
HTN	0.004	0.042	0.005	0.372
DM	0	0.006	0.001	0.066
Hypothyroid	0	0.013	0.001	0.12

Table 6 Showing all risk factors for development of post exercise LVDD.

4. Discussion

In our Hospital based cross-sectional observational study, we studied 318 patients who presented with exertional dyspnoea and had a normal LV function on baseline echocardiography.

The male and female sex distribution was comparable and without any statistical significant. These patients were exposed to mechanical stress with treadmill test according to Bruce protocol stage 1 and post exercise echocardiography was recorded.

In our analysis we found that significant number of these patients had an underlying diastolic dysfunction which was unmasked after exercise. The data analysis showed a statistically significant co-relation of this incipient diastolic dysfunction with presence of risk factors like hypertension, diabetes mellitus and hypothyroidism. The risk further increased with presence of multiple risk factors in a linear relation.

Multiple studies were conducted to unmask pre-clinical diastolic dysfunction and expose these group of patients to early medical therapy. In a large cross-sectional study of patients referred for exercise echocardiography and not limited by ischemia, Jasmine Grewal and group[13] showed that abnormalities of left ventricular diastolic function were independently associated with exercise capacity. They found that Diastolic dysfunction was strongly and inversely associated with exercise capacity. Compared with normal function those with moderate/severe [-1.3 (-1.52 to – 0.99) METs, p<0.0001], and mild resting diastolic dysfunction [-0.70 (-0.88 to -0.46) METs, p<0.0001] had substantially lower exercise capacity after multivariable adjustment. Variation of left ventricular systolic function within the normal range was not associated with exercise capacity. Left ventricular filling pressures measured by resting E/e' > 15 [-0.42 (-0.70 to -0.11) METs, p=0.004] or post-exercise E/e'> 15 [-0.41 (-0.71 to -0.11), p<0.0001] were similarly associated with a reduction in exercise capacity, each in separate multivariate analyses. Individuals with impaired relaxation or resting E/e' ≥15 had a progressive increase in the magnitude of reduction in exercise capacity with advancing age (p<0.001 and p=0.02, respectively). Other independent correlates of exercise capacity were age [unstandardized β coefficient -0.85 (95% CI -0.92 to -0.77) METs per 10 years increment, p<0.0001], female sex [-1.98 (-2.15 to -1.84) METs, p<0.0001], and body mass index >30 kg/m2 [-1.24 (-1.41 to -1.10) METs, p<0.0001].

In their article Siu-Hin Wan and group[14] said that that left ventricular function measured at rest can differ significantly from exercise tolerance and severity of heart failure symptoms[15].

Abhayaratna *et al.* also found that clinical predictors of DD with normal EF included hypertension, angina, myocardial infarction, and obesity. They also reported that the rates of isolated DD, that is DD with normal EF, increased with age.[16,17] In the PREDICTOR investigation, an Italian population study of 1720 elderly subjects 65 to 84 years old, Mureddu *et al.* found that 35.4% of the population had PDD[18].

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