Evaluation of Left Anterior Descending Coronary Artery Stenosis Severity From Myocardial End-diastolic Wall Stress Estimated by Tissue-Doppler Imaging

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ABSTRACT: *Purpose.* To identify patients with significant coronary artery disease by the noninvasive quantification of myocardial wall stress in diastole.

Methods. We studied 60 male subjects in sinus rhythm with significant (n = 30) or moderate (n = 30) proximal left anterior descending coronary artery stenosis, and 30 healthy subjects (control group). The average end-diastolic wall stress was estimated at left ventricle anterior and interventricular septum wall segments from regional wall thickness, meridional and circumferential regional radii of curvature, and noninvasively estimated left ventricular end-diastolic pressure.

Results. There were significant differences in left ventricular end-diastolic pressure between patients and controls ($p < 0.05$). End-diastolic myocardial wall stress was significantly different between patients with significant and moderate coronary stenosis and healthy subjects in all anterior and septal wall segments ($p < 0.05$) except for the anterior wall at mid level. The receiver-operating characteristic curves showed that septum apex wall stress has the highest discriminatory power for predicting significant stenosis versus healthy coronary artery with 83% area under the curve.

Conclusions. Estimated end-diastolic myocardial wall stress may help in evaluating regional myocardial dysfunction due to coronary artery disease. © 2013 Wiley Periodicals, Inc. *J Clin Ultrasound* **41**:297–304, 2013; Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jcu.22047

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Coronary artery disease (CAD) is the primary cause of death in the world. In the USA, an acute coronary event is the initial presentation of coronary artery disease in 650,000 previously asymptomatic patients every year.[1] Approximately one-third of individuals dying annually from sudden cardiac death have no identifiable Framingham risk indices that would predict a future severe cardiac event.[2] Therefore, the early detection of coronary heart disease is of great potential importance.

To provide the clinician with more advanced 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), which has been evaluated in terms of myocardial wall stress.[3] Systolic and diastolic wall stress has been determined by combining simultaneous measurements of left ventricular pressures with angiographic and echocardiographic measurements of left ventricular radius and wall thickness.[4–7] These methods, in addition to being cumbersome and time-consuming, require invasive procedures. The noninvasive

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assessment of left ventricular end-diastolic pressure (LVEDP) provides important information on the hemodynamic status[8] and may be an important clinical tool in these patients, offering the possibility of noninvasively quantifying myocardial wall stress in end-diastole. Wall stress may be calculated at the diastolic phase of the cardiac cycle; however, this calculation requires measurements of LV blood pressure. Recently, we demonstrated[7] the possibility of using color-coded tissue Doppler imaging (color-TDI) for the estimation of LVEDP in patients with CAD. An advantage of color-TDI is its ability to obtain simultaneously data from several sites (for instance, the lateral and medial parts of the mitral annulus) and the ability to quantify mean myocardial velocities.[9]

Therefore, the aims of our study were to estimate noninvasively and compare the regional myocardial wall stress in diastole between patients with significant coronary stenosis, moderate coronary stenosis, and healthy subjects.

MATERIALS AND METHODS

Sixty male CAD patients in sinus rhythm with significant (>70% diameter reduction; n = 30) or moderate (50–69% diameter reduction; n = 30) proximal left anterior descending coronary artery (LAD) stenosis and 30 healthy male subjects (controls) were enrolled in the study. Patients with myocardial infarction, patients receiving medical treatment other than antihypertensive drugs, and patients without any visual regional wall motion abnormality were not included. Exclusion criteria were a history of cardiovascular surgery, LV hypertrophy (LV mass/body surface area >80 g/m^2), pacemaker rhythm, severe valvular disease, and diabetes. The coronary angiography indications were angina onset, positive exercise tolerance test, or exertional chest pain.

The subjects in the control group did not undergo coronary angiography and were selected on the basis of Framingham study criteria[10,11] as healthy subjects with normal physical examination, electrocardiography (ECG), echocardiography, and no history of cardiovascular disease, angina, hypertension, or diabetes. Blood pressure was recorded in the left radial artery of the patient in a supine position, using a semiautomatic device (Riester 0124, Jungingen, Germany) before the echocardiographic examination. Systolic and diastolic blood pressures were measured three times for each subject and averaged. All subjects gave their informed consent before their participation in the study. This study was performed from June 2007 to January 2009 through random sampling and approved by the ethics committee of Tarbiat Modares University and Shaheed Rajaie Heart Research Center.

The patients underwent coronary angiography performed by expert cardiologists, through the femoral approach, using standard Judkin's technique with 6-F catheters. Selective injection of left and right coronary arteries was performed in multiple orthogonal views. The culprit lesion was identified by angiographic criteria for severity of stenosis. The percentage of luminal diameter stenosis was calculated as (1 − residual diameter)/lumen diameter at the most normal-appearing region proximal to the stenosis. Images were acquired and digitally recorded in at least two orthogonal optimal projection angles at 25 frames per second (Siemens, AXIOM Artis dBA eco, Erlangen, Germany). Transthoracic conventional and TDI echocardiography examinations were performed between 1 and 2 days after coronarography.

All echocardiographic studies were performed with a Vivid7 digital sonographic scanner (GE, Milwaukee, WI) equipped with an M3S transthoracic sector transducer with harmonic imaging capability. The images were acquired with the subjects at rest and lying in the left lateral decubitus position. Two-dimensional (2D) ECG was superimposed on the images and end-diastole was considered at the peak R-wave of the ECG. Left ventricular ejection fraction was calculated using Simpson's biplane method by measuring end-diastolic and end-systolic volumes in 2D images. TDI was performed using standard transthoracic apical two- and four-chamber views according to guidelines of the American Society of Echocardiography.[12]

The sample volume of the pulsed-wave Doppler was placed between the tips of the mitral leaflets with ultrasonic beam alignment to flow in the apical four-chamber view, and early transmitral flow velocity was obtained. Color Doppler myocardial imaging was performed by adjusting the signal filters until they reached a Nyquist limit of 16 cm/s. Color Doppler myocardial imaging raw data were recorded at depth of 16 cm, 2.4-MHz emitting frequency, and >150/s sample rate, during three cardiac cycles, and stored digitally as cine-loop. Off-line analysis was performed by the imbedded quantitative analysis software, and regional myocardial velocity was measured on tissue velocity curves from the 5-mm sample volume placed within the lateral mitral annulus.[7,8,13] The gain was

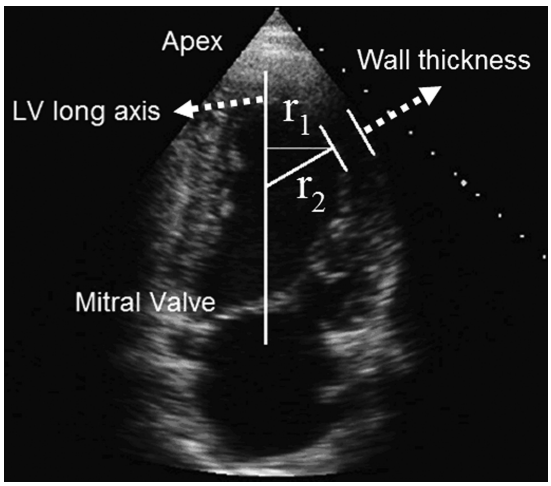

FIGURE 1. The local geometry of left ventricular (LV) wall. Endocardial circumferential radius (r_1) and endocardial meridional radius (r_2) are the variables used to calculate wall stress.

minimized so that the onset of the early-diastolic mitral annulus displacement could be reliably identified. ECG analysis was performed by an experienced observer who was unaware of the patient's angiographic results. All Doppler data were measured at end-expiration, and the average of three cardiac cycles was taken into account for analysis in this study.

The force per unit area of myocardium, or wall stress, is proportional to the LV blood pressure and dimensions, and inversely proportional to its wall thickness.[14] In this study, the radii and thickness of the left ventricular segments were measured on frozen apical four- and two-chamber 2D ECG images at end-diastole, at base, and at mid and apical segments, respectively, and measurements on three consecutive heartbeats were averaged. Endocardial meridional and circumferential radii were determined for each wall segment by considering each region to be locally ellipsoidal. The average end-diastolic wall stress (σ) was calculated using the formula proposed by Deanda et al,[15,16] taking into account regional wall thickness (h), mid wall meridional (r_φ) regional radii, and circumferential (r_θ) regional radii of curvature at the each segment, and LVEDP (Figure 1):

$$\sigma = 1.332 \times LVEDP \times \frac{r_\theta}{4h}\left(3 - \frac{r_\theta}{r_\varphi}\right)$$

where r_θ and r_φ are endocardial circumferential radius, $(r_1) + (h/2)$, and endocardial meridional radius $(r_2) + (h/2)$, respectively.

We estimated LVEDP noninvasively from the lateral early-diastolic annular velocity measured with color-TDI and mitral flow early velocity measured with pulsed Doppler echocardiography (lateral E/Ea ratio), as follows, and averaged on three consecutive heart beats[7]:

$$LVEDP = 0.44 + [1.36 \times (lateral E/Ea)]$$

It has been shown that the correlation coefficient between LVEDP and lateral E/Ea is higher and its limits of agreement are smaller than those of other mitral segments.[7,8,13,17] Therefore, we used only lateral E/Ea ratio for the estimation of LVEDP and quantification of myocardial wall stress.

All data are expressed as mean ± SD. Data were tested for normal distribution and homogeneity of variance by the Kolmogorov-Smirnov and Levene tests, respectively. One-way analysis of variance was used to test the hypothesis that the means of the three study groups were equal and post-hoc least-significant-differences test was used for multiple comparisons. A p value less than 0.05 was chosen as the level of statistical significance.[18,19]

The receiver operating characteristic (ROC) curve (ie, the plot of test sensitivity versus 1-specificity) was used to evaluate the quality or performance of the diagnostic modality and its accuracy, and to establish the optimal cut points.[20]

In this study, intraobserver and interobserver variability were defined as differences between repeated measures of myocardial wall stress in diastole and expressed as a percentage error of the means. Statistical analysis was performed using the SPSS software package (SPSS Inc., Chicago, IL).

RESULTS

The demographic and echocardiographic data of the 90 subjects are given in Table 1. Systolic blood pressure was significantly different between groups ($p < 0.05$), but there were no differences in left ventricular ejection fraction percentage (EF%), end-systolic volume, end-diastolic volume, diastolic blood pressure, stroke index, stroke volume, or cardiac index.

There was no difference in estimated LVEDP between groups (Table 2).

There were no significant differences between groups as regards wall radius and thickness except for the anterior wall thickness in the base and mid regions, the anterior wall circumferential radius in the apex region, and the septal wall thickness in the base region (Table 2).

TABLE 1
Mean ± Standard Deviation of Characteristics of the Subjects

Variables	Controls (N = 30)	Moderate LAD Coronary Artery Stenosis (N = 30)	Significant LAD Coronary Artery Stenosis (N = 30)	*p* Value*
Age (y)	50 ± 9	53 ± 7	52 ± 5	0.401
Stenosis (%)	--	61 ± 3	90 ± 3	0.001
Body mass index (kg/m^2)	25.0 ± 1.4	24.7 ± 1.5	24.5 ± 2.7	0.682
Heart rate (beats/min)	72 ± 9	73 ± 17	76 ± 12	0.715
Diastolic blood pressure (mmHg)	77 ± 6	81 ± 5	80 ± 6	0.013
Systolic blood pressure (mmHg)	127 ± 5	133 ± 8	135 ± 9	0.001
Left ventricular ejection fraction percent	53.44 ± 4.81	51.74 ± 4.54	50.27 ± 7.72	0.190
End-systolic volume (ml)	52.14 ± 15.60	49.36 ± 13.98	52.23 ± 15.47	0.263
End diastolic volume (ml)	111.12 ± 28.24	103.59 ± 22.22	113.88 ± 24.32	0.335
Stroke volume (ml)	59 ± 15	54 ± 13	57 ± 13	0.410
Cardiac index (ml/min/m^2)	2,202 ± 557	2,110 ± 674	2,269 ± 577	0.668
Stroke index (ml/m^2)	31 ± 8	29 ± 7	30 ± 7	0.635

*ANOVA's *p* value.

TABLE 2
Mean and SD of Estimated Left Ventricular End-Diastolic Pressure, Anterior and Septal Wall Radii (meridional and circumferential radii), and Wall Thickness Measured at the Base, Mid, and Apical Myocardial Segments, and Calculated End-Diastolic Myocardial Wall Stress, in Patients with Significant and Moderate Left Anterior Descending (LAD) Coronary Artery Stenosis and in Healthy Subjects

Segments		Healthy	Moderate LAD Coronary Artery Stenosis	Significant LAD Coronary Artery Stenosis	*p* Value*
Left ventricular end-diastolic pressure (mmHg)					
Anterior wall		12.0 ± 2.5	14.4 ± 5.4	16.1 ± 4.3	0.042
Meridional radius (mm)	Base	29.3 ± 1.9	29.8 ± 3.6	30.8 ± 2.4	0.238
	Mid	28.8 ± 2.8	28.7 ± 3.9	30.0 ± 4.2	0.449
	Apex	21.3 ± 2.4	21.8 ± 3.1	22.8 ± 2.8	0.250
Circumferential radius (mm)	Base	26.6 ± 2.4	27.4 ± 3.7	27.9 ± 2.5	0.327
	Mid	28.5 ± 2.7	28.4 ± 3.8	29.4 ± 4.4	0.647
	Apex	19.5 ± 2.3	19.1 ± 2.3	20.9 ± 2.9	0.048
Thickness (mm)	Base	10.2 ± 1.5	11.5 ± 1.5	11.3 ± 2.2	0.020
	Mid	10.2 ± 1.4	11.4 ± 1.4	11.6 ± 2.9	0.029
	Apex	9.9 ± 1.4	10.9 ± 1.3	10.4 ± 2.2	0.077
End-diastolic myocardial wall stress (kdyn/cm^2)	Base	26.1 ± 5.4	27.9 ± 11.7	34.6 ± 14.3	0.033
	Mid	26.8 ± 5.6	29.9 ± 18.3	34.9 ± 16.5	0.199
	Apex	20.5 ± 4.3	23.2 ± 13.5	29.2 ± 13.3	0.042
Septum wall					
Meridional radius (mm)	Base	23.1 ± 1.8	23.4 ± 2.8	23.8 ± 3.1	0.675
	Mid	20.8 ± 2.1	21.0 ± 2.5	22.2 ± 3.2	0.183
	Apex	19.2 ± 1.8	19.5 ± 3.8	20.6 ± 2.5	0.305
Circumferential radius (mm)	Base	21.9 ± 1.9	22.7 ± 2.9	22.9 ± 2.8	0.446
	Mid	20.5 ± 2.1	20.7 ± 2.4	21.9 ± 3.2	0.198
	Apex	18.0 ± 1.8	18.1 ± 3.8	19.2 ± 2.2	0.293
Thickness (mm)	Base	9.1 ± 1.2	10.9 ± 1.4	10.1 ± 1.9	0.001
	Mid	10.4 ± 1.3	11.3 ± 1.2	10.8 ± 2.4	0.144
	Apex	10.2 ± 1.3	10.6 ± 1.3	10.5 ± 2.4	0.596
End-diastolic myocardial wall stress (kdyn/cm^2)	Base	24.1 ± 5.8	27.2 ± 14.4	31.3 ± 12.6	0.014
	Mid	20.1 ± 4.9	21.8 ± 10.4	28.5 ± 12.6	0.019
	Apex	18.8 ± 4.9	20.7 ± 9.9	26.4 ± 9.2	0.012

*ANOVA's *p* value.

Patients with significant LAD stenosis had greater end-diastolic myocardial wall stress than patients with moderate or no stenosis (Table 2). The average end diastolic wall stress of the anterior and septum walls was approximately 12% and 36% greater in patients with moderate or significant LAD stenosis, respectively, than in healthy subjects, and this difference was shown by least-significant-differences analysis to be significant between healthy

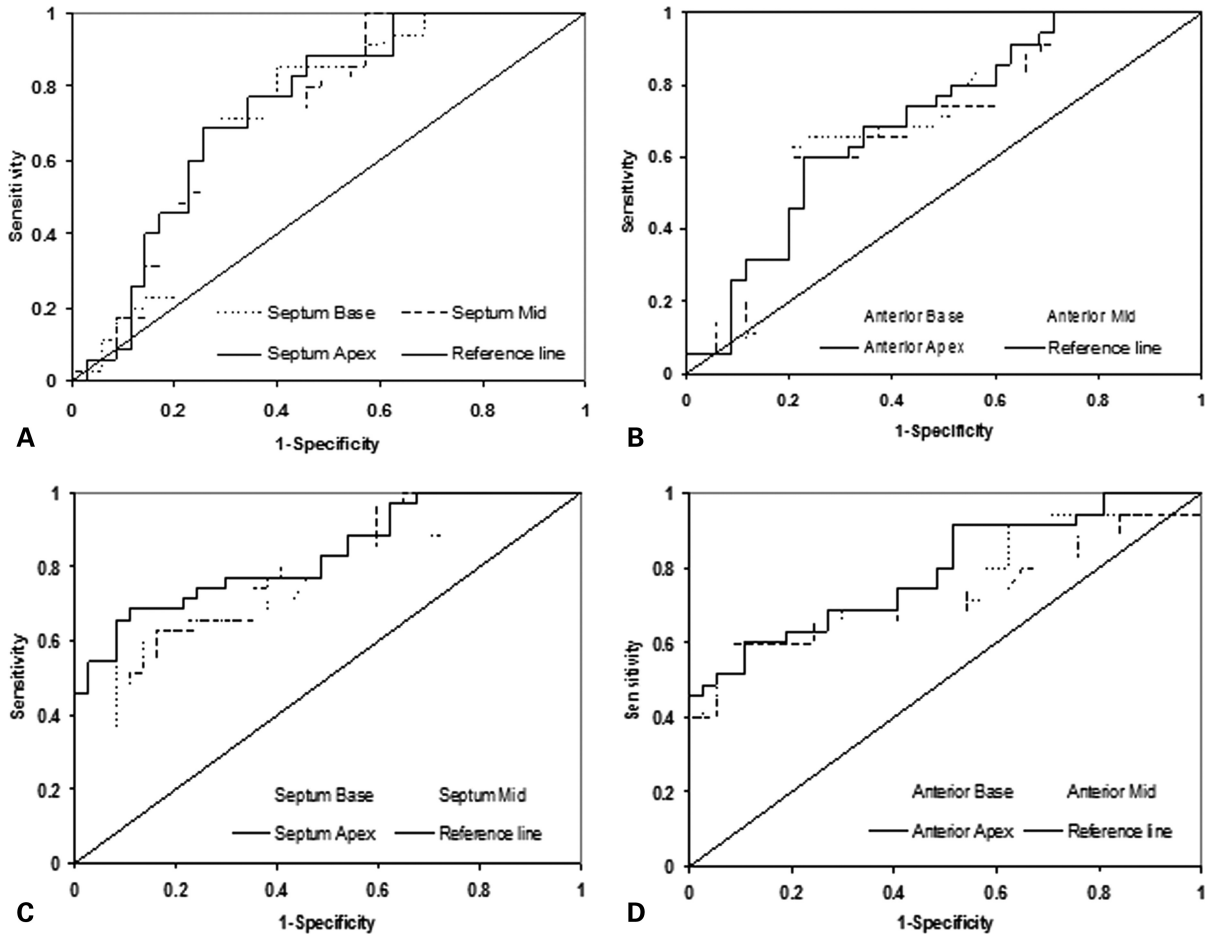

FIGURE 2. ROC curves for myocardial wall stress for base, mid, and apex segments of the septum **(A, C)** and LV anterior wall **(B, D)** for discriminating patients with moderate from patients with significant coronary artery stenosis **(A, B)**, and healthy subjects from patients with significant coronary artery stenosis **(C, D)**.

subjects and patients with significant coronary stenosis.

ROC of area under the curve are shown in Figure 2. All results were significant with 95% confidence level ($p < 0.05$).

The corresponding cutoff values, sensitivity, specificity, and diagnostic accuracy (with 0.95% confidence intervals) of wall stress are summarized in Table 3.

Septum apex wall stress had the highest discriminatory power for predicting significant stenosis versus healthy coronary artery, with 82% area under the curve as compared with 80% in septum mid wall stress and 77% in septum base wall stress. Similarly, anterior base wall stress had the highest discriminatory power for predicting significant stenosis versus healthy coronary artery, with 79% area under the curve as compared with 78% in anterior apex and 74% in anterior mid wall stress. The optimally combined sensitivity and specificity were 72% and 66%, respectively, for septum apex wall. Septum apex wall stress had the highest discriminatory power for predicting significant versus moderate coronary artery stenosis, with 74% area under the curve as compared with 73% in septum base wall stress and septum mid wall stress. Similarly, anterior wall stress in three segments of base and apex had the highest discriminatory power for predicting significant versus moderate coronary artery stenosis with 71% area under the curve. The optimally combined sensitivity and specificity for differentiating significant from moderate stenosis were 64% and 63%, respectively, for septum mid and base wall and anterior mid wall.

The ROC could not be exploited for wall stress to differentiate healthy subjects from patients with moderate coronary stenosis because there was no significant difference between these groups.

Intraobserver and interobserver variability of wall stress measurements were in the range of 4.1–7.6% and 4.8–8.5%, respectively.

TABLE 3
Cutoff Point and Diagnostic Performance of Average Wall Stress Indices

Segments	Cutoff Point (kdyn/cm^2)	Sensitivity (%)	Specificity (%)	AUC (CI)	*p* Value
Healthy versus significant stenosis groups					
Anterior wall					
Base	31.2	60	61	0.79 (0.65–0.85)	<0.05
Mid	32.2	63	60	0.74 (0.62–0.80)	<0.05
Apex	25.5	66	63	0.78 (0.69–0.88)	<0.05
Septum wall					
Base	27.9	65	60	0.77 (0.65–0.85)	<0.05
Mid	25.0	68	64	0.80 (0.72–0.87)	<0.05
Apex	23.1	72	66	0.82 (0.73–0.91)	<0.05
Moderate versus significant stenosis groups					
Anterior wall					
Base	32.0	62	60	0.71 (0.59–0.82)	<0.05
Mid	31.6	64	56	0.67 (0.55–0.79)	<0.05
Apex	27.0	60	49	0.71 (0.58–0.83)	<0.05
Septum wall					
Base	28.6	64	61	0.73 (0.60–0.85)	<0.05
Mid	25.5	64	63	0.73 (0.61–0.85)	<0.05
Apex	20.9	63	60	0.74 (0.62–0.86)	<0.05

Abbreviations: AUC, area under the curve; CI: 95% confidence interval.

DISCUSSION

CAD is the end result of the accumulation of atheromatous plaques within the walls of the coronary arteries that supply the myocardium with oxygen and nutrients.[6,21] The quantitative assessment of LV properties and ventricular muscle in terms of myocardial wall stress have been used in the investigation of various heart diseases.[22–24] Wall stress may be calculated at diastole; however, this calculation requires invasive measurements of LV blood pressure by retrograde left heart catheterization.[25] In a previous study,[3] we concluded that the E/Ea ratio provided an index of LVEDP that could be measured noninvasively with color-TDI. Although the lateral E/Ea ratio determined by color-TDI yielded better results than the septal E/Ea ratio in predicting end-diastolic LV pressure,[7] this may depend on the underlying disease. We used color-TDI to evaluate lateral early-diastolic annular velocity (E) and pulsed Doppler echocardiography to estimate mitral flow early velocity (Ea); however, it has been previously demonstrated that these two methods do not give similar results, with color-TDI underestimating velocities.

The wall stress, calculated by the Deanda et al formula,[15] represents the mean value of the average stress across the LV wall, with local maximal stress occurring on the endocardial and local minimal stress on the epicardial surface. The assumptions used for simplification in this calculation were that: (1) the myocardium was isotropic, linearly elastic, and homogeneous; (2) bending moments could be neglected; (3) the meridional and circumferential mid wall radii of curvature could be derived as the endocardial radius of curvature plus one-half of the wall thickness; (4) the mid wall LV wall stress was the average of the epicardial and endocardial stresses; and (5) the only load on the ventricle was internal pressure.

In this study, we estimated regional end-diastolic myocardial wall stress in the anterior and septum walls for base, mid, and apex segments. The results showed that the variation of end-diastolic myocardial wall stress in atherosclerotic patients were significantly greater than in the healthy group ($p < 0.05$). Significant differences were found for this variable only between patients with significant LAD stenosis and controls, and not between those with moderate LAD stenosis and controls. However, the diagnostic suspicion of myocardial ischemia in patients with significant coronary artery disease is often supported by typical ischemic symptoms and abnormalities in systolic function. A potentially incremental usefulness of diastolic LV wall stress may be more evident in patients with subclinical coronary artery disease, normal ejection fraction, and no abnormalities in segmental wall systolic thickening.

We determined the cutoff, diagnostic accuracy, sensitivity, and specificity of myocardial wall stress to differentiate significant CAD patients using coronary angiography as the standard of reference and compared with ejection fraction percentage. Septo-apical wall stress had the

highest discriminatory power for differentiating significant coronary artery stenosis from healthy coronary artery with 82% area under the curve, and from moderate coronary artery stenosis, with 74% area under the curve. However, ejection fraction remains the standard and global variable, although it cannot always demonstrate regional biomechanical abnormalities.

In the same way, coronary angiography remains the standard clinical tool for assessing coronary artery anatomy and is the gold standard for diagnosing CAD, but there is no strict parallelism between angiographic data and regional myocardial perfusion. The relationship between stenosis severity and reduction of coronary flow is quite variable, even when there are no imaging artifacts or limitations, for example, eccentric stenosis or obscure areas due to thrombus.

One of the reasons for investigating the relationship between mechanical myocardial parameters and coronary stenosis is the search for noninvasive ways for differentiating normal from diseased tissues. Most previous tissue characterization studies focused on elasticity acoustic parameters. More recently, progress has been made with strain rate imaging. Elasticity determines the relation between forces acting on an object and its resulting deformation, as described by Hooke's law. This relation remains valid when applied to myocardium, but all forces acting on it have to be taken into account to describe its total deformation.[26]

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 mitral annulus, and other mitral segments were not evaluated in this study. We chose the lateral aspect of the mitral annulus because this site is easy to obtain from the apical window and, in contrast to the parasternal window, the velocity measurement should not be influenced by anteroposterior translation.[27] The main disadvantages of color-TDI are its requirement for offline analysis for quantifying myocardial velocities, its inability to provide real-time display of the Doppler information, and its dependence on the angle of incidence (which can be overcome by speckle tracking). In our study, we measured E and Ea noninvasively with color-TDI and calculated E/Ea to estimate wall stress. Further studies are required to compare E/Ea calculated using pulsed-TDI versus color-TDI for the noninvasive estimation of LVEDP and wall stress. We derived indices of regional wall stress from estimated LVEDP and echocardiographic segmental LV diameter and wall thickness in the LAD coronary artery territory, and further studies are required for other coronary arteries.

Our study included only male subjects, which is another limitation. An ejection fraction of 50–75% is considered normal.[28] In our study, the average value in the control group was slightly less than 55%, but differences between groups were significant and enabled us to observe that the end-diastolic myocardial wall stress was significantly greater in atherosclerotic patients than in healthy subjects.

In conclusion, noninvasive evaluation of diastolic function is an important role of clinical echocardiography in the research setting. End-diastolic myocardial wall stress may be an important index in evaluating regional myocardial dysfunction due to coronary artery disease.

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