Diagnostic accuracy and clinical utility of echocardiographic indices for detecting left ventricular diastolic dysfunction in patients with coronary artery disease and normal ejection fraction

Ejeksiyon fraksiyonu normal olan koroner arter hastalarında sol ventrikül diyastolik işlev bozukluğunu saptamada kullanılan ekokardiyografik göstergelerin tanısal değeri ve klinik yararı

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ABSTRACT

Objective: The aim of present study was to assess the clinical utility and diagnostic accuracy of diastolic dysfunction criteria that were recommended in current American Society of Echocardiography and European Association of Echocardiography recommendations for prediction of increased LVEDP (>16 mmHg) in patients with coronary artery disease and normal EF.

Methods: Forty-five consecutive patients (mean age=61.5±10.3 years) referred for cardiac catheterization were enrolled in this prospective study. All patients underwent transthoracic echocardiography and tissue Doppler imaging within 24 hours before cardiac catheterization. Patients were divided into 2 groups according to left ventricular end diastolic pressure (LVEDP) (LVEDP>16 mmHg, n=23; LVEDP≤16 mmHg, n=22). Receiver operating characteristics curve analyses were performed and sensitivity, specificity, positive predictive value and negative predictive value were calculated for indices to detect high LVEDP.

Results: Among the indices, left atrial volume index (LAVI) ≥34 ml/m^2 (sensitivity=60.0% and specificity=90.0%) and ratio of transmitral to septal annular velocities during early filling (septal E/e' ratio) ≥15 (sensitivity=30.4% and specificity=95.5%) had more reasonable sensitivity and specificity. Receiver operating characteristics curve analysis revealed that best predictors of high LVEDP were septal E/e' [area under curve (AUC)=0.694, standard error (SE)=0.66, p=0.01] and LAVI (AUC=0.669, SE=0.63, p=0.045]. There were statistically significant correlations between LVEDP and septal E/e' (r=0.541, p=0.001) and LAVI (r=0.461, p=0.002). A proposed algorithm consisting LAVI ≥34 ml/m^2 and septal E/e' >8 could determine diastolic dysfunction with a 95.6% sensitivity and 54.5% specificity.

Conclusion: Septal E/e' (≥15) and LAVI (≥ 34 ml/m^2) were the better predictors of the increased LVEDP than the other echocardiographic parameters. There were statistically significant moderate positive correlations of LVEDP with septal E/e' and LAVI. Combination of LAVI and septal E/e' is useful to detect diastolic dysfunction. *(Anadolu Kardiyol Derg 2011; 11: 666-73)*

Key words: Diastolic function, echocardiography, left ventricular end-diastolic pressure, diagnostic accuracy, sensitivity, specificity

ÖZET

Amaç: Bu çalışmada ejeksiyon fraksiyonu normal olan koroner arter hastalarında sol ventrikül diyastol sonu basıncındaki artışı ön görmede Amerikan Ekokardiyografi Cemiyeti ve Avrupa Ekokardiyografi Birliği tarafından önerilen güncel diyastolik işlev bozukluğu göstergelerinin tanısal değeri ve klinik yararının araştırılması amaçlandı.

Yöntemler: Bu ileriye dönük çalışmaya kalp kateterizasyonu için yönlendirilen toplam 42 hasta (ortalama yaş=61.5±10.3 yıl) alındı. Tüm hastalara kalp kateterizasyonu yapılmadan önceki 24 saat içinde transtorasik ekokardiyografi ve doku Doppler görüntüleme yapıldı. Hastalar sol ventrikül diyastol sonu basıncına (SoVDSB) göre 2 gruba ayrıldı (SoVDSB>16 mmHg, n=23; SoVDSB≤16 mmHg, n=22). Göstergeler için işlem karakteristik eğrisi analizi yapıldı ve yüksek LVEDP'yi saptamada duyarlılık, özgüllük, pozitif ve negatif ön gördürücü değerleri hesaplandı.

Bulgular: Göstergeler arasında, sol atriyal hacim indeksi (SAHİ≥ 34 ml/m^2, duyarlılık=%60.0 ve özgüllük=%90) ve septal E/e' (≥15, duyarlılık=%30.4 ve özgüllük=%95.5) en makul duyarlılık ve özgüllüğe sahipti. İşlem karakteristik eğrisi analizinde yüksek SoVDSB'yi öngörmede en iyi

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göstergelerin septal E/e' [eğri altındaki alan (EAA)=0.694, standart hata (SH)=0.66, p=0.01] ve SAHİ (EAA=0.669, SH=0.63, p=0.045) olduğu bulundu. Septal E/e' (r=0.541, p=0.001) ve SAHİ (r=0.461, p=0.002) ile SoVDSB arasında istatistiksel anlamlı korelasyon saptandı. Bu göstergelerin kullanıldığı bir algoritmada SAHİ ≥34 ml/m^2 ve septal E/e' >8 oluşunun diyastolik işlev bozukluğunu %95.6 duyarlılık ve %54.5 özgüllük ile belirlediği bulundu.

Sonuç: Septal E/e' (≥15) ve SAHİ (≥ 34 ml/m^2) diğer ekokardiyografik parametrelere göre artmış SoVDSB'nin daha iyi öngördürücüleridir. Septal E/e' ve SAHİ ile SoVDSB arasında istatistiksel anlamlı orta derece korelasyon bulunmaktadır. SAHİ ve septal E/e'nin kombinasyonu diyastolik işlev bozukluğunu saptamada yararlıdır. *(Anadolu Kardiyol Derg 2011; 11: 666-73)*

Anahtar kelimeler: Diyastolik işlevler, ekokardiyografi, sol ventrikül diyastol sonu basıncı, tanısal değer, duyarlılık, özgüllük

Introduction

Approximately half of patients with new diagnoses of heart failure have normal or near normal ejection fraction (EF) (1, 2). These patients are diagnosed with "diastolic heart failure" or "heart failure with preserved EF (1-4). The assessment of left ventricular (LV) diastolic function and filling pressures is important to distinguish this syndrome from other diseases such as pulmonary disease resulting in dyspnea, to assess prognosis, and to identify underlying cardiac disease and its best treatment. Elevated filling pressures are the main physiologic consequence of diastolic dysfunction (2, 5). Filling pressures are considered elevated when the mean pulmonary capillary wedge pressure (PCWP) is 12 mmHg or when the left ventricular end-diastolic pressure (LVEDP) is 16 mmHg (6).

Echocardiography has played a central role in the evaluation of LV diastolic function over the past two decades. Several echocardiographic techniques have been described for noninvasive estimation of LV filling pressures. Tissue Doppler imaging (TDI) provides rapid assessment of ventricular diastolic function, and adds incremental value to the standard Doppler echocardiographic measurements. Relatively load-independent measurements of LV relaxation such as tissue Doppler early diastolic annular (e'), color M-mode-derived flow propagation (Vp) velocities, mitral E/e' and E/Vp ratios have been used to evaluate LV diastolic function more accurately (7). Recently American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE) provided a comprehensive review of the techniques and the significance of diastolic parameters, as well as recommendations for nomenclature and reporting of diastolic data in adults based on a critical review of the literature and the consensus of a panel of experts (6).

However, clinical utility and diagnostic accuracy of these parameters did not fully evaluated in coronary artery disease (CAD) and normal EF.

The aim of present study was to assess the clinical utility and diagnostic accuracy of diastolic dysfunction criteria that were recently published in ASE/EAE recommendations in prediction of increased LVEDP (LVEDP >16 mmHg) in patients with CAD and normal EF.

Methods

Participants

In this prospective study, 45 consecutive patients (mean age 61.5±10.3 years; 8 females and 37 males) with CAD and normal EF who were undergoing clinically indicated left ventriculography and coronary angiography were enrolled. Patient selection and clinical evaluation were performed between May 2009 and December 2009 in Hacettepe University Department of Cardiology. All patients had sinus rhythm. Patients with previous myocardial infarction, mitral stenosis, aortic stenosis or more than mild mitral or aortic regurgitation and unsatisfactory echocardiographic images were excluded from the study. The patients were assessed a day prior to coronary angiography and a full clinical history was obtained, including information about cardiovascular risk factors and ongoing medications. All patients underwent transthoracic echocardiography and tissue Doppler imaging within 24 hours before cardiac catheterization. Analysis of the echocardiographic data was performed while blinded to the results the hemodynamic data. Patients were divided into 2 groups according to left ventricular end diastolic pressure (LVEDP) (LVEDP>16 mmHg, n=23; LVEDP≤16 mmHg, n=22). Informed consent was obtained from all patients and the study was approved by the Hospital Ethic Committee.

Test methods

Echocardiographic measurements

Standard imaging was performed in the left lateral decubitus position using a commercially available system (Vingmed System Five GE ultrasound, Horten, Norway). Images were obtained using a 2.5-3.5 MHz transducer in the parasternal and apical views. Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters were determined with M-mode echocardiography under two-dimensional guidance in the parasternal long-axis view, according to the recommendations of the American Society of Echocardiography (8). Left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were calculated from apical four-chamber views, according to the modified Simpson's rule.

Pulsed-wave (PW) Doppler was performed in the apical 4-chamber view to obtain mitral inflow indices to assess LV filling according to the recommendations of the American Society of Echocardiography (6). Measurements of mitral inflow include the peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, deceleration time (DT) of early filling velocity, and the isovolumic relaxation time (IVRT), derived by placing the cursor of CW Doppler in the LV outflow tract to simultaneously display the end of aortic ejection and the onset of mitral inflow.

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Flow propagation velocity (Vp) was measured as the slope of the first aliasing velocity during early filling, measured from the mitral valve plane to 4 cm distally into the LV cavity. Gain is set at sub-saturation levels and the Nyquist range limit is adapted to ±75% of the spectral E velocity to obtain overflow ('aliasing') on M-mode spatio-temporal velocity map. E/Vp ratio was calculated in all patients.

Pulsed-wave TDI was performed in the apical views by placing a 3 mm sample volume at the lateral, septal, anterior and inferior mitral annulus. To minimize the angle between the beam and the direction of annular motion, care was taken to keep the ultrasound beam perpendicular to the plane of the annulus. Peak systolic (s), early (e') and late diastolic myocardial velocities (a') were recorded. Several cardiac cycles were evaluated and the best three consecutive ones were analyzed and averaged.

The time intervals between the peak of R wave and onset of mitral E velocity, and between peak of R wave and onset of e' at the four areas of the mitral annulus were measured. Subsequently, the difference between these time intervals ($T_{E-e'}$) was calculated for each of the four areas, and an average value was derived. IVRT/ $T_{E-e'}$ was calculated for all patients as an indicator of diastolic function.

The left atrial (LA) dimension was measured at end-ventricular systole in the parasternal long axis view according to ASE recommendations (8). Left atrial volume was calculated at ventricular end-systole using the following formula: Left atrial volume (LAV) = (A1 × A2) × 0.85/L. A1 was defined as the left atrial area using apical ventricular four chamber view at end-systolic phase. A2 was defined as the left atrial area using apical two chamber view in end-systolic phase. L was defined as the long-axis length of the left atrium in the apical four-chamber view. Left atrial volume index (LAVI) was calculated by dividing LAV to the body surface area (BSA) (8, 9). Presence of mitral regurgitation (MR) was noted and MR severity was quantified by effective regurgitant orifice area (EROA) using the simple proximal isovelocity surface area method. An EROA of MR value less than 0.20 cm^2 was accepted as minor and greater than 0.40 cm^2 was accepted as severe MR (10).

Resting regional left ventricular function was evaluated by the echocardiographic derived wall motion score index (WMSI). As recommended by the American Society for Echocardiography a 16-segment model was used for left ventricular segmentation (8). Each segment was analyzed individually and scored on the basis of its motion and systolic thickening. Each segment's function was confirmed in multiple views. Segments were scored are as: normal or hyperkinesia=1, hypokinesia=2, akinesia=3 and dyskinesia (or aneurysmatic)=4. WMSI was derived as the sum of all scores divided by the number of segments visualized.

Cardiac catheterization, coronary angiography and Gensini score

Left heart catheterization was performed in all patients under local anesthesia via femoral arterial approach. All recordings were obtained at end-expiration by a pigtail catheter connected with a fluid-filled transducer before left ventriculography and coronary angiography. Three executive heart cycles were evaluated and the mean value of LVEDP was calculated. The beat to beat variability of LVEDP was less than 5%. Patients were allocated into 2 groups according to left ventricular end diastolic pressure (LVEDP) (Group 1: LVEDP>16 mmHg n=23 patients, group 2: LVEDP≤16 mmHg, n=22 patients).

All coronary angiograms were evaluated by two experienced cardiologists who were not aware of the laboratory results of the patients. The severity of the each lesion was assessed by quantitative coronary angiography. The total severity of coronary artery disease (CAD) was assessed according to the Gensini scoring system (11, 12). In this system, angiographic stenosis between 0% and 25% is scored as 1 point, between 25% and 50% is scored as 2 points, between 50% and 75% is scored as 4 points, between 75% and 90% is scored as 8 points, between 90% and 99% is scored as 16 points, and total occlusion is scored as 32 points. These scores are multiplied by the coefficient defined for each coronary artery and segment, and the results are then added. In cases with discrepancies between Gensini scores, angiograms were re-evaluated to reach a consensus.

Statistical analysis

SPSS 15.0 statistical analysis software (SPSS Inc., Chicago, IL, USA) was used to evaluate variables and tests. Distribution of data was assessed by using a one-sample Kolmogorov-Smirnov test. Data are demonstrated as mean±standard deviation (SD) for normally distributed continuous variables, median (minimum-maximum) for skew-distributed continuous variables, and frequencies for categorical variables. For numerical variables, an independent samples t-test and the Mann-Whitney U test (in case of skew-distribution) were used for inter-group comparisons LVEDP (>16 mmHg or ≤16 mmHg). Categorical variables and the patients who were under or above the cut-off points were compared by using Fisher's exact (in case of small sample size) and Pearson's Chi-square tests. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated according to the values of LVEDP (>16 mmHg or ≤16 mmHg). Inter-observer and intra-observer agreement were assessed with intra- and interclass correlation coefficient, and with the average difference between readings, corrected for their mean (variability). Receiver operating characteristics (ROC) curve analysis was performed to establish both the parameters that can best predict the diastolic dysfunction (LVEDP>16mmHg) and the best cut-off points for those parameters. A two tailed p value <0.05 was considered significant.

Results

Participants

The mean LVEDP of the 23 patients (mean age 62.3±9.1 years, 18 males) with increased LVEDP (Group 1) was 23±3 mmHg and mean LVEDP for the 22 patients (mean age 60.6±11.5 years, 19 males) with normal LVEDP (Group 2) was 12±2 mmHg. The mean

Gensini score was similar between the two groups (21.4±5.3 vs. 22±5.0, respectively). Groups were also similar in terms of baseline characteristics shown in Table 1.

When echocardiographic parameters were compared, Group 1 and Group 2 were similar with respect to LA diameter, LVEDD, LVESD, LVEDV, LVESV, LVEF, presence of MR, mitral Epeak, mitral Apeak, mitral E/A ratio, IVRT, DT and mitral Vp.

Reproducibility

Intra-observer correlation coefficient and variability for septal E/e′ were 0.891 and 3.2%, for lateral E/e′ were 0.881 and 3.4%, for average E/e′ were 0.863 and 3.8%, for LAVI were 0.903 and 2.0%, for mitral E/Vp were 0.799 and 4.5%, for IVRT/$T_{E\text{-}e'}$ 0.731 and 7.3%, respectively ($p<0.001$ for all). The inter-observer correlation coefficient and variability for septal E/e′ were 0.767 and 5.2%; for lateral E/e′ were 0.771 and 5.2%, for average E/e′ were 0.742 and 6.7%, for LAVI were 0.853 and 4.1%, for mitral E/Vp were 0.732 and 7.0%, for IVRT/$T_{E\text{-}e'}$ 0.631 and 10.3%, respectively ($p<0.001$ for all).

Test results

Echocardiographic indices of diastolic dysfunction

The patients in Group 1 had a higher mean LAVI (35.3±16.4 ml/m^2 vs. 25.8±7.8 ml/m^2, p=0.018), mitral E/Vp (1.95±0.28 vs. 1.43±0.25, p=0.001), septal E/e′ (11.1±6.3 vs. 7.6±2.5, p=0.019), lateral E/e′ (9.6±5.3 vs. 6.4±2.8, p=0.016) and average E/e′ (10.2±5.7 vs. 6.8±2.5, p=0.014) than the Group 2, respectively. Lateral e′ (8.9±2.8 cm/s vs. 11.1±2.8, p=0.011) and average e′ (8.3±2.5 cm/s vs. 10.1±2.3 cm/s, p=0.016) values were significantly lower in Group 1 than Group 2. Among the diastolic indices, septal e′ (7.8±2.3 cm/s vs. 9.1±2.4, p=0.070) and IVRT/$T_{E\text{-}e'}$ (4.5±1.4 vs. 4.6±1.5, p=0.818) were similar between two groups (Table 2).

Table 1. Baseline clinical characteristics

Variables	LVEDP >16mmHg (n=23)	LVEDP ≤16mmHg (n=22)	p*
Age, years	62.3±9.1	60.6±11.5	0.584
Gender, M/F	18/5	19/3	0.870
Hypertension, %	65	63	0.954
Diabetes mellitus, %	43	41	0.935
Systolic blood pressure, mmHg	138.4±28.2	139.1±27.2	0.932
Diastolic blood pressure, mmHg	84.2±14.4	83.5±13.6	0.867
ACE-I or ARB use, %	39	41	0.932
β-Blocker use, %	39	36	0.894
Diuretic use, %	52	50	0.924
Calcium channel blockers	22	23	0.902
Mean Gensini score	21.4±5.3	22±5.0	0.698

Data are demonstrated as mean±standard deviation and frequencies
*Independent samples t-test and Pearson's Chi-square test
ACE-I - angiotensin converting enzyme inhibitors, ARB - angiotensin receptor blockers, F-female, LVEDP - left ventricular end diastolic pressure, M - male

When the recommended cut-off values for the indices of left ventricular diastolic function compared between 2 groups, LAVI (≥34 ml/m^2, 61% vs 9%, p=0.001) and septal E/e′ (≥15, 30% vs. 4.5%, p=0.047) were found to be higher in Group 1. However there was no significant difference between other indices of left ventricular diastolic function between 2 groups (Table 3).

Diagnostic accuracy of diastolic dysfunction parameters

Sensitivity, specificity, PPV and NPV values of the recommended cut-off values for the indices of left ventricular diastolic function were shown in Table 4. Among these indices LAVI (≥34

Table 2. Comparison of the echocardiographic variables

Variables	LVEDP >16 mmHg (n=23)	LVEDP ≤16 mmHg (n=22)	p*
LA diameter, mm	36.1±6.2	34.4±5.8	0.348
LAVI, ml/m^2	35.3±16.4	25.8±7.8	0.018
LV end-diastolic diameter, mm	46.1±3.7	46.8±3.6	0.523
LV end-systolic diameter, mm	31.1±0.8	30.9±0.8	0.406
LV end-diastolic volume, ml	95.7±20.3	97.2±18.7	0.798
LV end-systolic volume, ml	40.8±12.7	43.2±13.8	0.547
*LV ejection fraction, %	61.1±10.0	62.1±9.2	0.729
EROA of MR, n			0.758
- <0.20 cm^2	9	7	
- 0.20 - 0.39 cm^2	-	1	
- >0.40 cm^2	-	-	
WMSI	1.17±0.12	1.14±0.11	0.367
Mitral Epeak, cm/s	66.9±21.4	62.3±13.9	0.399
Mitral Apeak, cm/s	83.4±16.9	77.8±16.3	0.264
Mitral E/A	0.82±0.27	0.83±0.24	0.896
IVRT, ms	96.0±29.3	90.4±28.2	0.517
DT, ms	187.6±31.8	199.6 ± 37.7	0.254
$T_{E\text{-}e'}$, ms	19.4±3.6	18.1±2.8	0.184
IVRT/$T_{E\text{-}e'}$	4.5±1.4	4.6±1.5	0.818
Mitral Vp, cm/s	40.7±12.6	43.5±11.3	0.437
Mitral E/Vp	1.95±0.28	1.43±0.25	0.001
Septal e′, cm/s	7.8±2.3	9.1±2.4	0.070
Lateral e′, cm/s	8.9±2.8	11.1±2.8	0.011
Average e′, cm/s	8.3±2.5	10.1±2.3	0.016
Septal E/e′	11.1±6.3	7.6±2.5	0.019
Lateral E/e′	9.6±5.3	6.4±2.8	0.016
Average E/e′	10.2±5.7	6.8±2.5	0.014

Data are demonstrated as mean±standard deviation and frequencies
*Independent samples t-test, Fisher's exact and Pearson's Chi-square tests
DT - deceleration time, EROA - effective regurgitant orifice area, IVRT - isovolumetric relaxation time, LA - left atrium, LAVI - left atrial volume index, LV - left ventricle, LVEDP - left ventricular end-diastolic pressure, MR - mitral regurgitation, Vp - velocity propagation, WMSI - wall motion score index
*LV ejection fraction was calculated according to the modified Simpson's rule

Table 3. Comparison of the recommended parameters that were used for the evaluation of left ventricular diastolic function

Variables	LVEDP >16 mmHg (n=23)	LVEDP ≤16 mmHg (n=22)	p*
E/A <1, n (%)	17 (74)	18 (82)	0.722
Septal e′ < 8 cm/s, n (%)	13 (57)	10 (45)	0.555
Lateral e′ <10 cm/s, n (%)	16 (70)	9 (41)	0.074
Septal E/e′ ≥15, n (%)	7 (30)	1 (4.5)	0.047
Septal E/e′ (8-15), n (%)	7 (30)	9 (41)	0.542
Lateral E/e′ ≥12, n (%)	6 (26)	1 (4.5)	0.095
Lateral E/e′ (8-12), n (%)	6 (26)	5 (23)	0.950
Average E/e′ ≥13, n (%)	6 (26)	1 (4.5)	0.095
Average E/e′ (8-12), n (%)	6 (26)	5 (23)	0.950
LAVI ≥34 ml/m^2, n (%)	14 (61)	2 (9)	0.001
IVRT/T_{E-e}′ <2, n (%)	5 (22)	3 (13.5)	0.699
Mitral E/Vp ≥2.5, n (%)	6 (26)	2 (9)	0.242

Variables are presented as number and percentages
*Fisher's exact and Pearson's Chi-square tests
E/e′ - ratio of transmitral and mitral annular velocities during early filling, IVRT-isovolumetric relaxation time, LAVI - left atrial volume index, LVEDP - left ventricular end-diastolic pressure, Vp - velocity propagation

Table 4. Diagnostic properties of the recommended parameters for detecting the diastolic dysfunction (LVEDP >16mmHg)

Variables	Sensitivity, %	Specificity, %	PPV, %	NPV, %
E/A <1	73.9	18.2	48.5	40.0
Septal e′ < 8 cm/s	56.5	54.5	56.5	54.4
Lateral e′ <10 cm/s	69.6	59.1	64.0	65.0
Septal E/e′ ≥15	30.4	95.5	87.5	56.7
Lateral E/e′ ≥12	26.1	95.5	85.7	55.2
Average E/e′ ≥13	26.1	95.5	85.7	55.2
LAVI ≥34 ml/m^2	60.0	90.0	85.7	69.2
IVRT/T_{E-e}′ <2	21.7	86.3	62.5	51.3
Mitral E/Vp	26.1	90.9	75.0	54.0

E/e′ - ratio of transmitral and mitral annular velocities during early filling, IVRT - isovolumetric relaxation time, LAVI- left atrial volume index, LVEDP - left ventricular end-diastolic pressure, NPV - negative predictive value, PPV - positive predictive value, Vp - velocity propagation

Table 5. Pearson's correlation coefficients between indices of LV diastolic function and LVEDP

Parameter	Correlation coefficient (r)	p
E/A	-0.111	0.466
Septal e′	-0.240	0.112
Lateral e′	-0.202	0.184
Septal E/e′	0.541	0.001
Lateral E/e′	0.302	0.044
Average E/e′	0.353	0.017
LAVI	0.461	0.002
IVRT/T_{E-e}′ <2	-0.189	0.219
Mitral E/Vp	0.371	0.012

E/e′ - ratio of transmitral and mitral annular velocities during early filling, IVRT-isovolumetric relaxation time, LAVI - left atrial volume index, LV - left ventricle, LVEDP - left ventricular end-diastolic pressure, Vp - velocity propagation

ml/m^2, sensitivity=60.0% and specificity 90.0%) and septal E/e′ (≥15, sensitivity=30.4% and specificity 95.5%) had more reasonable sensitivity and specificity.

Analysis of ROC curves revealed that best predictors were septal E/e′ [Area under curve (AUC) = 0.694, Standard error (SE)=0.66, p=0.01] and LAVI (AUC=0.669, SE=0.63, p=0.045) (Fig.1- 2). The sensitivity of a septal E/e′ >9.62 for identifying a LVEDP >16 mmHg was 52%, with a specificity of 90%. The sensitivity of LAVI >35.7 ml/m^2 for identifying a LVEDP >16 mmHg was 60%, with a specificity of 90%.

There were statistically significant moderate positive correlations between LVEDP and septal E/e′ (r=0.541, p=0.001) and LAVI (r=0.461, p=0.002). There were weak positive correlations of LVEDP with lateral E/e′ (r=0.302, p=0.044), average E/e′ (r=0.353, p=0.017) and mitral E/Vp (r=0.371, p=0.012) (Table 5).

On the basis of the data presented above, a proposed algorithm consisting LAVI (≥34 ml/m^2) and septal E/e′ (>8) can determine diastolic dysfunction with a high to excellent sensitivity (95.6%) and reasonable specificity (54.5%) (Fig. 3).

Discussion

The main findings of the present study are as follows: (i) LAVI (≥34 ml/m^2) and septal E/e′ (≥15) were the better predictors for the increased LVEDP than the other echocardiographic parameters, (ii) There were statistically significant moderate positive correlations of LVEDP with septal E/e′ and LAVI, (iii) a proposed algorithm consisting LAVI (≥34 ml/m^2) and septal E/e′ (>8) can determine diastolic dysfunction with a highest sensitivity and reasonable specificity.

Non-invasive prediction of pulmonary capillary wedge pressure (PCWP) or LVEDP is a topic of active investigation (6, 13-16). Several echocardiographic indices such as transmitral Doppler parameters, tissue Doppler velocities, and various combined ratios such as septal E/e′, lateral E/e′, average E/e′, mitral E/Vp or IVRT/T_{E-e}′ are supposed to be useful in the prediction of LVEDP (6, 17). LAVI is also another echocardiographic indices of diastolic function that reflects LVEDP, LA pressure and remodeling (6).

Compared with mitral inflow velocities, mitral annular velocities (e′) are less influenced by the left atrial pressure and preload changes (18, 19). The ratio of mitral E to e′ could correct for the influence of relaxation on E velocity and it relates to filling pressures. In addition, several investigators have shown that E/e′ ratio can be used to predict elevated filling pressures especially in patients with decreased EF (13, 20). It has also been shown that E/e′ yielded accurate estimation of filling pressures in many clinical conditions including sinus tachycardia, atrial fibrillation and hypertrophic cardiomyopathy (21-23). On the other hand, the relationship between E/e′ and filling pressure is

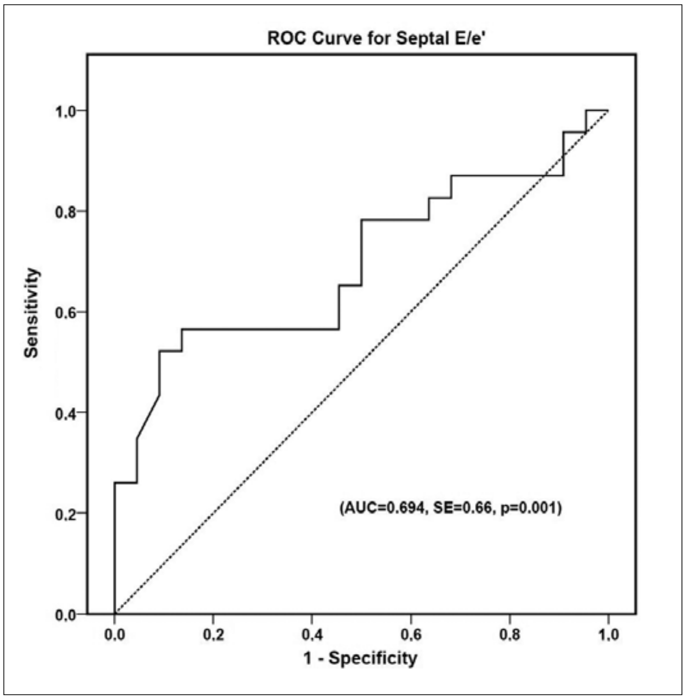

Figure 1. ROC curve analysis for septal E/e′ in predicting the diastolic dysfunction (LVEDP>16 mmHg)
AUC - area under the curve, E - transmitral velocity during early filling, e′ - septal annular velocity during early filling, LVEDP - left ventricular end-diastolic pressure, ROC - receiver operating characteristics curve, SE - standard error

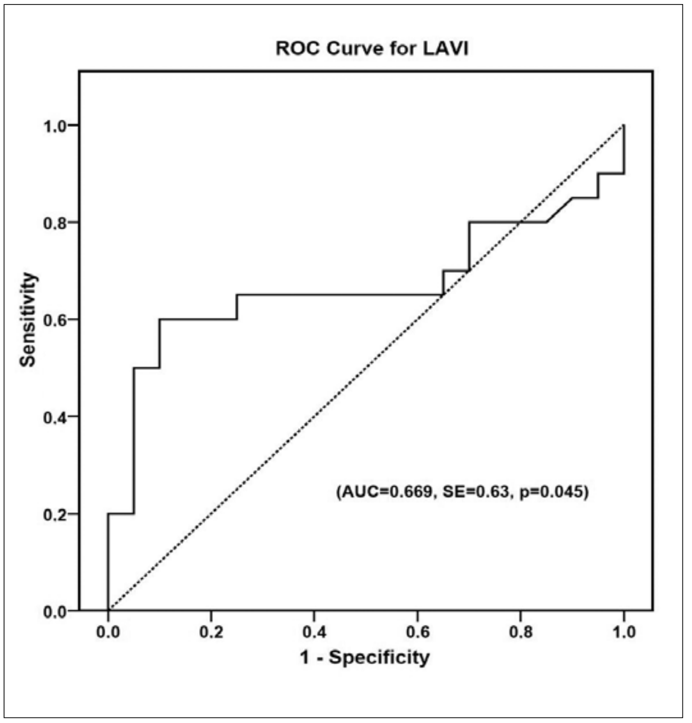

Figure 2. ROC curve analysis for LAVI in predicting the diastolic dysfunction (LVEDP>16 mmHg)
AUC - area under the curve, LAVI - left atrial volume index, LVEDP - left ventricular end-diastolic pressure, ROC - receiver operating characteristics curve, SE - standard error

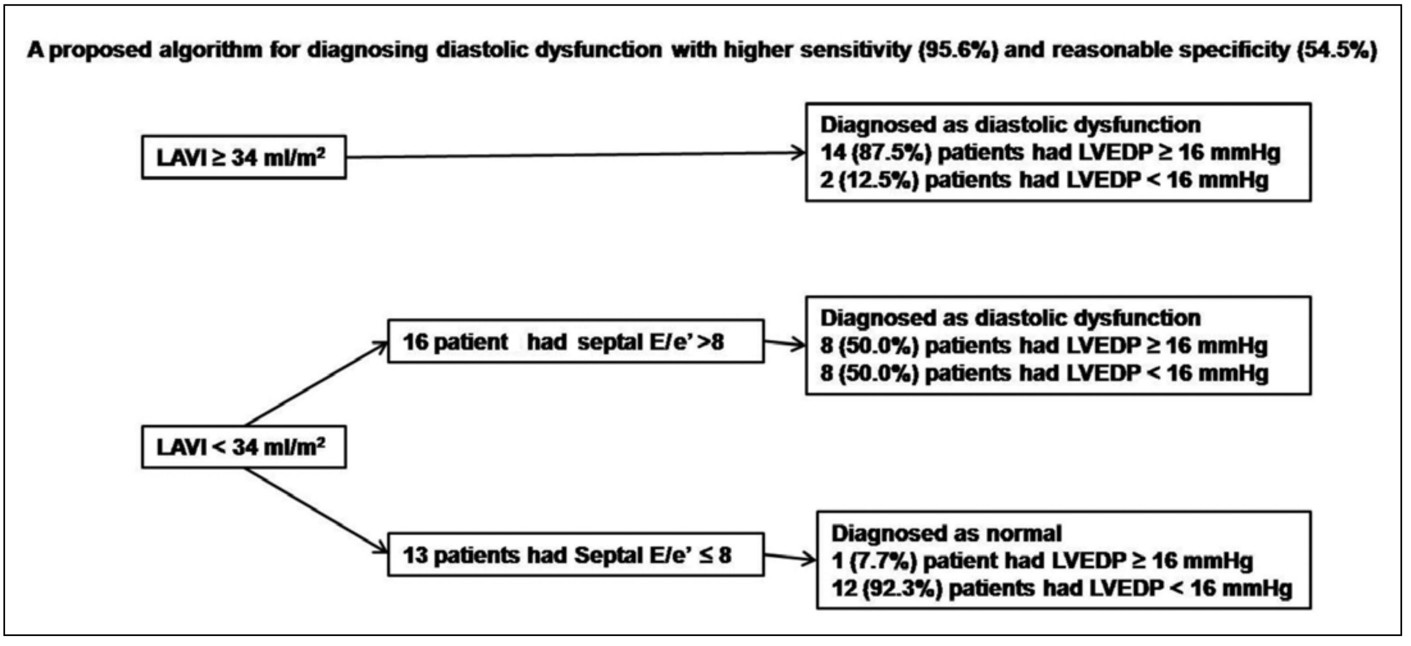

Figure 3. A proposed algorithm for diagnosing diastolic dysfunction

weaker in patients with a normal EF. In our study; septal E/e′, lateral E/e′ and average E/e′ were found to be higher in group with higher LVEDP. However, when we compared the recommended cut-off values for E/e′ only septal E/e′ ≥15 has statistically significant difference between the two groups. Besides septal E/ e′ had better diagnostic properties than the lateral E/e′ and average E/e′. Importantly, if we evaluate these indices as a continuous variable, all these indices had significant correlation with LVEDP.

Velocity propagation is an index of diastolic function and relatively independent of loading conditions (24, 25). A Vp value of less than 40 cm/s implies diastolic dysfunction with slow relaxation and can be used to distinguish pseudonormal pattern from normal relaxation (24, 25). A ratio of mitral E velocity to Vp greater than 2.5 has been shown to be an index of increased PCWP (26). In our study, mitral E/Vp was found to be higher in group with higher LVEDP. However, frequently used cut-off for mitral E/Vp did not reach statistically important significance. This might be due to smaller study population or relatively load dependent property of mitral E velocity. Importantly, Vp might be measured higher in patients with normal EF and higher LVEDP. Therefore, the sensitivity of mitral E/Vp for detecting an elevated LVEDP in patients with normal EF is known to be low and this also supports our findings (27).

Recently, the time interval between onset of mitral inflow and onset of early diastolic velocity ($T_{E-e'}$) was proposed to be useful for predicting cardiac filling pressure (6). In a canine study, Rivas-Gotz et al. (28) reported significant prolongation of $T_{E-e'}$ after ischemia induction. They found a significant correlation between tau and $T_{E-e'}$ in canine and human models. In our study, we could not find a significant relation between $T_{E-e'}$ and LVEDP in patients with CAD. Rivas-Gotz et al. (28) also shown that an IVRT/$T_{E-e'}$ ratio < 2 has reasonable accuracy in identifying patients with increased LV filling pressures. However, Sohn et al. (29) did not find a correlation between $T_{E-e'}$ and tau. In our study, we could not find any significant relationship of these two parameters and increased LV filling pressures. This might be due to smaller study population or relatively lower reproducibility of IVRT/$T_{E-e'}$ ratio.

The measurement of LA volume is highly feasible and reliable in most echocardiographic studies, with the most accurate measurements obtained using the apical 4-chamber and 2-chamber views (8, 30). This evaluation is clinically important, because there is a significant relationship between left atrial remodeling and echocardiographic indices of diastolic function (6, 31). Abhayaratna et al. (32) have shown that LAVI ≥34 mL/m^2 is an independent predictor of death, heart failure, atrial fibrillation, and ischemic stroke. However, one must recognize that dilated left atria may be seen in patients with bradycardia and 4-chamber enlargement, anemia and other high-output states, atrial flutter or fibrillation, and significant mitral valve disease in the absence of diastolic dysfunction (8). In our study; LAVI was found to be higher in group with higher LVEDP. Recommended cut-off value for LAVI (≥34 ml/m^2) significantly differentiate the two groups. As septal E/e', LAVI had also better diagnostic properties than the other parameters. Importantly, if we evaluate these indices as a continuous variable, LAVI had significant correlation with LVEDP. If LAVI (≥34 ml/m^2) and septal E/e' (>8) are combined, diastolic dysfunction could be diagnosed with a highest sensitivity and reasonable specificity.

Study limitations

The major limitations of the present study are the relatively small number of patients and the results are based on a single center experience. Lack of healthy control group prevents to compare the results. The onsets of mitral inflow and mitral annulus velocities could not be compared during the same cardiac cycle. The measurement of $T_{E-e'}$ and average E/e' can lead to erroneous results when hemodynamic parameters are not the same during two separate measurements. Owing to lack of indication, right heart catheterization was not performed. Another limitation of our study is that we could not perform echocardiographic and hemodynamic evaluations at the same time.

Conclusion

Several echocardiographic techniques have been described for noninvasive estimation of LV hemodynamics. In our study, LAVI (≥34 ml/m^2) and septal E/e' (≥15) were the better predictors for the increased LVEDP than the other echocardiographic parameters. There were statistically significant moderate positive correlations of LVEDP with septal E/e' and LAVI. Based on these results, it may be better to use an algorithm consisting LAVI (≥34 ml/m^2) and septal E/e' (>8) to determine diastolic dysfunction with a higher sensitivity and reasonable specificity in patients with CAD and normal ejection fraction. Further researches with larger populations were needed in order to better understanding these parameters and to propose better algorithms.

Conflict of interest: None declared.

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