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Original Article

To determine the correlation between echocardiographic diastolic parameters and invasively measured left ventricular end diastolic pressure in patients with heart failure with preserved ejection fraction- an observational, descriptive study. (CEAL-HFpEF study)

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ABSTRACT

Objectives: Though invasive monitoring is the most accurate to estimate diastolic dysfunction but it has its own risk. The purpose of this study was to find out any standardized correlation between invasive and non -invasive parameters.
Methods: It is an observational, descriptive study comprising of a total of 500 patients. The primary objective of the study was to determine the correlation between echocardiographic diastolic parameters and invasively measured left ventricular end diastolic pressure (LVEDP).
Results: On studying correlation of different invasive and non-invasive data it was reported that there was a weak correlation between peak E velocity ($r = 0.14$, $p = 0.631$), Peak A velocity ($r = 0.67$, $p = 0.59$), IVRT ($r = -0.35$, $p = 0.178$), Mitral deceleration time (DT) ($r = -0.06$, $p = 0.842$), pulmonary venous peak systolic ($r = -0.02$, $p = 0.966$) and diastolic flows ($r = 0.47$, $p = 0.201$) to LVEDP. There was a good positive correlation between elevated LVEDP and difference in duration of pulmonary venous and mitral flow at atrial contraction (A-Ard) and E/Ea at all four longitudinal segments of the left ventricle. The sensitivity and specificity for detecting an elevated LVEDP of more than 12 mm Hg, using a cut off value of E/Ea< 8, were 89% and 90%.Lateral E/Ea ≥ 12, LAVI ≥34 mL/m2, and Ard−Ad > 30 msec have the greatest diagnostic value for diagnosing diastolic dysfunction in HFpEF patients.
Conclusion: Lateral E/Ea ≥ 12, LAVI ≥34 mL/m2, and Ard−Ad > 30 msec have the greatest diagnostic value for diagnosing diastolic dysfunction in HFpEF patients and have good correlation with invasively measured LVEDP.

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) is still an undiscovered field of cardiology despite a lot of research in this field. In various registry studies, the number of patients with HFpEF varies from 30 to more than 50%.[1] In the majority of these patients there was myocardial hypertrophy and interstitial fibrosis leading to increased ventricular stiffness and prolonged ventricular relaxation and higher diastolic pressures.[2,3] These increased diastolic pressures are transmitted through atrial and pulmonary venous systems, reducing lung compliance which further leads to symptoms.[4,5] Because of its high prevalence and poor prognosis over time, the diagnosis of HFpEF should be made accurately and timely. Till date no single non-invasive diagnostic investigation has withstood the test of time. Though invasive monitoring is the most accurate to estimate left ventricular filling pressure to aid in evaluation and management of diastolic dysfunction, it has its own risk. In real world practice there is no doubt that 2D echocardiography is the widely and easily accessible tool to diagnose it but validity of echocardiographic parameters and its correlation with well-

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established invasive parameters is still unknown and debated.[6,7] The purpose of this study was to evaluate critically the usefulness and limitations of Doppler echocardiography for the evaluation of diastolic filling with same-day direct high-fidelity measurement of left ventricular end diastolic pressure (LVEDP) to find out any standardized correlation between invasive and non-invasive parameters.

2. Materials and methods

It is an observational, descriptive study done at a tertiary care, cardiac teaching center for two years. A total of 500 patients was recruited for the study from both outdoor and indoor patient clinics. Determination of sample size was done using the formula, $n = z^2pq/e^2$, here n = sample size, z = 1.96 at 95% confidence level, p = prevalence of HFpEF i.e., 40–50% and taken maximum as 50%.[8] q = (1-p), and e = Absolute precision/margin of error (5%). On using the formula and above values, calculated sample size was 384. For the ease of calculations, a total sample size of 500 was taken.

2.1. Aims and objectives of the study-

The primary objective was to determine the correlation between echocardiographic diastolic parameters and invasively measured left ventricular end diastolic pressure (LVEDP) in patients with Heart Failure with preserved Ejection Fraction (HFpEF).

Study flow and recruitment criteria were depicted in Fig. 1.

3. Methodology

Inclusion criteria- Patients who fulfilled the definition of heart failure with preserved ejection fraction were included in the study. We investigated patients who were consecutively admitted with the features of congestive heart failure as per Framingham criteria and diagnosis of heart failure with preserved ejection fraction (HF-PEF) as per Consensus Recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) on HFpEF,[9] between March 2018 and February 2020. All patients underwent basic blood and urine tests, brain natriuretic peptide (BNP), chest X-ray, electrocardiography, echocardiography and left heart catheterization for invasive LVEDP measurement. The diagnosis of HFpEF requires four conditions to be satisfied:

1. Symptoms typical of Heart Failure (HF)
2. Signs typical of HF (Signs may not be present in the early stages of HF especially in HF-PEF and in patients treated with diuretics)
3. Normal or only mildly reduced left ventricular ejection fraction (LVEF) and Left Ventricle (LV) not dilated
4. Relevant structural heart disease -LV hypertrophy/Left Atrial (LA) enlargement and/or diastolic dysfunction

Exclusion Criteria:

1. Hemodynamically unstable patients.
2. Uncontrolled arrhythmias.
3. Prosthetic heart valves.
4. Congenital heart diseases.
5. Valvular heart disease

Parameters analyzed:

4. Age and sex distribution

2. Functional NYHA class in which the patient belongs.
3. Etiology of diastolic dysfunction and other co-morbidities i.e., coronary artery disease (CAD), type 2 diabetes mellitus(DM), systemic hypertension (HTN), chronic obstructive pulmonary disease(COPD), Hypertrophic cardiomyopathy(HOCM), chronic renal failure, and obesity.
4. Correlation between echocardiography parameters and invasive LVEDP measurement.

Peripheral venous blood samples were collected into tubes containing EDTA for assessment of N-terminal pro-brain natriuretic peptide (NT-proBNP) level. Samples were collected after 10 min of rest and within 24 h of the echocardiographic examination. The NT-proBNP level was measured using an electrochemiluminescence immunoassay on an Elecsys 2010 system (Roche Diagnostics, Mannheim, Germany). The analytic measurement range for NT-pro BNP was 5–35,000 pg/mL. The normal value is being <100 pg/mL. Other hematological and biochemical tests were performed by standard procedures.

All patients were in stable hemodynamic condition with no drug administration during the periods of data collection. An ultrasonography instrument with a 2.5-MHz Doppler transducer (SIEMENS, ACUSON-CV70, Germany) was used with a multi frequency phased array. Parasternal and apical views were obtained according to the recommendations of the American Society of Echocardiography. All data were recorded during end-expiratory apnea. Recordings were made at a sweep speed of 100 mm/s and stored on magnetic optical discs. The sample volume from pulsed tissue Doppler echocardiography(TDE) was defaulted to 5.7 mm and the acoustic power and filter frequencies were adjusted and optimized for detecting myocardial velocities.

Separate measurements were made for each subject with 2D, M-mode and Doppler echocardiography recordings. Left ventricular (LV) internal diameter at end-diastole and end-systole was measured and fractional shortening was calculated as recommended by the American Society of Echocardiography(ASE)and European Society of Echocardiography(ESE).[9] Ejection fraction was derived from Simpson's modified single plane method using the apical 4-chamber view. Left atrial volume index (LAVI) was measured using the cylinder method with two orthogonal apical views. Left ventricular dimensions, as well as wall thickness, were measured according to the recommendations of the ASE. Left ventricular mass (LVM) was calculated using the Devereux formula.[10]

Peak blood flow velocities from trans mitral and pulmonary venous flow were registered. From the trans mitral flow, the peak early (E) and late atrial (A) diastolic velocities, mitral flow deceleration time (MF DT) and isovolumic relaxation time (IVRT) were all measured. Trans mitral flow during Valsalva was noted. Duration of reversed pulmonary vein atrial systolic flow (Ard) was obtained at the right upper pulmonary vein by pulsed wave Doppler in the apical four chamber view. Difference in duration of pulmonary venous and mitral flow at atrial contraction (Ard-Ad) calculated as per ESE recommendations.[11] Since mitral flow and pulmonary venous flow are affected by respiration; measurements were made from recordings taken at end-expiration. Tissue Doppler echocardiography (TDE) was used to measure left ventricular longitudinal myocardial wall motion from the apical 4 and 2 chamber view using 1–2 mm sample volume. Peak Ea and Aa were measured and E/Ea and Ea/Aa ratios were calculated for the four segments. Cardiac catheterization was done to assess the hemodynamic status and ascertain the correlation of left ventricular end diastolic pressure with various echocardiographic indices of diastolic dysfunction.

Cardiac catheterizations were performed with standard techniques. To provide conscious sedation during the procedure, all patients were treated with benzodiazepines. 5F pigtail catheter

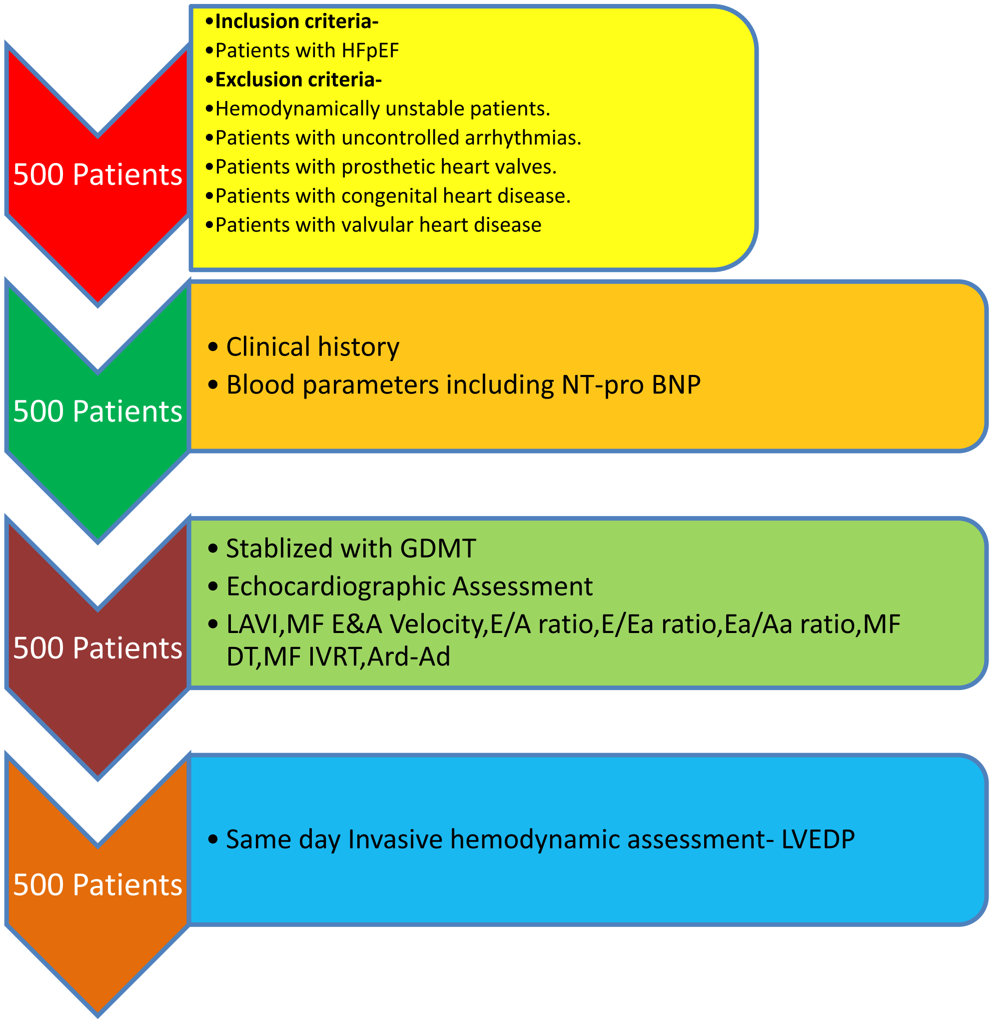

Fig. 1. Study flow diagram. Total 500 patients who fulfilled the definition of heart failure with preserved ejection fraction were included in the study based on different inclusion and exclusion criteria. After performing blood biochemistry analysis, the detailed echocardiographic study was done followed by same day invasive hemodynamic assessment to find a correlation between both non-invasive and invasively measured parameters. LAVI = Left atrium Volume Index, E = Trans mitral peak early filling velocity; A = Late atrial diastolic filling velocity; IVRT = isovolumic relaxation time; DT = deceleration time; LVEDP = Left ventricular end-diastolic pressure; Ard-Ad = Difference in duration of pulmonary venous and mitral flow at atrial contraction; MF = Mitral Flow; Ea = early diastolic mitral annular velocities by TDI; Aa = late diastolic mitral annular velocities by TDI; GDMT = Guideline directed medical therapy; NT-pro BNP= N terminal- Natriuretic peptide.

connected with fluid-filled transducer (Terumo Corp, Tokyo, Japan) was introduced across the aortic valve into the left ventricle (LV). The high-fidelity LV pressure was zeroed and calibrated to the fluid-filled LV pressure measured by the fluid-filled lumen of the catheter before recordings. All pressures were recorded on a strip chart at a paper speed of 100 mm/s. Averaged values of three consecutive beats during end-expiratory apnea was used for analysis. Pressures were registered with a Cathcor® system 3.3 (Philips, Elema AB, Electromedical systems divisions, Solna, Sweden).[12] We measured LV systolic, early and mid-diastolic and LV end-diastolic pressures. LV end diastolic pressure (LVEDP) was defined as the pressure after atrial contraction just before the LV systolic pressure rise. LVDEP>16 mm Hg was taken as a major indicator of LV diastolic dysfunction.[13] All patients gave their written consent to participate in the study, which was approved by the local ethical committee.

4.1. Statistical analysis

A commercially available statistical program, Statistical Package of Social Sciences (SPSS 14.0, Chicago, Ill. USA), was used. All data are presented as the mean ± SD. Pearson's and when relevant additional Spearman's correlation was applied and the linear regression plot was used to show relationships. A *p*-value less than 0.05 were considered significant. Inter and intra observer variability analysis was performed by calculating the coefficient of variation in ten patients (standard deviation of difference between two measurements divided by the mean).

5. Result

The mean age of the subjects was 55.43 ± 9.07 years; with no difference in sex distribution. With regard to the severity of heart failure; 180(36%) patients were in NYHA Class II, 220(44%) patients were in Class III, and 100(20%) patients were in Class IV. Other demographic profile parameters were listed in Table 1. Multiple co-morbidities were present in 395(79%) out of 500 patients. 52% of patients had a history of hypertension, and 42% had a history of coronary artery disease (CAD). The prevalence of diabetes, obesity and COPD was 36%, 44% and 5% respectively. The NT-proBNP level was 93.64 ± 18.8 pg/mL (normal value < 100). Different 2D

Table 1
Demographic profile of patients. Mean age group is 55.43 ± 9.07 years; with no difference in sex distribution.

Patient's anthropometric data	Mean ± SD	Range
Age (years)	55.43 ± 9.07	39–76
Female/Male (no.)	53%/52%	
Height (in cm)	162.27 ± 8.86	148–182
Weight (in kg)	76.31 ± 8.55	57–98
BMI	29.14 ± 3.73	19–36.8
Systolic blood pressure (mm Hg)	147.42 ± 27.01	108–196
Diastolic blood pressure (mm Hg)	90.77 ± 13.21	68–116
Heart rate (beats/min)	88.44 ± 14.35	64–120
NYHA Class I, II, III and IV	0%/36%/44%/20%	

Echocardiographic and hemodynamic parameters measured were shown in Table 2. On studying the correlation of different invasive and non-invasive data it was reported that there was a weak correlation between peak E velocity ($r = 0.14$, $p = 0.631$), Peak A velocity ($r = 0.67$, $p = 0.59$), IVRT ($r = -0.35$, $p = 0.178$), Mitral DT ($r = -0.06$, $p = 0.842$), pulmonary venous peak systolic ($r = -0.02$, $p = 0.966$) and diastolic flows ($r = 0.47$, $p = 0.201$) to LVEDP. The correlation between elevated LVEDP and A-Ard was positive and strong ($r = 0.77$, $p < 0.001$)[Table 3] [Fig. 2]. On the other hand on studying correlation between Tissue Doppler study and catheterization data, it was observed that a highly significant correlation was found between E/Ea. at all four longitudinal segments of the left ventricle ($r = -0.53$, $p < 0.05$, $n = 28$ for lateral) ($r = -0.64$, $p < 0.05$, $n = 28$ for septal) ($r = -0.57$, $p < 0.01$, $n = 28$ for anterior), and ($r = -0.64$, $p < 0.05$ $n = 28$ for posterior). The sensitivity and specificity for detecting an elevated LVEDP of more than 12 mm Hg, using a cut off value of E/Ea.< 8, were 89% and 90% and the positive predictive and negative predictive values were 94% and 82%, respectively. The correlation between Ea./Aa and LVEDP in all segments was weak ($r = 0.08$, $p = 0.814$ in lateral) ($r = 0.09$, $p = 0.784$ in septal) ($r = -0.15$, $p = 0.645$ in anterior) and ($r = -0.22$, $p = 0.502$ in posterior segment)[Table 4].

6. Discussion

This was a study on patients of HFpEF and we attempted to correlate various known echocardiographic diastolic parameters

Table 2
Echocardiography and Catheterization Data. LAVI >34 mL/m^2 is a strong indicator of HFpEF. LA: Left atrium, LV: Left ventricle, LVEDVI: Left ventricular end-diastolic volume index, E = early diastolic; A = atrial diastolic; IVRT = isovolumic relaxation; DT = deceleration time; LVEDP = Left ventricular end-diastolic pressure.

LA and LV dimensions and function	Mean ± SD	Range
Left atrial diameter (mm)	39.52 ± 2.48	35–44
LV septal wall thickness, diastole (mm)	13.88 ± 2.35	11–25
LV posterior wall, diastole (mm)	12.36 ± 1.56	10–15
LV diastolic diameter (mm)	42.68 ± 2.72	38–48
LV systolic diameter (mm)	26.8 ± 1.39	23–29
LV fractional shortening (%)	38.16 ± 2.48	33–43
LV ejection fraction (%)	60.31 ± 3.6	50–68
LV Mass(gm)	210.17 ± 37.47	142–286
LA Volume index (ml/m^2)	36.79 ± 4.04	26–46
LVEDVI (mL/m2)	61.06 ± 4.28	48–70
E (cm/s)	77.92 ± 28.11	44–171
A (cm/s)	30.04 ± 8.24	21–68
Mitral *E*/*A* ratio	2.73 ± 1.11	0.75–6.1
Mitral IVRT (ms)	97.31 ± 17.36	72–134
Mitral DT (ms)	134.02 ± 31.78	100–268
Ard-Ad (ms)	35.76 ± 5.81	17–45
Peak TR Velocity (ms)	2.93 ± 0.56	1.8–3.8
LVEDP (mm Hg)	18.59 ± 3.98	10–26
LV Peak Systolic Pressure (mm Hg)	147.38 ± 27.04	108–196

Table 3
Correlation between Doppler and Catheterization Data. There is strong positive correlation of LVEDP with Ard-Ad.

Spectral doppler	Mean ± SD	Range	Correlation to LVEDP
MF *E*, cm/s	71 ± 47	25–266	$r = 0.14$, $p = 0.631$
MF *A*, cm/s	65 ± 66	15–335	$r = 0.67$, $p = 0.593$
E/A	1.7 ± 0.3	1,4–2.0	*$r = 0.57$, $p = 0.0162$*
MF IVRT, ms	93 ± 49	20–220	$r = -0.35$, $p = 0.178$
MF DT, ms	167 ± 65	80–350	$r = -0.06$, $p = 0.842$
PVF systole cm/s	34 ± 16	13–76	$r = -0.02$, $p = 0.966$
PVF diastole cm/s	48 ± 14	25–79	$r = 0.47$, $p = 0.201$
Ard-Ad (ms)	36 ± 10	26–46	*$r = 0.77$ $p = 0.001$*

with left ventricular end-diastolic pressures. A total of 500 subjects was recruited in the present study, which was a sizable population as compared to previous studies. The demographic pattern in the present study was similar to those of other population-based studies. Similar to previous reports, we too identified older age, and a history of hypertension, CAD and obesity as correlates of preserved LVEF.[1,2] The NT-pro-BNP level in the present study was 93.64 ± 18.8 pg/mL. (Normal value, < 100). It is widely used as a marker for the evaluation of diastolic HF and assessment of prognosis.[14–16] Similar to this several other recent studies have also demonstrated that a great proportion of HFpEF patients have normal NT-pro-BNP levels.[17–19] The major finding in the present study was that objective measures of abnormal LV diastolic function were present in the overwhelming majority of patients. Thus, 75% of the patients who met the clinical definition of diastolic heart failure exhibited an abnormal LVEDP. Such high filling pressures in the setting of a normal chamber size indicate an abnormality in the physical properties of the ventricle (i.e., increased LV diastolic stiffness). The major indicator of diastolic dysfunction (i.e., an LVEDP ≥16 mm Hg) was present in 75% of the patients. Majority of the patients had systolic hypertension too. Among the non-invasive parameters proposed by the ESC consensus statement and the recommendations of the ASE and EAE[20,21] for diagnosing HFpEF, lateral E/Ea. ≥ 12, LAVI ≥34 mL/m2, and Ard–Ad > 30 msec had the greatest diagnostic value for identifying patients with HFpEF. A ratio of E/Ea. less than 8 has been shown to be useful in identifying patients with normal LV filling pressure and an E/Ea. above 15 indicating elevated LV filling pressure.[22,23] It had a greater diagnostic accuracy at the lateral mitral annulus than at the septal level.[4–6,24] This is in concordance with previous observations confirmed by conductance catheter analysis.[25–29] In contrary to our findings however, Per Lindqvist, Gerhard Wikström and Anders Waldenström et al[30] found that, there was only positive but a modest relationship between E/Ea and LVEDP. Left atrial volume index (LAVI) was demonstrated to have important value for diagnosing patients with HFpEF in the present study.[31,32] A cutoff point of 28 mL/m2 for LAVI provided high sensitivity (85%) and moderate specificity (61%). While a cutoff value of 34 mL/m2 yielded a higher specificity of 84% with a slightly lower sensitivity of 47%.[33] Our present study also showed that Ard–Ad > 30 msec had great diagnostic value in detecting HFpEF with a sensitivity of 45% and a high specificity of 90%. Previous studies have demonstrated that difference in duration of reversed pulmonary vein atrial systole flow (Ard) and duration of mitral A wave flow (Ad) i.e., Ard–Adhada strong correlation with LV end-diastolic pressure, which could be used to separate patients with abnormal LV relaxation into those with normal filling pressure and those with elevated LV end-diastolic pressure but normal mean left atrial pressure. Thus, Ard–Ad is better than other non-invasive parameters at detecting diastolic dysfunction at an early stage. However, some studies have shown that the use of Ard–Ad is hindered to some extent by the

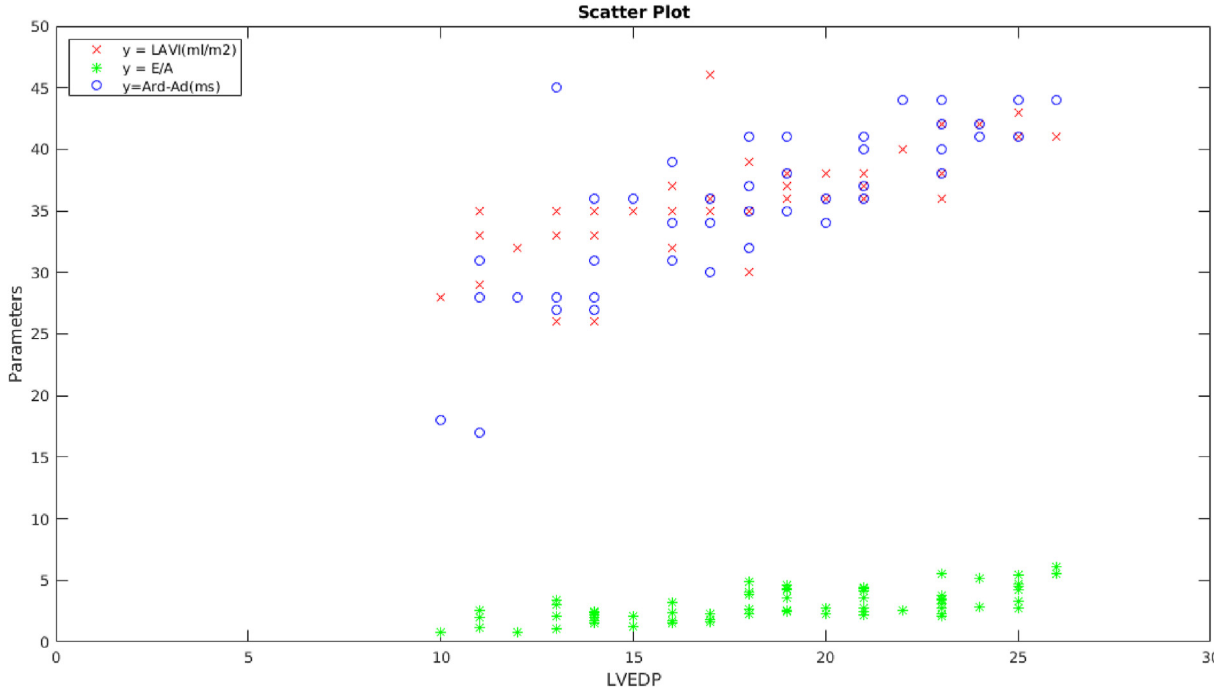

Fig. 2. Scatter plot to delineate correlation between LVEDP (*x* axis) and LAVI, E/A & Ard-Ad (*r* 0.77) (*y* axis).LVEDP has good positive correlation with all the three non-invasive echocardiographic criteria. LAVI- red cross, E/A-green circle, Ard-Ad- blue circle.

Table 4
Correlation between Tissue Doppler and Catheterization Data. There is good positive correlation between LVEDP with septal, anterior & lateral E/A in diagnosing HFpEF. LV = left ventricular; E = early diastolic; A = atrial diastolic; IVRT = isovolumic relaxation time; DT = deceleration time; EDP = end-diastolic pressure; PCWP = pulmonary capillary wedge pressure; *m* = myocardial; MF = mitral flow; PVF = pulmonary venous flow; TDE = tissue Doppler echocardiography.

Tissue doppler echocardiography	Mean ± SD	Range	Correlation to LVEDP
E/Ea, Lat	9.8 ± 4.9	7.1–21.7	$r = 0.53$, $p < 0.05$
E/Ea, Sep	11.7 ± 5.4	5.8–27.3	$r = 0.64$, $p < 0.05$
E/Ea, Ant	11.4 ± 6.6	5.0–27.5	$r = 0.57$, $p = 0.01$
E/Ea, Post	11.8 ± 6.1	7.3–30.7	$r = 0.64$, $p < 0.05$
Ea/Aa, Lat	1.6 ± 1.1	0.3–5.6	$r = 0.08$, $p = 0.814$
Ea/Aa, Sep	1.1 ± 0.6	0.5–3.0	$r = 0.09$, $p = 0.784$
Ea/Aa, Ant	1.2 ± 0.7	0.3–3.0	$r = -0.15$, $p = 0.645$
Ea/Aa, Post	1.1 ± 0.8	0.3–2.7	$r = -0.22$, $p = 0.502$

difficulty in obtaining high-quality pulmonary venous flow velocity recordings that are suitable for analysis.[34–37] In our present study, the success rate for obtaining Ard was lower (79%) than for other parameters but was still acceptable. Therefore, we still consider Ard–Ad as a valuable parameter with broad clinical applicability, which has also been confirmed by other observations. In our study, a negative correlation between LVEDP and IVRT was found. This is explained by an increasing decline in LV relaxation and increasing LVEDP, Ea falls and the onset of Ea is delayed concomitant with an increase in E velocity and shortening of IVRT.[25,38] In the present study, we have assessed the diagnostic accuracy of LVMI >149 (male) and >122 g/m2 (female), as proposed by the 2016 ESC consensus statement and found that it yielded a high specificity but a particularly low sensitivity for detecting HFpEF patients in our population. The prevalence of LV hypertrophy in our HFpEF patients was similar to results reported by previous investigators.[24] Additionally, the specificity of LV hypertrophy to predict HFpEF in our population was not as high as some of the other parameters such as E/Ea, LAVI, and Ard–Ad. Therefore, LVMI is less valuable for identifying patients with HFpEF. In the present study, the combination of E/A < 0.5 and DT > 280 msec had low diagnostic value for detecting HFpEF, with particularly low sensitivity; this is consistent with previous observations.[21–24]

6.1. Study limitations

Our study had few limitations; first, the evaluation of LA maximum dP/dt by Doppler parameters is required to demonstrate LA contractility. Unfortunately, this was not evaluated in the present study. Additionally, LVEF was measured by the biplane Simpson's method in the present study, which might be a poor tool for detecting longitudinal systolic dysfunction. However, previous authors have demonstrated depressed longitudinal strain in HFpEF.

7. Conclusion

Our study suggests that, Doppler echocardiography is a rapid and accurate non-invasive method for the evaluation of cardiac function. Among all the parameters assessed in this study, lateral E/Ea ≥ 12, LAVI ≥34 mL/m2, and Ard–Ad > 30 msec, have the greatest diagnostic value for diagnosing diastolic dysfunction in HFpEF patients and have strong correlation with LVEDP. We propose that evaluation of these three parameters can be used as a simplified tool for the estimation of LV filling pressure.

Ethical clearance

Not required.

What was known?

Although, Doppler echocardiography is used as a rapid and accurate non-invasive diagnostic tool for the diagnosis of heart failure, accurate measurement of LVEDP is difficult; therefore, exact diagnosis is sometimes elusive. However, invasive measurements of left ventricular end-diastolic pressure (LVEDP) and/or pulmonary capillary wedge pressure (PCWP) still remain the gold standard.

What is new?

This study was undertaken to get the best approximate of LVEDP by various echocardiographic criteria and to see which of the suggested criteria give us the best value of elevated LVEDP. Our study suggests that, of all the parameters assessed in this study, lateral E/Ea $\geq$ 12, LAVI $\geq$34 mL/m2, and Ard–Ad > 30 msec, have the greatest diagnostic value for diagnosing diastolic dysfunction in HFpEF patients.

Declaration of competing interest

The authors declare no conflicts of interest.

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