Estimation of LV End-Diastolic Pressure Using Color-TDI and Its Application to Noninvasive Quantification of Myocardial Wall Stress

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Background: This study was undertaken to evaluate early-diastolic annular velocity (Ea) by color-TDI, combined with the early transmitral filling velocity (E) by pulsed Doppler echocardiography for estimation of left ventricular end diastolic pressure (LVEDP). We applied LVEDP to noninvasive quantification of myocardial wall stress in end-diastole. Forty-one coronary artery disease (CAD) patients with sinus rhythm underwent echocardiography and cardiac catheterization evaluated in the study. Methods: First linear regression analysis was performed to assess the relationships between E/Ea and LVEDP. Second LVEDP estimation with these two methods was tested prospectively in 59 additional CAD patients, and average end-diastolic wall stress was calculated at rest by measuring the principal radii, the thickness of the LV segments, and the estimated LVEDP. The results were compared to the wall stress that was calculated using catheter-measured LVEDP. Linear regression analysis was performed to assess the relationships between calculated wall stress using Doppler-estimated LVEDP (WSEP) and calculated wall stress using catheter-measured LVEDP (WSMP). Results: The results showed that LVEDP had a strong correlation to the lateral E/Ea (r = 0.85; P < 0.001) and medial E/Ea ratios (r = 0.73; P < 0.001). No significant differences were found between the WSEP and WSMP. There were highly significant correlations (at least r = 0.85, P < 0.001) between the WSMP and WSEP at all the myocardial sites. Conclusions: The current data demonstrate that the lateral E/Ea ratio obtained by Doppler echocardiography and color-TDI is a powerful estimator of LVEDP in CAD patients and provides pressure information required for noninvasive quantification of LV myocardial wall stress with reasonable accuracy in diastole. (ECHOCARDIOGRAPHY, Volume 26, April 2009)

LVEDP, color-TDI, myocardial wall stress

Chronic coronary artery disease (CAD) is most commonly due to obstruction of the coronary arteries by atherosclerotic plaque.[1] In order to provide the clinician with more sophisticated diagnostic techniques, one must gain a better understanding of the mechanics and performance of the myocardium. This requires analysis of the forces and stresses developed in the wall of the left ventricle (LV).[2] Systolic and diastolic wall stress has been previously determined by combining simultaneous measurements of left ventricular pressures with angiographic and echocardiographic measurements of left ventricular radius and wall thickness.[3–5] These methods, in addition to being cumbersome and time consuming, require invasive procedures. A simple noninvasive and accurate index of wall stress would be desirable. The noninvasive assessment of left ventricular end-diastolic pressure (LVEDP) provides important information on the hemodynamic status[6] and may be an important clinical tool in these patients, taking advantage of noninvasive quantification of myocardial wall stress in end-diastole. Recently, the ratio of the early transmitral filling velocity (E) to early-diastolic mitral annular velocity (Ea) has been proposed as a novel index to assess left ventricular filling pressure. The primary advantage of Doppler measurement is its ability to noninvasively calculate hemodynamic indexes.[7–11]

The aims of this study were as follows: (1) The first aim was to determine how the ratio

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of E measured by pulsed Doppler echocardiography to Ea of the lateral or medial mitral annulus measured by color tissue Doppler imaging (color-TDI) (or the E/Ea ratio) correlates with LVEDP in CAD patients. An advantage of color-TDI is its ability to obtain data from more than one site at a given time and the ability to quantify mean myocardial velocities.[12] Therefore, specific sample volumes for acquiring velocity traces can be measured simultaneously. (2) The second aim was to determine the role of color-TDI in noninvasive estimation of LVEDP, apply it for quantification of end-diastolic myocardial wall stress in these patients as an important index in evaluating myocardial performance.

Materials and Methods

Study Population

One hundred CAD male patients with significant or moderate left anterior descending coronary artery (LAD) stenosis in the proximal portion (41 patients used for regression analysis and 59 patients were used for the test group and wall stress assessment), aged from 40 to 60 years old with sinus rhythm, were evaluated in this study. Exclusion criteria included a history of cardiovascular surgery, LV hypertrophy, pacemaker rhythm, severe valvular disease, or diabetes. All subjects gave informed consent prior to participation in the study. The study protocol has been approved by the ethics committee of Tarbiat Modares University and Shaheed Rajaie Heart Research Center.

Echocardiographic and Catheterization Studies

All echocardiography studies were done with a Vivid7 digital ultrasound scanner (GE, Milwaukee, WI, USA) equipped with an M3S transthoracic sector transducer with harmonic capability. The images were acquired with the subjects at rest and lying in the lateral decubitus position. Two-dimensional ECG was superimposed on the images. TDI was performed using standard transthoracic apical two- and four-chamber views according to the guidelines of the American Society of Echocardiography (ASE).[13] The sample volume of the pulsed wave Doppler was placed between the tips of the mitral leaflets in the apical four-chamber view, and early transmitral flow velocity was obtained (Fig. 1A).
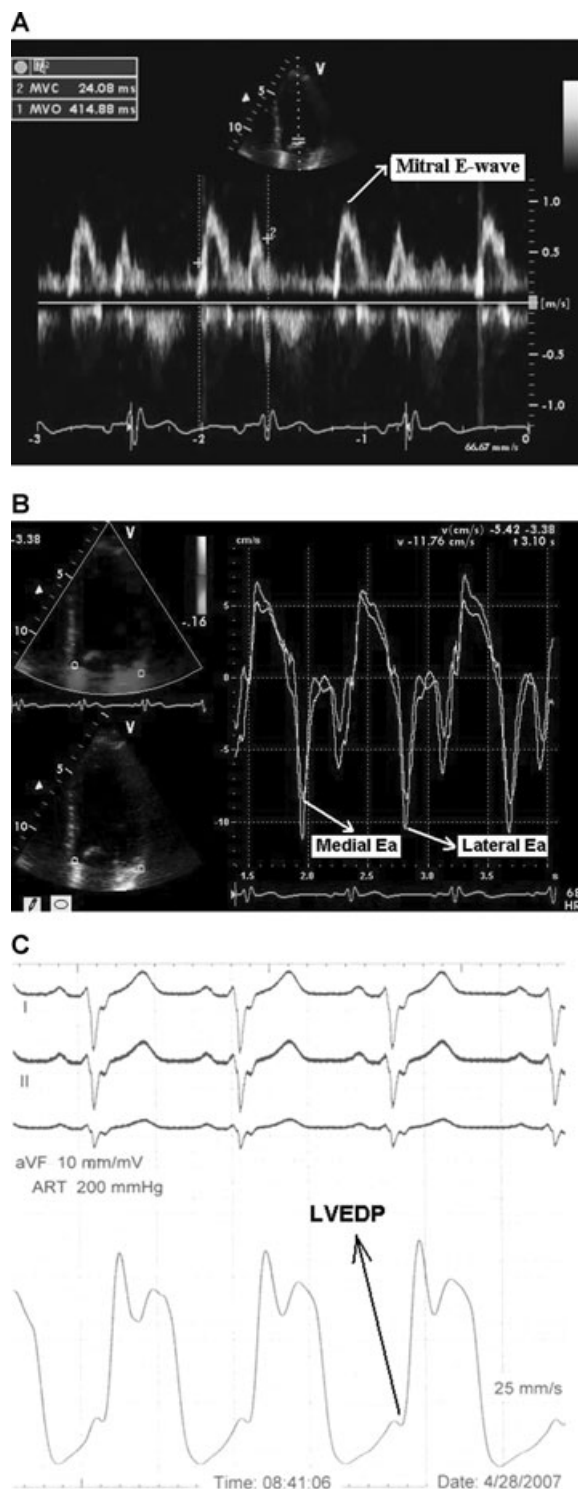
Figure 1. A. *Doppler echocardiography of mitral filling pattern.* **B.** *Medial and lateral mitral annular velocities by color-TDI.* **C.** *LV pressure traces from a CAD patient and the pressure portion utilized for determination of LVEDP.*

Color Doppler myocardial imaging (CDMI) was performed by adjusting the signal filters until they reached a Nyquis limit of 16 cm/sec. CDMI raw data recorded at depth of 16 cm, a frequency of 2.4 MHz, and frame rates higher than 150 frames/sec throughout the three cardiac cycles and stored digitally as cine-loop format on the memory of the scanner. Offline analysis was performed by quantitative analysis software equipped to obtain regional myocardial velocity. Two digital 5 mm sample volumes were placed within the medial and lateral mitral annulus and tissue velocity curves were acquired from the same heartbeats (Fig. 1B). The interventricular septum and anterior wall thickness and LV radii at end-diastole were determined from four- and two-chamber B-mode echocardiograms. The left ventricular ejection fraction (LVEF) was measured using Simpson's biplane method by measuring end-diastolic and end-systolic volumes in 2D images. Doppler echocardiography (color-TDI and transmitral flow measurements) was done immediately after the catheterization came to an end. The catheterization for LVEDP measurement was performed using a pigtail fluid-filled catheter attached to a pressure transducer. The transducer was balanced before acquisition of hemodynamic data with zero level at the mid-axillary line, and baseline pressure measurements were acquired before cardiac catheterization. Subsequent to LV pressure trace obtained, LVEDP was determined before the rise in systolic pressure with the average of three cardiac cycles (Fig. 1C).

Echocardiographic analysis was performed by an experienced observer who was unaware of the patient's catheterization and angiographic outcomes. All Doppler data and LVEDP were measured at end-expiration, and the average of three cardiac cycles was taken into account for analysis in this study.
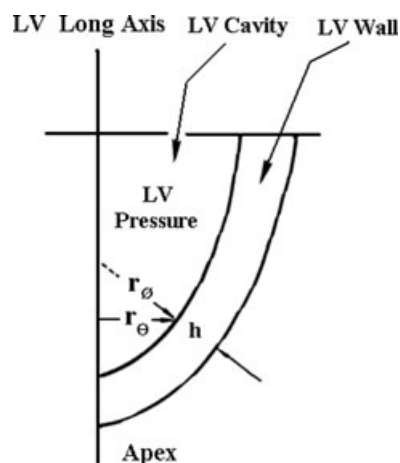
Regional Wall Stress Calculation

Wall stress is the force exerted on the myocardium per unit area and is proportional to the LV pressure and the LV cavity dimension and inversely proportional to wall thickness.[14] In this study, the radii and thickness of the left ventricle were measured from the apical four- and two-chamber echocardiograms with the patient lying in the left lateral position by freezing the 2D image at end-diastole. In these echocardiograms, septal and anterior wall radii and thickness quantities were mea-

sured at the base, mid, and apical segments, respectively, by averaging three consecutive heartbeats. Before the radii measurements can be carried out, the LV long axis must be located. The LV long axis was defined as a line drawn from the apex to meet the mitral annulus plane at a right angle. Meridional and circumferential radii (principal endocardial radii) were determined for each wall segment by considering each region to be locally ellipsoidal (Fig. 2). From these two radii, local wall thickness and LV pressure, midwall tension that is the average of the circumferential, and meridional tension can be calculated for each LV segment using the formula proposed by Deanda et al.:[15,16]

$$T = \text{LVEDP} \times R_\theta \left(\frac{3}{4} - \frac{R_\theta}{4R_\phi} \right) \qquad (1)$$

where LVEDP, T, R_ϕ, and R_θ are left ventricular end-diastolic pressure, midwall tension, midwall meridional, and circumferential radii at the equator of each segment, respectively (Fig. 2). Derivation of regional LV average wall stress (kdyn/cm^2) is then

$$\sigma = 1.332 \times \text{LVEDP} \times R_\theta \left(\frac{3}{4h} - \frac{R_\theta}{4hR_\phi} \right), \quad (2)$$

Figure 2. *A diagram depicting the variables used to calculate wall stress. An illustration of how local LV wall geometry can be described by wall thickness (h), endocardial circumferential radius of curvature (r_θ) and endocardial meridional radius of curvature (r_ϕ).*

where σ and h are the average wall stresses and regional wall thickness, respectively. Thus,

$$R_\theta = r_\theta + \frac{h}{2}$$

$$R_\phi = r_\phi + \frac{h}{2}, \tag{3}$$

where r_θ and r_ϕ are endocardial circumferential and meridional radii, respectively. In this study, LVEDP was measured directly and was also estimated according to the regression equation obtained in this study by using the Doppler E/Ea ratio.

Statistical Analysis

All data are expressed as mean ± standard deviation (SD). Linear regression analysis was used to correlate continuous variables with each other and the correlation coefficient was estimated to assess relationships between E/Ea and LVEDP and also between calculated wall stresses using measured and estimated LVEDP. Comparison of segmental wall stress calculated with estimated and measured LVEDP differences was performed by a paired t-test. Results were considered significant when the P-value was <0.05.

Bland–Altman analysis[17] with the 95% limit of agreements (LOA) (i.e., mean difference ± 2 SD of the difference) was calculated to assess agreements between catheter-measured and Doppler-estimated LVEDP and also between the two wall stresses calculated. The receiver operating characteristic (ROC) curve, which is defined as a plot of test sensitivity versus its 1-specificity, was used to evaluate the quality or performance of the diagnostic modality, to compare the accuracy and to establish the optimal cut points.[18] Intraobserver and interobserver variabilities were differences between measurements expressed as a percentage of the error of the means. Independent sample t-tests were used to assess differences in wall stress between patients with significant stenosis (>70%) and moderate stenosis (50–70%). All of the statistical analyses were performed using the SPSS software package (SPSS Inc., Chicago, IL, USA).

Results

The clinical, echocardiographic, and hemodynamic characteristics of the subjects evaluated in this study including CAD patients used for regression analysis (CAD group 1) and the test

group (CAD group 2) are presented in Table I. The groups were comparable in regard to age, sex, heart rate, and LV ejection fraction, body mass index, and systolic and diastolic blood pressure (P = NS). In CAD group 1 and CAD group 2, 34 (58%) and 22 patients (56%) had LVEF lower than 50%, respectively.

E/Ea Ratio and LVEDP Estimation

Figure 3 shows correlations between catheter-measured LVEDP and the E/Ea ratio in 41 CAD patients. A LVEDP of 14 ± 7 mmHg (range, 5–35 mmHg) significantly correlated with the lateral E/Ea (r = 0.85; P < 0.001) and medial E/Ea ratio (r = 0.73; P < 0.001), and LVEDP could be estimated with lateral and medial E/Ea velocities as follows: 0.44 + [1.36 × (lateral E/Ea)] or 3.39 + [0.90 × (medial E/Ea)], respectively. Both lateral and medial E/Ea ratios significantly correlated with LVEDP, although the lateral E/Ea ratio had the stronger relationship with LVEDP (r = 0.85 vs. r = 0.73, P < 0.001). For Bland–Altman analysis, the difference between Doppler-estimated and catheter-measured LVEDP was plotted against the average of both observations. The middle line indicates the average difference between the two methods, whereas the outer lines represent 2 SD or the 95% limits of agreement (LOA). The mean difference between the Doppler estimate and catheter measurement

TABLE I

Demographic, Hemodynamic, and Echocardiographic Characteristics of Study Subjects

Variables	Values (Means ± SD or Number)	
	CAD Group1*	CAD Group2**
Age (years)	51 ± 5	52 ± 5
No. of subjects (male)	41	59
No. of patients with >70% LAD stenosis	21 (51%)	30 (51%)
No. of patients with 50–70% LAD stenosis	20 (49%)	29 (49%)
Systolic BP (mmHg)	134 ± 7	133 ± 9
Diastolic BP (mmHg)	80 ± 5	80 ± 5
LVEF (%)	46 ± 11	47 ± 10
BMI (kg/ m²)	24.5 ± 1.7	24.6 ± 1.5
Heart rate (beats/min)	71 ± 13	74 ± 14

BP = blood pressure, LVEF = left ventricular ejection fraction, BMI = body mass index.
*CAD subjects used for linear regression analysis.
**CAD subjects used to test LVEDP estimation and wall stress calculations.
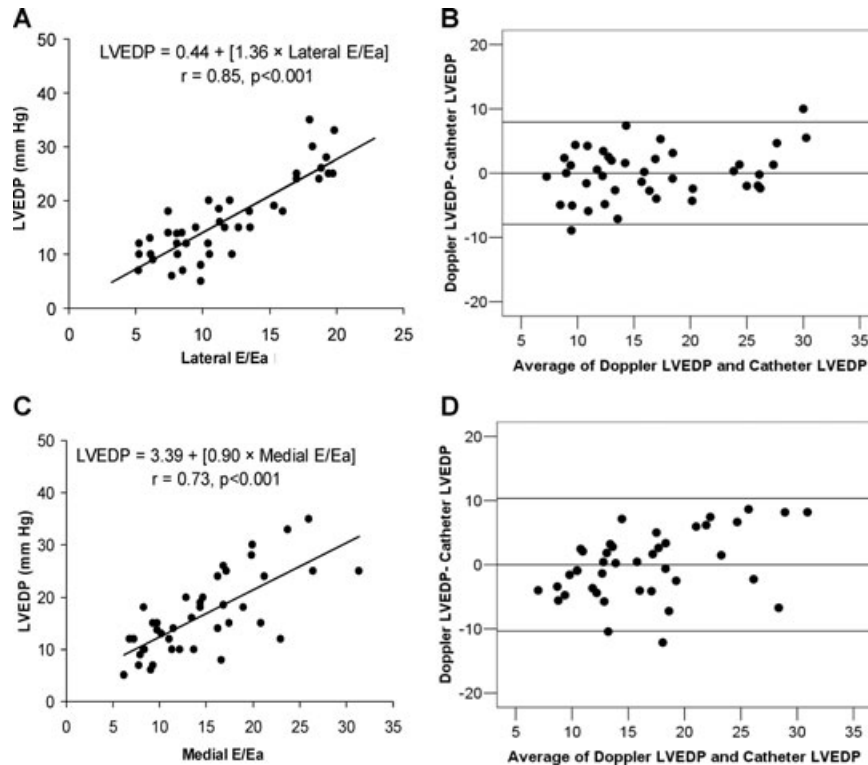
Figure 3. A. *Left upper and* **C.** *lower correlation of catheter-measured LVEDP with the lateral and medial E/Ea ratio, respectively, in 41 CAD patients.* **B.** *Right upper and* **D.** *lower relative Bland–Altman plots of the difference between Doppler-estimated and catheter-measured LVEDP.*

was 0.0 ± 5.2 mmHg when the medial E/Ea was used, and 0.0 ± 3.8 mmHg with the lateral E/Ea (Bland–Altman plots in Figs. 3B and 3D). Intraobserver and interobserver variabilities were found 5.7% and 6.5%, respectively, for the E/Ea ratio.

A value of ≥ 15 mmHg was chosen as a definition of significant elevation of LVEDP,[10] and the area under the ROC curve (AUC) for prediction of elevated LVEDP was computed for lateral and medial E/Ea (Fig. 4). For lateral E/Ea, a ratio ≥ 10.5 had the best combination of sensitivity (86%) and specificity (94%) for LVEDP ≥ 15 mmHg and area under receiver operating characteristic curve (AUC) was 0.92. A lower ratio (≥ 9) had a higher sensitivity (93%) with a lower specificity (81%), whereas a ratio ≥ 11 was more specific (96%) but less sensitive (75%). For medial E/Ea, a ratio ≥ 11.7 had a sensitivity of 82% with a specificity of 77% and AUC was 0.84 (Fig. 4). A lower ratio (≥ 10) had a higher sensitivity (86%) with a lower specificity (48%), whereas a ratio ≥ 13 was more specific (84%) but less sensitive (71%).

The equations derived to estimate LVEDP were tested in 59 additional CAD patients using the same criteria as the initial group that underwent echocardiography and cardiac catheterization to obtain Doppler and pressure data. Doppler measurements and calculations were made without knowledge of hemodynamics. The estimated LVEDP by the lateral E/Ea ratio was used for noninvasive quantification of myocardial wall stresses.

Wall Stress Calculation

Regional average end-diastolic wall stress that is the average of the circumferential and meridional wall stress is calculated and presented in Table II for the base, mid, and apical segments of LV anterior and septum walls using equation 2. In this study, we chose the anterior and septum wall segments for regional wall stress assessment because the aim was to assess the myocardial function in the LAD coronary disease. The wall stress was calculated not only by catheter-measured LVEDP (WSMP) but
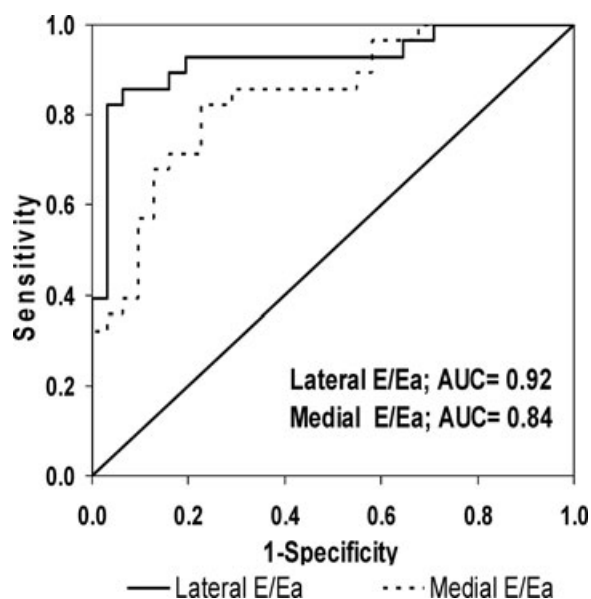
Figure 4. *ROC curve analysis of lateral and medial E/Ea for prediction of LVEDP ≥15 mmHg.*

also by Doppler-estimated LVEDP (WSEP) in all patients. Since our results showed that the correlation coefficient between LVEDP and lateral E/Ea was higher than that medial E/Ea (Figs. 3A and C) and its LOA was fewer than medial E/Ea (Figs. 3B and D), we applied only the lateral E/Ea ratio to the estimation of LVEDP and quantification of myocardial wall stress.

No significant differences were found between the WSEP and WSMP at the base, mid, and apical segments of anterior and septum walls. At the anterior base, WSMP was 30.9 ± 15.2 kdyn/cm^2 compared with 32.0 ± 14.5 kdyn/cm^2 for WSEP (P = NS). Similarly, WSMP at the anterior mid was 31.6 ± 17.1 kdyn/cm^2 compared with 32.7 ± 16.8 kdyn/cm^2 for WSEP (P = NS), and WSMP at the anterior apex was 25.3 ± 13.3 kdyn/cm^2 compared with 26.2 ± 12.9 kdyn/cm^2 for WSEP (P = NS). At the septum base, WSMP was 27.1 ± 12.9 kdyn/cm^2 compared with 28.1 ± 13.0 kdyn/cm^2 for WSEP (P = NS). Similarly, WSMP at the anterior mid was 24.6 ± 12.7 kdyn/cm^2 compared with 25.5 ± 12.0 kdyn/cm^2 for WSEP (P = NS), and WSMP at the anterior apex was 23.8 ± 11.9 kdyn/cm^2 compared with 24.6 ± 11.7 kdyn/cm^2 for WSEP (P = NS). There were significant correlations between the WSMP and WSEP at all the myocardial sites (Table II). The correlation of coefficients (with the significant P-value), mean differences (MD) with related standard deviations at base, mid, and apical segments of anterior and septum walls are presented in Table II. Intraobserver and interobserver variabilities were found 6.8% and 7.5% for wall stress calculation, respectively.

The comparison of the calculated wall stress between patients with significant and moderate stenosis showed that there are statistically significant differences in all anterior and septum wall segments (Table III).

TABLE II

Average End-Diastolic Myocardial Wall Stress Calculated Using Catheter-Measured (WSMP) and Doppler-Estimated LVEDP (WSEP) and the Comparisons of Results

| | Calculation Results | | Comparison Results | | |
Segments	WSEP	WSMP	P-value*	MD	r (P-value**)
Lateral (anterior wall)					
Base	32.0 ± 14.5	31.0 ± 15.2	0.311	0.06 ± 7.6	0.87 (P < 0.001)
Mid	32.7 ± 16.8	31.6 ± 17.1	0.305	0.05 ± 7.8	0.89 (P < 0.001)
Apex	26.2 ± 12.9	25.3 ± 13.3	0.282	0.09 ± 6.3	0.88 (P < 0.001)
Septum wall					
Base	28.1 ± 13.0	27.1 ± 12.9	0.287	0.13 ± 6.8	0.85 (P < 0.001)
Mid	25.5 ± 12.0	24.6 ± 12.7	0.295	0.10 ± 6.3	0.87 (P < 0.001)
Apex	24.6 ± 11.7	23.8 ± 11.9	0.326	0.07 ± 6.2	0.85 (P < 0.001)

WSEP = calculated wall stress using estimated LVEDP (kdyn/cm^2); WSMP = calculated wall stress using measured LVEDP (kdyn/cm^2); MD = mean difference or bias (kdyn/cm^2) and r = correlation of coefficient.
*t-test's P-value.
**Correlation of coefficient's P-value.

TABLE III

Comparison of the End-Diastolic Myocardial Wall Stress (kdyn/cm^2) between Patients with Significant and Moderate Stenosis

Segments	Group 1 (n = 30)	Group 2 (n = 29)	P-value*
Anterior wall			
Base	27.4 ± 13.1	34.0 ± 11.9	0.047
Mid	27.2 ± 13.5	35.0 ± 14.6	0.041
Apex	21.7 ± 10.7	28.3 ± 10.8	0.025
Septum wall			
Base	23.7 ± 11.6	30.2 ± 10.4	0.029
Mid	21.3 ± 10.3	27.6 ± 10.3	0.023
Apex	20.9 ± 11.5	26.3 ± 8.3	0.048

Group 1 = patients with moderate stenosis
Group 2 = patients with significant stenosis
* *t*-test's P-value.

Discussion

Although transmitral filling patterns are fundamental to the assessment of LV diastolic function, the conventional mitral inflow velocities have a weak correlation to filling pressures[19] with several major shortcomings. These velocities may change rapidly with variations in preload and pseudonormalization of the inflow pattern despite moderate elevation of filling pressures.[20] To overcome this, less load-dependent indices of LVEDP can be used, usually in combination with transmitral parameters. One of the most extensively validated indices is the tissue Doppler assessment of mitral annulus motion in diastole.[21] Because mitral E-wave velocity (E) is dependent on relaxation and preload, and since mitral annular early-diastolic velocity by TDI (Ea) is related to LV relaxation, the ratio of E to Ea has been used to predict filling pressures.[11] Several investigators have demonstrated that the combination of E and Ea bears a linear relationship to filling pressures measured with cardiac catheterization. This relationship has held true in patients with tachycardia, atrial fibrillation, and a broad range of cardiovascular diseases.[7,9,11,22] To our knowledge, this study demonstrates the use of color-TDI in estimating the LVEDP in patients with CAD as well as the use of the color E/Ea ratio, which is a relatively novel finding. We observed a definite relationship between the E/Ea variables and invasive LVEDP measurements (Figs. 3A and 3C).

It can be concluded from our experience that the noninvasively obtained Doppler E/Ea ratio is an interesting application of TDI, and provides an index of LVEDP in CAD patients, which can be measured using CDMI. Based on initial encouraging results (LVEDP related strongly to lateral E/Ea, r = 0.85; P < 0.001), we plan to perform the present study to identify noninvasive myocardial wall stress in end-diastole. This study examines the usefulness of noninvasive estimation of LVEDP for noninvasive quantification of myocardial wall stress in CAD patients. This technique is also offered due to its clinical attractive usefulness.

The importance of the assessment of the properties of the left ventricle (LV) and ventricular muscle and their quantification has been evaluated in terms of myocardial wall stress. These calculations have been used in the investigation of various heart diseases.[23–26] Wall stress may be calculated at the diastolic phase of the cardiac cycle although this calculation requires invasive measurements of LV blood pressure. LVEDP is measured routinely in the cardiac catheterization laboratory during retrograde left heart catheterization.[27] In this study, we apply the noninvasive estimation of LVEDP for quantification of end-diastolic myocardial wall stress in patients with CAD. The average end-diastolic wall stress was calculated at LV anterior and interventricular septum wall segments using the formula proposed by Deanda et al. with taking into account LV pressure, regional wall thickness, and meridional and circumferential regional radii of curvature. The stress calculated by this formula represents the mean value of the average stress across the thickness of the LV wall, with local maximal stress occurring on the endocardial and local minimal stress on the epicardial surface. The assumptions used in this analysis were as follows: (1) the myocardium was isotropic, linearly elastic, and homogeneous; (2) bending moments were ignored; (3) the meridional and circumferential midwall radii of curvatures could be derived as the endocardial radius of curvature plus one-half of the wall thickness; (4) the midwall LV wall stress is an average of the epicardial and endocardial stresses; and (5) the only load on the ventricle was an internal pressure.[15]

Clinical Implication

Several approaches using the basis of Doppler modalities (pulse-wave Doppler, color

M-mode Doppler, and pulsed-TDI) have been proposed as useful methods for the evaluation of left ventricular filling.[9,19,28] However, there is no report that shows the role of color-TDI in estimating LVEDP. The high sensitivity and specificity of TDI, as well as its simplicity, inexpensive and noninvasive specialty encouraged us to use this method for estimating the LVEDP in CAD patients and apply the results for calculating myocardial wall stress in diastole. LV wall stress has been traditionally assessed by analytic methods that are based on simplified geometric models. A simple noninvasive and accurate index of wall stress would be desirable. Besides LV blood pressure, the regional stress equation requires measurements of local wall thickness and principal curvatures. These parameters can be measured directly in two-dimensional or M-mode ultrasound images. Myocardial ischemia and many other cardiac pathologies are associated with regional ventricular dysfunction. Availability of LVEDP and wall stress may be an important tool in the diagnosis and treatment of heart diseases and in the differentiation of CAD patients with different stenosis.

Evaluation of diastolic function is an important role of clinical echocardiography, and our results emphasize end-diastolic myocardial wall stress in these patients as an important index in evaluating myocardial performance noninvasively. The method presented here could easily be employed in a clinical setting such as cardiac ultrasound clinic to assess LV pressure and myocardial wall stress in diastole. Regional stress assessment might give additional information since it can estimate regional mechanical work combined with strain measurements.

Limitation

In this study, the E/Ea in the assessment of left ventricular diastolic function is not well defined. The ranges of these parameters need to be determined in various age and disease groups. Annular velocities may vary with the site of sampling, and thus, the utility of this method is dependent on the location of the sample volume. Tissue Doppler recordings were obtained only from the lateral and medial mitral annulus, and other mitral segments were not evaluated in this study. We chose the lateral and medial aspects of the mitral annulus because these sites are easy to obtain from the apical window and, in contrast to the parasternal window, the velocities should not be influenced by anteroposterior translation.[7] The main disadvantage of color-TDI is the requirement for an offline analysis for quantifying myocardial velocities and inability to provide instantaneous display of the Doppler information, which can be time consuming. In this study, E/Ea was calculated using color-TDI. Further studies are needed to compare E/Ea-calculated values using pulsed-TDI and E/Ea-calculated values using color-TDI to noninvasive estimated LVEDP.

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