Original Article

Doppler Tissue Imaging: A Non-Invasive Technique for Estimation of Left Ventricular End Diastolic Pressure in Severe Mitral Regurgitation

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Abstract

Background: *Conventional Doppler measurements, including mitral inflow and pulmonary venous flow, are used to estimate left ventricular end diastolic pressure (LVEDP). However, these parameters have limitations in predicting LVEDP among patients with mitral regurgitation. This study sought to establish whether the correlation between measurements derived from tissue Doppler echocardiography and LVEDP remains valid in the setting of severe mitral regurgitation.*

Methods: *Thirty patients (mean age: 57.37 ± 13.29 years) with severe mitral regurgitation and a mean left ventricular ejection fraction (EF) of 46.0 ± 14.95 were enrolled; 16 (53.4%) patients were defined to have EF < 50% and 14 (46.6%) patients had EF ≥ 50%. Doppler signals from the mitral inflow, pulmonary venous flow, and Doppler tissue imaging indices were obtained, and LVEDP was measured invasively through cardiac catheterization.*

Results: *The majority of the standard Doppler and Doppler tissue imaging indices were not significantly correlated with LVEDP in the univariate analysis. In the multiple linear regression, however, early (E) transmitral velocity to annular E' (E/E') ratio (ß = 1.09, p value < 0.01), E wave velocity to propagation velocity (E/Vp) ratio (ß = 7.87, p value < 0.01), and isovolumic relaxation time (ß = 0.21, p value = 0.01) were shown as independent predictors of LVEDP (R^2 = 91.7%).*

Conclusion: *The ratio of E/Vp and E/E' ratio and also the isovolumic relaxation time could be applied properly to estimate LVEDP in mitral regurgitation patients even in the setting of severe mitral regurgitation.*

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Introduction

Information on left ventricular end diastolic pressure (LVEDP) is essential when one considers the presence or absence of clinical symptoms in patients with mitral regurgitation (MR).[1] Supposedly, patients with pulmonary disease and significant MR but with cardiac compensation may have dyspnea because of a pulmonary rather than a cardiac cause. It is, therefore, advantageous to assess LVEDP in these cases in an attempt to prove or refute a cardiac cause for the shortness of breath. However, the only method to determine this pressure is via cardiac catheterization. Consequently, if one were to be able to estimate LVEDP non-invasively, it would be a valuable tool for evaluating the clinical status of patients. Doppler echocardiography has become the non-invasive technique of choice for the evaluation of diastolic function,[2-6] and the Doppler mitral inflow and pulmonary venous flow are used to clinically

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estimate LVEDP in several diseases.[7-10] On the other hand, MR modifies both of these measurement types, resulting in a pseudonormalized transmitral inflow pattern and in a blunted systolic pulmonary venous flow, independent of the "true" changes of left ventricular (LV) diastolic function.[9, 11, 12] Because of LV preload influence, these indices are unreliable to predict LV filling pressure in the presence of MR.[13] As a result, a combination of the mitral inflow velocities and other Doppler parameters can be performed.[9, 10] New echocardiographic techniques such as Doppler tissue imaging (DTI) and color M-mode Doppler can provide an accurate quantification of LV diastolic function.[14] In particular, the peak early diastolic (E') mitral annular velocities from DTI and the velocity of the early LV flow propagation (Vp) from color M-mode have been demonstrated to be sensitive indices of LV relaxation, relatively independent of preload variations in different clinical settings.[14-17]

In the setting of MR, E can be elevated as a result of increased left atrial pressure, and E' may or may not be normal even though it is thought to be a less load-dependent index. Although the ratios of early (E) transmitral velocity to annular E' (E/E') or Vp (E/Vp) are indicators of LV filling pressures,[15, 17] it remains controversial whether these indices maintain their predictive value in the setting of severe MR. The present study sought to establish whether the correlation between measurements derived from tissue Doppler echocardiography and LVEDP remains valid in the setting of severe MR.

Methods

The present study prospectively enrolled 30 patients (14 men and 16 women), with a mean age of 57.37 ± 13.29 years, who underwent diagnostic cardiac catheterization with a measurement of LV filling pressure. All the patients had severe MR. Exclusion criteria were concomitant aortic valvular disease, mitral stenosis, congenital heart disease, and atrial fibrillation rhythm. In addition, patients with mitral annular calcification were also excluded because of the possible interface of calcifications on the annular DTI signals.

The patients studied in the echocardiography laboratory were imaged in the left lateral decubitus position with Vivid 3 Ultrasound Machine (General Electrics, USA) and MyLab50 XVision (Biosound Esaote, USA) within a maximum of three hours before cardiac catheterization. Two-dimensional measurements were performed according to the recommendations of the American Society of Echocardiography.[18] Left ventricular ejection fraction (LVEF) was measured with the Simpson biplane method. The severity of MR was semi quantified from none (0) to severe (4+) based on integrated assessment. An EF $\geq 50\%$ was defined as normal, and an EF < 50% was defined as reduced.[19] Pulsed Doppler was used to record the transmitral

and pulmonary venous flows in the apical four-chamber view.[20] For DTI measurements, in the apical four-chamber view and pulsed wave Doppler mode for DTI, a 5-mm sample volume was placed at the septal annular site of the mitral valve. The velocities of DTI were recorded at a sweep speed of 100 mm/s for 5 to 10 cardiac cycles. The early diastolic mitral annular (E') and late diastolic (A') velocities by DTI were measured, and the E/E' ratio was computed. The mitral inflow measurements included early mitral filling (E) and late (A) velocities, E/A ratio, deceleration time of E velocity, and duration of A.[20] The cursor was positioned midway between the LV outflow and the mitral inflow to record the isovolumic relaxation time (IVRT). For the pulmonary venous flow, measurements included peak systolic, diastolic, and atrial reversal (AR) velocities and durations.[20] From color M mode, Vp was measured from the slope of the first aliasing velocity in the four-chamber view.[14] The time-interval difference between the onset of the R wave in the QRS complex in the electrocardiogram (ECG) to the transmitral early inflow (E) and the onset of the R wave in the QRS complex in the ECG to the early diastolic (E') velocity of the mitral annulus [T(E-E')], E/Vp and IVRT/T(E-E') ratios, and also the difference in duration between the pulmonary reverse flow and the mitral inflow A wave duration (PVadur-MVadur) were computed as the other DTI indices. Intra-observer variability in measurement ranged from 5% for the DTI indices to 7% for the transmitral indices and 10% for Vp from color M-mode.

A 6F fluid-filled catheter was placed in the LV from the right femoral approach. The fluid-filled pressure was balanced and calibrated with the external pressure transducer positioned at the mid axillary level. All the recordings were performed before the injection of the contrast agent. The measurement of LVEDP was made at the nadir of the atrial contraction wave before the onset of rapid LV systolic pressure rise.[21] In cases without a clear atrial contraction wave, LVEDP was measured at the point 50 msec after the onset of the QRS complex.[22] LV mid diastolic (Pre A) pressure was also measured at the onset of atrial contraction.[23, 24]

The statistical analyses were performed with SAS System Version 9 for Microsoft Windows. The data are expressed as mean value ± SD or percentages. The linear correlations were analyzed by the Pearson method. The stepwise backward multiple linear regression analysis was performed to identify the independent predictors of LVEDP. The normal distribution for LVEDP (dependent variable) was investigated by the Kolmogrov-Smirnov test, and model fitness was assessed by R square. A p value ≤ 0.05 was considered statistically significant, and greater values up to 0.15 were defined as a trend.

Results

All the patients had severe MR: 16 (53.4%) patients had 3+ MR and 14 (46.6%) had 4+ MR. Mitral regurgitation was determined as ischemic MR in 13 (43.3%) patients, rheumatic in 6 (20%), myxomatous degeneration in 10 (33.3%), and degenerative in 1 (3.4%). The mean LVEF was $46.0 \pm 14.5\%$ (range: 16% - 73%). According to the LVEF values, 16 (53.4%) patients were defined to have impaired LV systolic function (EF < 50%), and the remaining 14 (46.6%) patients had normal LV systolic function (EF ≥ 50%). The demographic and baseline echocardiographic characteristics in the patient population are reported in Table 1.

Table 1. Demographic and baseline echocardiographic characteristics (N=30)[*]

Age (y)	57.37±13.29
Female (%)	16 (53.4)
ESV (ml/m²)	71.05±6.80
EDV (ml/m²)	131.84±61.13
Regurgitant area (cm²)	8.47±3.73
Left atrium area (cm²)	24.63±7.62
Vena contracta (mm)	5.63±1.73
Regurgitate volume (ml)	36.05±22.70
EF (%)	46.00±14.95

[*]Data are presented as mean±SD
ESV, End systolic volume; EDV, End diastolic volume; EF, Ejection fraction of left ventricle

The patients with a reduced LVEF had a significantly higher LVEDP compared with those who had a normal systolic function (18.66 ± 11.16% vs. 11.67 ± 6.62%; p value = 0.05); in addition, they had a higher end systolic volume (89.68 ± 38.94 ml/m² vs. 57.18 ± 31.10 ml/m²; p value = 0.019). Systolic (44.50 ± 14.52 cm/s vs. 59.55 ± 17.06 cm/s; p value = 0.07) and diastolic (48.80 ± 15.76 cm/s vs. 65.41 ± 24.39 cm/s; p value = 0.056) pulmonary vein flows were reduced as a trend in the patients with impaired LV systolic function, but there were no significant differences between the two groups in terms of the other Doppler mitral and pulmonary venous flow parameters (Table 2).

The univariate correlations of LVEDP with Doppler echocardiography and DTI measurements in the overall study population are depicted in Table 3. LVEDP correlated with A peak velocity, DTI A' peak velocity, E' peak velocity, and Vp just in the form of trend. The univariate correlations of LVEDP with standard Doppler and DTI measurements were separately assessed in the patients with an EF < 50% and those with an EF ≥ 50%. In these subgroups, LVEDP was correlated significantly with none of the measurements, whereas LVEDP positively correlated in the form of trend with the mitral inflow deceleration time of E (r = 0.48; p value = 0.084) in the patients with an EF ≥ 50%. In the patients with an EF < 50%, LVEDP negatively correlated with DTI A' peak velocity (r = -0.60; p value = 0.029) and E' peak velocity (r = -0.55; p value = 0.05), also positively correlated as a trend with E/E' ratio (r = 0.53; p value = 0.063) and E/A ratio (r = 0.46; p value = 0.11).

Table 2. Doppler echocardiography and Doppler tissue imaging parameters in patients with EF<50% and ≥50%[*]

	EF≥50% (n=14)	EF<50% (n=16)	p value
EF (%)	58.57±6.38	33.56±9.17	<0.01
LVEDP (mmHg)	11.67±6.62	18.66±11.16	0.05
E peak velocity (cm/s)	112.43±26.82	98.00±24.07	0.13
A peak velocity (cm/s)	84.78±47.25	69.62±30.53	0.30
E velocity DT (ms)	216.57±88.76	166.50±74.82	0.10
E/A ratio	1.62±0.72	2.14±2.04	0.37
A velocity duration (ms)	156.71±63.35	130.73±37.43	0.18
IVRT (ms)	77.00±22.82	87.66±29.23	0.29
PVs (cm/s)	59.55±17.06	44.50±14.52	0.07
PVd (cm/s)	65.41±24.39	48.80±15.76	0.05
PV AR velocity (cm/s)	62.75±96.85	24.50±10.46	0.15
E' peak velocity (cm/s)	18.71±27.21	17.93±23.75	0.93
A' peak velocity (cm/s)	19.42±26.98	21.68±29.95	0.83
E/E' ratio	11.57±9.16	12.23±8.99	0.84
Vp (cm/s)	59.38±16.62	51.15±25.49	0.34
E/Vp ratio	2.06±0.75	2.12±0.65	0.81
T(E-E') (cm/s)	31.27±158.29	69.71±70.90	0.42
IVRT/T(E-E') ratio	2.99±10.72	12.25±30.82	0.15
PVadur-MVadur (ms)	0.92±30.55	8.21±40.36	0.53

[*]Data are presented as mean±SD
EF, Ejection fraction; LVEDP, Left ventricular end diastolic pressure; E, Early transmitral velocity; A, Atrial peak velocity; DT, Deceleration time; IVRT, Isovolumic relaxation time; PVs, Pulmonary vein flow systolic; PVd, Pulmonary vein flow diastolic; PV, Pulmonary vein; Vp, Propagation velocity; T(E-E'), Time interval between onset of transmitral early inflow (E) and onset of early diastolic (E') velocity of the mitral annulus; PVadur-MVadur, The difference in duration between the pulmonary reverse flow and the mitral inflow A wave duration

The univariate correlation was assessed separately in the patients with 3+ and +4 MR. In the patients with 3+ MR, LVEDP had a significant negative correlation with DTI A' peak velocity (r = -0.55; p value = 0.032) and E' peak velocity (r = -0.51; p value = 0.049), as well as a significant positive correlation with E/E' ratio (r = 0.64; p value = 0.01). Also, LVEDP correlated as a trend with E/Vp ratio (r = 0.50; p value = 0.095) in these patients. In the 4+ MR patients, LVEDP had a significant negative correlation with A peak

velocity (r = -0.56; p value = 0.05) and DTI A' peak velocity (r = -0.68; p value = 0.015); thus, there was a trend for LVEDP to be correlated with the pulmonary vein flow AR velocity (r = -0.27; p value = 0.147), E/A ratio (r = 0.46; p value = 0.13), and difference in duration between the pulmonary reverse flow and the mitral inflow A wave duration (PVadur-MVadur ; r = 0.48; p value = 0.14).

Table 3. Correlations of left ventricular end diastolic pressure with Doppler and Doppler tissue imaging measurements

	Pearson's correlation factor	p value
E peak velocity (cm/s)	-0.79	0.69
A peak velocity (cm/s)	-0.35	0.07
E velocity DT (ms)	0.04	0.83
E/A ratio	0.27	0.18
IVRT (ms)	-0.49	0.82
PVs (cm/s)	-0.29	0.28
PVd (cm/s)	-0.42	0.84
PV AR velocity (cm/s)	-0.18	0.45
E' peak velocity (cm/s)	-0.30	0.13
A' peak velocity (cm/s)	-0.34	0.08
E/E' ratio	0.24	0.23
Vp (cm/s)	-0.33	0.12
E/Vp ratio	0.21	0.33
IVRT/T(E-E') ratio	0.05	0.83
PVadur-MVadur (ms)	-0.03	0.86

E, Early mitral inflow; A, Atrial mitral inflow; DT, Deceleration time; IVRT, Isovolumic relaxation time; PVs, Systolic pulmonary vein flow ; PVd, Diastolic pulmonary vein flow ; PV AR, Pulmonary vein atrial reversal; E', Early diastolic velocity of the mitral annulus; A', Atrial diastolic velocity of the mitral annulus; Vp, Propagation velocity; T(E-E'), Time interval between onset of transmitral early inflow (E) and onset of early diastolic (E') velocity of the mitral annulus; PVadur-MVadur, The difference in duration between the pulmonary reverse flow and the mitral inflow A wave duration

According to the multiple linear regression analysis, including E/A ratio, E velocity deceleration time, IVRT, E' peak velocity, E/E' ratio, pulmonary vein flow AR velocity, PVadur-MVadur, E/Vp, and IVRT/T (E-E') ratios, the R square (R^2) in this model was 91.7% and E/E' ratio (ß = 1.09, p value < 0.01), E/Vp ratio (ß = 7.87, p value < 0.01), and IVRT (ß = 0.21, p value = 0.01) were shown as the independent predictors of LVEDP (Table 4.)

Discussion

A new development in ultrasonography, DTI applies the Doppler principle (both in the pulsed wave and color modes)

Table 4. Multiple linear regression in the overall population

Determinant of LVEDP	ß Coefficient	p value
E velocity DT (ms)	0.14	0.77
E/A ratio	-0.61	0.75
IVRT (ms)	0.21	0.01
E' peak velocity (cm/s)	-0.01	0.38
E/E' ratio	1.09	<0.01
PV AR velocity (cm/s)	0.01	0.75
E/Vp ratio	7.87	<0.01
IVRT/T (E-E') ratio	0.10	0.84
PVadur-MVadur (ms)	-0.09	0.52

E, Early mitral inflow; A, Atrial mitral inflow; DT, Deceleration time; IVRT, Isovolumic relaxation time; PV AR, Pulmonary vein atrial reversal; E', Early diastolic velocity of the mitral annulus; Vp, Propagation velocity; T (E-E'), Time interval between onset of transmitral early inflow (E) and onset of early diastolic (E') velocity of the mitral annulus; PVadur-MVadur, The difference in duration between the pulmonary reverse flow and the mitral inflow A wave duration

to record tissue velocities. As a result, DTI can be used to quantitate the velocity of mitral annulus displacement during systole and diastole. These velocities reflect the longitudinal vector of myofiber shortening and lengthening, with each corner of the annulus being influenced more by the adjacent LV wall. Earlier studies using M-mode and two-dimensional echocardiography have demonstrated the importance of the longitudinal vector of contraction to global LV function.[25-32] The mitral E wave velocity is directly influenced by left atrial pressure and inversely altered by changes in the time constant of relaxation.[33, 34] It is, therefore, not surprising that by itself, the E wave velocity relates poorly with left atrial pressure,[35-39] given that abnormal relaxation and high filling pressures commonly coexist in the cardiac patient. Nonetheless, it is conceivable that correcting E wave velocity for the influence of relaxation will improve its relation with left atrial pressure. Studies using the early propagation velocity of the LV inflow by color M-mode echocardiography support this hypothesis. The propagation velocity behaves as an index of LV relaxation,[40, 41] and the ratio of E wave velocity to propagation velocity (or its inverse) relates well with LVEDP.[17, 42, 43]

In this study, we observed that in patients with severe MR, the ratio of E wave to E' wave and the division of the E wave velocity by propagation velocity may be usefully applied to predict LVEDP (Figure 1). Furthermore IVRT could predict LVEDP in the presence of MR.

Eustachio Agricola et al.[44] studied 43 patients with severe MR. Catheterization was performed on the same day as echocardiography. They excluded patients with coronary

artery disease. In both groups with an LVEF > 50% and an LVEF < 50%, E/E' was the only independent predictor of LVEDP. Our study is very similar to the above study with respect to methods and results; be that as it may, performing echocardiography within a maximum of 3 hours before catheterization makes our study somewhat superior.
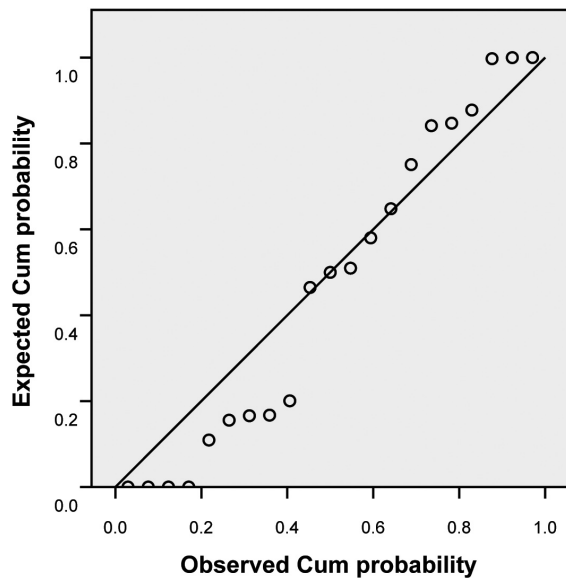

Figure 1. Estimated left ventricular end diastolic pressure by three predictors IVRT, Isovolumic relaxation time; E/E', E peak velocity (cm/s) / E' peak velocity (cm/s); E/Vp, E peak velocity (cm/s) / Propagation velocity

In addition, while we measured E/V_P and found it useful, the above authors did not evaluate this important parameter. Christian Bruch et al.[45] also suggested the ratio of E wave to E' wave for a reliable estimate of filling pressures only in subjects with significant secondary MR to ischemic or dilated cardiomyopathy, but not with primary MR. However, the fact that they evaluated only 11 patients with significant primary MR renders their results unreliable. In line with the aforementioned authors, they failed to measure the important parameter of E/V_P. Jeffery J. Olson et al.[46] recommended that the E/E' ratio not be used to estimate LV filling pressures in patients with severe MR. This study introduced the mitral deceleration time of E as a better indicator of the degree of filling pressure elevation. The major pitfall in this study was the prolonged interval between echocardiography and catheterization (about 72 hours), which makes the results unreliable. In addition, a recent study by Diwan et al.[1] proposed a new parameter derived from the ratio between IVRT and timing intervals from the QRS to E and E'. This ratio was found to correlate well with pulmonary capillary wedge pressure despite significant mitral valve disease. In our study, this parameter had no significant correlation with LVEDP. One previous study found a strong correlation between filling pressure and the difference between mitral A wave and pulmonary vein A-wave duration.[11] However, we

did not find a similar condition as regards this parameter.

Conclusion

The current investigation demonstrated that excluding the patients with atrial fibrillation and multivalvular disease, the ratio of E wave velocity to Vp and E/E' ratio and also IVRT could be applied properly to estimate LVEDP in MR patients even in the setting of severe MR.

Acknowledgment

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