

**How to Cite:**

Bakeer, M. H. N. M., Maklady, F. A., Kamal, H. M., Gawwad, I. M. A., & Mahmoud, I. Z. (2024). Left ventricular mass index versus results of diastolic stress echocardiography in patients with heart failure with preserved ejection fraction. *International Journal of Health Sciences*, 8(S1), 73–82. <https://doi.org/10.53730/ijhs.v8nS1.14715>

## **Left ventricular mass index versus results of diastolic stress echocardiography in patients with heart failure with preserved ejection fraction**

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**Abstract**---Background: Left ventricular mass and left ventricular mass index (LVMI) is an index reflecting the thickness of the cardiac muscle, and the E/e' ratio is a specific indicator for identifying increased left ventricular filling pressure. Limited data exist regarding the prognostic value of incorporating left ventricular mass index in heart failure with preserved ejection fraction (HFpEF). Aim: This study aimed to assess diagnostic value of LVMI at rest versus diastolic stress echo results in patients with HFpEF. Patients and methods: This study is a cross sectional descriptive study. In our study, we investigated 80 patients with unexplained exertional dyspnea with normal resting LV filling pressure at rest. Some of these patients may show elevated LV filling pressure with exercise. The current guidelines recommend to do diastolic stress echocardiography for those patients. All patients underwent complete resting echocardiography including assessment of diastolic dysfunction using the recommended 2016 guidelines and left ventricular mass index. Then we did diastolic stress echocardiography for all participants and the result of diastolic

stress echocardiography was compared with the resting LVMI results. Results: At rest, the mean E, average medial and lateral  $e'$  velocities and E/ average  $e'$  of the study population were all within normal range at rest. In terms of diastolic stress echocardiography results, 52.5% of the study population had negative results, 2.5 percent had unclear data, and 45% of the study population had positive results. The mean of the E/ average  $e'$  of the study population was 17 cm/s which is elevated indicating increased LV filling pressure with stress. E/ $e'$  in stress echo significantly increase with higher classes of dyspnea ( $p < 0.001$ ). LVMI showed moderate positive correlation with E/ $e'$  during stress. Conclusion: In patients with HFpEF, an echo-derived integrated approach incorporating resting LVMI and E/ $e'$  ratio remained to be a powerful prognostic predictor and may be useful to risk-stratify patients with this heterogeneous syndrome.

**Keywords**---LVMI, diastolic stress echocardiography, HFpEF.

## Introduction

Left ventricular (LV) diastolic function may be evaluated noninvasively using transthoracic echocardiography (TTE). The main symptoms suggesting diastolic dysfunction (DD) are dyspnea, exertional fatigue, or poor exercise tolerance. The key variables recommended for assessment of LV diastolic function include simple parameters of mitral inflow and annular velocities, peak velocity of tricuspid regurgitation jet, and the left atrial volume index (LAVI) [1].

However, rest TTE may provide borderline diastolic abnormalities or inconclusive data. The gold standard for the diagnosis of LV DD is invasive testing with direct left ventricular pressures and/or pulmonary capillary wedge pressure measurements. Hence, this method is relatively rarely used in clinical practice, especially with invasive measurements of the pressures during exercise stress. Therefore, the current European Society of Cardiology guidelines recommend diastolic stress echocardiography (DSE) in patients with heart failure (HF) symptoms and normal or indeterminate diastolic function. A substantial number of patients with hypertension, diabetes, or LV hypertrophy, do not meet the criteria for DD on rest TTE [2].

While heart failure with decreased ejection fraction (HFrEF) has a worse prognosis than heart failure with peripheral ejection fraction (HFpEF), the factors influencing prognosis are still not well understood. To date, no treatment for HFpEF has demonstrated a significant reduction in morbidity and death [3,4]. Given that HFpEF is a non-uniform condition, its pathophysiologic complexity contributes to the paucity of available therapies. Enhancing patient phenotypic characterization and identifying particular patient groups that may benefit from customized treatment are essential to therapeutic advancement [5].

In HFpEF, a normal LVEF may be associated with reduced cardiac output and/or increasing LV filling pressure, which is the intrinsic characteristic of this heterogeneous syndrome. Therefore, a combined assessment of both systolic and

diastolic LV functions might be a better approach to decipher pathophysiological mechanisms and determine the prognosis of HFpEF, beyond the simplistic evaluation by LVEF. In recent years, novel hemodynamic classifications taking into account both LV anterograde flow and filling pressure have been proposed in the general HF population and patients with heart failure with reduced EF (HFrEF). However, there are few studies regarding the prognostic impact of incorporating LV pump function and filling pressure in HFpEF [6].

### **Patients and Methods**

This cross sectional study was conducted in Cardiology Department – Non-invasive measurements unit, Suez Canal University Hospital. The study included 80 patients presenting to cardiology department Suez Canal university hospital with unexplained dyspnea and normal resting LV filling pressures assessed by echocardiography were included in the study. While patients with evident cardiac causes of dyspnea, prosthetic valves, pulmonary causes of dyspnea, other causes of dyspnea, poor echocardiographic window that prevent assessment at rest or during exercise, inability to exercise or with morbid obesity were excluded from the study.

All patients were subjected to history taking (included age, gender, history of chronic diseases, main cardiac symptoms), general and cardiac examinations and ECG. Conventional echocardiographic study was done for all participants using the standard views parasternal long, short axis, apical 2, 4 and 5 chamber views at rest by using a Philips EPIC ultrasound machine (Philips Medical Systems) with a broadband transducer (S5-1, 2–5 MHz).

Diastolic function was determined using the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging tissue according to the following algorithm [7].

- All patients with normal LV filling pressure complaining from exertional dyspnea were the candidates of our study and were subjected to diastolic stress echocardiography.
- The following echocardiographic parameters that were measured at rest, peak exercise and recovery:
  - Peak mitral inflow velocity in early diastole (E wave).
  - Peak mitral inflow velocity in late diastole (A wave).
  - The E/A ratio was calculated.
  - Tissue Doppler early diastolic relaxation velocity (E').
  - Peak mitral inflow velocity in early diastole /tissue Doppler early diastolic relaxation velocity to detect the filling pressure (E/ E').
  - Tricuspid regurgitation velocity for pulmonary artery pressure(TR).
  - Left atrial volume and indexed left atrial volume.
- All echocardiographic data were

### Diastolic stress Echocardiography:

- When normal subjects exercise, they are able to increase stroke volume without significantly increasing filling pressures because of augmented myocardial relaxation along with more powerful early diastolic suction. patients with diastolic dysfunction may not be able to augment myocardial relaxation with exercise compared with normal subjects. Hence, these patients can only achieve the required cardiac output at the expense of increased LV filling pressures [7].
- Diastolic stress testing is indicated when resting echocardiography does not explain the symptoms of heart failure or dyspnea, The most appropriate patient population for diastolic exercise testing is the group of patients with dyspnea and normal LV filling pressure at rest [7].
- Ideally a semi-supine bicycle test with imaging during exercise, or else a treadmill or upright bicycle exercise protocol with imaging at or immediately after peak stress, is recommended. It is recommended to use a stepped up protocol until the patient has reached his maximal predicted workload and/ or maximal predicted heart rate ( $220 - \text{age in years}$ ) and/or developed limiting symptoms [8].
- The mitral E/e` ratio and peak TR velocity was acquired at baseline, during each stage including peak exercise, and during a submaximal stage before fusion of the mitral E and A velocities or during the first 2 min of the recovery phase when mitral E and A velocities are no longer fused [9].

### Interpretation of diastolic stress echocardiography

A- The test is considered definitely abnormal indicating diastolic dysfunction and raised LV filling pressure after exercise when all of the following three conditions are met:

- 1- average E/e` > 14 or septal E/e` ratio > 15 with exercise
- 2- peak TR velocity > 2.8 m/sec with exercise
- 3- septal e` velocity is < 7 cm/sec or if only lateral velocity is acquired

B- The results are normal when:

1. average (or septal) E/e` ratio is <10 with exercise and
- 2- peak TR velocity is < 2.8 m/sec with exercise

C- In the absence of these results, the test is considered indeterminate [7].

The results of left atrial function and left atrial strain at rest were compared to the results of diastolic stress echocardiography

### Results

Table 1: Demographic clinical and laboratory findings in the study population:

Age (years)	45 ± 9
Gender	Male 39 (49 %)
	Female 41 (51%)
HTN	40 (50%)
DM	38 (47.5%)
Smoker	25 (31.3%)

According to the data above, there were approximately half as many male participants as female participants, with a mean age of  $45 \pm 9$  years. The study population included about 50% hypertensive individuals. Smokers made up 31.3% of the study group, and diabetes made up about 47.5%.

Table 2: Resting echocardiographic parameters for Assessment of LV filling pressure

Parameter	Mean $\pm$ SD
LVMI(gm/m <sup>2</sup> )	Male 89.8 $\pm$ 22.1 Range: (67-141)
	Female 76.9 $\pm$ 16.9 Range: (50.5-136)
E at rest (cm/s)	67.4 $\pm$ 9.6
Average e' at rest (cm/s)	11.2 $\pm$ 1.9
E/average e' at rest (cm/s)	6 $\pm$ 0.9

In table 2, At rest, the mean E, average medial and lateral e` velocities and E/average e` of the study population were all within normal range at rest. The mean LVMI for both males and females were all within normal range. LVMI in our patients ranged from 50.5 – 141 gm/m<sup>2</sup>

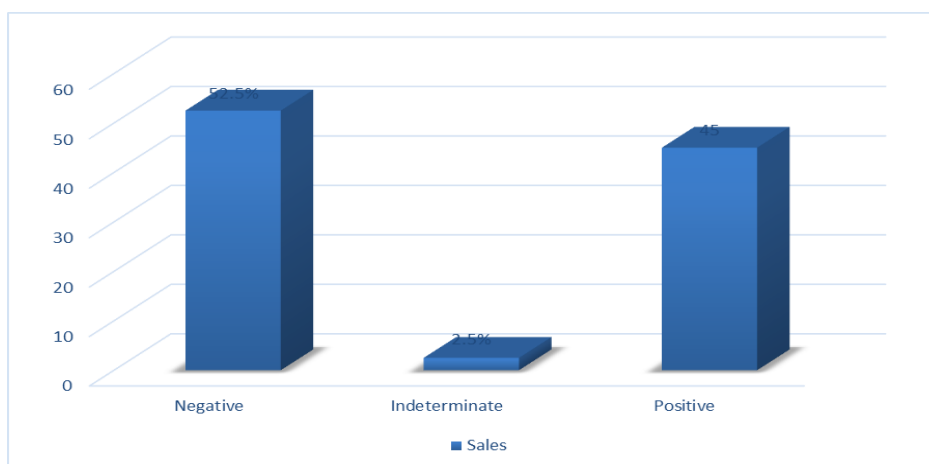


Figure 1: Result of diastolic stress echocardiography:

In terms of diastolic stress echocardiography results, 52.5% of the study population had negative results, 2.5 percent had unclear data, and 45% of the study population had positive results.

Table 3: Echocardiographic parameters for diastolic stress echocardiography assessment

Parameter	Mean $\pm$ SD
E stress (cm/s)	114 $\pm$ 34.3
Average E' stress (cm/s)	8.9 $\pm$ 3.8
E/ average e' stress (cm/s)	17 $\pm$ 11.2

TV Max. velocity stress (m/s)	2.8 ± 1.8
Peak HR / Max. age predicted HR (%)	93 ± 4
Stress METS	10.8 ± 1.2

Table 3 shows the study participants achieved a mean of 93.3% of the maximum age predicted heart rate and 10.8 METS with stress. The mean of the E/ average e' of the study population was 17 cm/s which is elevated indicating increased LV filling pressure with stress.

Table 4: Relationship between class of dyspnea and age, obesity and some echocardiographic parameters

Variable	Dyspnea class I	Dyspnea class II	Dyspnea class III	Sig.
Age (years) (Mean ± SD)	43.7 ± 8.4	45.1 ± 9.1	49.9 ± 9	0.067
BMI (Kg/m <sup>2</sup> ) (Mean ± SD)	28 ± 6.5	30.6 ± 8.1	34.9 ± 8.6	0.012*
LVMi (gm/m <sup>2</sup> ) (Mean ± SD)	83.1 ± 21.1	81.2 ± 22.5	86.8 ± 15.8	0.683
E/e' rest (cm/s) (Mean ± SD)	6.1 ± 1.1	6 ± 1	6.1 ± 2	0.952
E/e' stress (Mean ± SD)	11.1 ± 7.8	18.1 ± 11.7	28.2 ± 7.4	<0.001*

As shown in table 4. E/e' in stress echo significantly increase with higher classes of dyspnea (p<0.001).

Table 5: Correlations between stress E/e', rest E/e', and LVMi

		LVMi
E/e' stress	Pearson Correlation	.409(**)
	Sig.	0.001
E/e' rest	Pearson Correlation	0.209
	Sig.	0.063

Table 5 shows LVMi showed moderate positive correlation with E/e' during stress.

## Discussion

The resulting examined population is in line with the most recent classifications of HFpEF because our study's inclusion and exclusion criteria were quite stringent. The proportion of women in our cohort was 51%, an observation which is in line with the results of other studies that mention a higher prevalence of female gender which seems to be one of the main distinguishing features of HFpEF from heart failure with reduced ejection fraction [10-12].

Dyslipidemia, obesity and DM in women, who are already more prone to inflammation than men, lead to accelerated endothelial dysfunction, ventricular fibrosis and hypertrophy, followed by chamber stiffness and diastolic dysfunction. DM doubles the risk to develop heart failure in diabetic women, as compared to men [13].

Indeed, in another study there was predominantly female and with a predominance of diabetic women vs. men (67.7% vs. 41%). Also, women were more frequently dyslipidemic (87% vs. 72%) and obese (61.2% vs. 58.6%). Dyslipidemia has a potential role in insulin resistance and myocardial stiffness. Consequently, this comorbidity burden leads to more frequent rehospitalization (37% women vs. 20% men) and death (11.3% vs. 3.4%). Interestingly, more women had an E/e' ratio > 13.8 (37% vs. 20%) [14]. DM is a common hallmark in patients with HFpEF. Diabetes was present in 50% of the patients in our study.

As previously mentioned, hyperglycemia contributes to cardiac stiffness and impaired cardiac relaxation and consequently to diastolic dysfunction [15]. Hypertension was present in 50% of our study population justifying the presence of concentric left ventricular hypertrophy (LVH) in the patients. This is in agreement with the literature, which reports that approximately one-third to two-thirds of patients with HFpEF do not have LVH. Also, in their studies, Katz and Shah detect that a low percentage (12% and 9% respectively) of the patients have an eccentric pattern of LVH rather than a concentric one [9,15].

A hypothesis, entitled the “obesity paradox”, states that although obese patients with cardiovascular disease have a higher risk of rehospitalization, their mortality risk is lower compared to normal-weight patients [16]. In our study, BMI significantly increase with grade of dyspnea. The same seems to be true for other study patients who were obese (BMI > 30) in 63.71% of the cases and were characterized by a rehospitalization rate of 73.3%, yet a mortality of only 40%. Also, NT-proBNP is lower in obese patients than in patients with normal BMI. In the high E/e' group there were 30 patients with obesity with a mean BMI = 32.63 and in the low E/e' group there were 24 obese patients with a mean BMI = 31.51. This partly explains the fact that there is no significant difference in NT-proBNP between the two groups [17].

In the current study, E/e' in stress echo significantly increase with higher classes of dyspnea ( $p < 0.001$ ). LVMI showed moderate positive correlation with E/e' during stress. Similarly, Blanco et al. found a prognostic cut-off of 14 for the E/e' ratio. However, their study used the discharge assessment for the statistical analysis, not the admission evaluation [18]. The fact that they reported a very close cut-off value to the one we calculated (13.8) is indeed intriguing, as there seems to be little difference between the admission and discharge prognostic cut-off value of E/e' [18].

Also, Blanco et al. found that a >50% reduction in admission E/e' was correlated with better outcomes. Therefore, patients with worse prognosis have a constantly higher E/e' ratio. Also, a sub-analysis of the KaRen study found that increased E/e' values at 4–8 weeks after discharge have prognostic value. The ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity (E/e' ratio)

derived from echocardiography is a robust diastolic index that reflects left ventricular filling pressure (LVFP) and is associated with outcomes in HF. Despite its modest correlations with outcomes in HFpEF, E/e' ratio displays prominent specificity for identifying patients with increased LV filling pressure <sup>[19]</sup>.

A recent study conducted by Dini et al. <sup>[20]</sup>, which involved 727 outpatients with HFrEF, demonstrated that a functional hemodynamic stratification approach based on a cardiac index (using 2.0 L/min/m<sup>2</sup> as the threshold for low output) and E/e' ratio (using a value  $\geq 15$  as a marker of increased LV filling pressure) is useful in predicting survival. A similar pathophysiological stratification approach based on an assessment of cardiac hemodynamics (ventricular forward flow and filling pressure) has also been proposed in patients with cardiogenic shock <sup>[21]</sup>. Our results extend previously published observations and suggest that combining resting CP/mass with E/e' could effectively predict clinical outcomes in patients with HFpEF.

## Conclusion

In patients with HFpEF, an echo-derived integrated approach incorporating resting power/mass and E/e' ratio remained to be a powerful prognosis predictor and may be useful to risk-stratify patients with this heterogeneous syndrome.

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