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Original Research Article

Dobutamine-stress echocardiography speckle-tracking imaging in the assessment of hemodynamic significance of coronary artery stenosis in patients with moderate and high probability of coronary artery disease

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ABSTRACT

Background and objective: Myocardial deformation indices are considered as sensitive markers of ischemia and may be useful in the quantification of hemodynamic significance of coronary artery disease (CAD). We sought to determine the diagnostic value of speckle-tracking echocardiography derived myocardial deformation parameters at rest and during stress to determine hemodynamically significance coronary artery stenosis in patients with moderate and high probability of CAD.

Materials and methods: In 81 patients (mean age, 64 ± 8.6 years) with stable CAD inducible myocardial ischemia was evaluated by dobutamine stress echocardiography (DSE) and adenosine magnetic resonance imaging (AMRI). Based on AMRI patients were divided into two groups: nonpathologic ($n = 41$) and pathologic ($n = 40$). Strain and strain rate (SR) parameters and their changes from the rest (BASE) to low stress (MIN), peak stress (MAX), and recovery (REC) were analyzed using 2D speckle-tracking imaging (STI).

Results: In the nonpathologic group, systolic longitudinal and circumferential strain increased significantly from BASE to MIN, as well as systolic SR from BASE to MIN and from MIN to MAX in longitudinal plane. In contrast, in the pathologic group, insignificant longitudinal systolic SR increase and radial and circumferential systolic SR decrease from MIN to MAX was observed. Discriminant function analysis revealed that select STI derived

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parameters best classify patients into predefined AMRI groups (pathologic and nonpathologic) with the accuracy respectively 90.9% and 83.3%. According to ROC analysis these myocardial deformation parameters had the greatest predictive value of significant coronary artery stenoses: longitudinal strain at high dose (AUC 0.811, sensitivity 89.4%, specificity 64.7%), longitudinal strain rate at high dose (AUC 0.855, sensitivity 88.1%, specificity 71.0% at high doses). The sensitivity and specificity of inducible wall motion abnormalities were 74.0% and 85.0% (AUC 0.798) and was lower compared with the diagnostic value of longitudinal myocardial deformation parameters.

Conclusions: Left ventricular strain and strain rate analyses during DSE can be used in the assessment of hemodynamic significance of coronary artery stenosis in patients with moderate and high risk for CAD.

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1. Introduction

Deaths from coronary artery disease (CAD) account for more than half of cardiovascular (CV) mortality; hence, early diagnosis and treatment are warranted [1]. The choice of treatment strategy should be primarily based on the hemodynamic significance of coronary artery stenosis [2]. Myocardial deformation indices are considered as sensitive markers of ischemia and may be useful in the quantification of hemodynamic significance of coronary artery stenosis [3–5]. Currently there are no published studies that analyzed the association of speckle-tracking echocardiography (STI) derived myocardial deformation parameters and myocardial perfusion evaluated by cardiac adenosine magnetic resonance imaging (AMRI) that has sensitivity and specificity noninferior to invasive fractional flow reserve testing [6].

The aim of this study was to determine the diagnostic value of STI-derived myocardial deformation parameters at rest and during dobutamine stress to determine the hemodynamic significance of coronary artery stenosis in patients with moderate and high probability of CAD.

2. Materials and methods

This was a cross-sectional prospective study that included patients without known CAD with moderate and high probability of CAD, determined by a Diamond–Forrester score [7].

2.1. Study population

Patients admitted to the Department of Cardiology, Hospital of Lithuanian University of Health Sciences, for investigation of suspected CAD during the period from April 2013 to April 2014 were enrolled into the study. A total of 81 patients with a moderate or high risk of CAD and a good LV systolic function defined as LV ejection fraction (EF) ≥55% with no wall motion abnormalities (WMA) at rest were included. Patients with any of the following criteria were excluded from the study: history of cardiovascular or valvular heart disease, left ventricular ejection fraction <55% on echocardiography, known hypersensitivity to contrast agents, mental diseases, pregnancy or breast-feeding, severe renal impairment (estimated glomerular filtration rate ≤30 mL/min/1.73 m^2), contraindications to cardiac AMRI.

All patients gave written informed consent before undergoing DSE.

The study was approved by the local ethics committee.

2.2. Evaluation of myocardial ischemia

In all patients myocardial ischemia was evaluated by two imaging techniques: echocardiography (at rest and during dobutamine stress echocardiography [DSE]), and cardiac magnetic resonance imaging (myocardial perfusion at rest and adenosine stress myocardial perfusion, AMRI). Beta-blockers and nitrates were discontinued 48 h before to the study. Intravenous dobutamine was initiated at 5 μg/kg/min and the dose was increased every 3 min to 10, 20, 30 and 40 μg/kg/min. Atropine up to 1 mg was added if necessary. The conventional echocardiography system (Vivid 7, GE Healthcare, Horten, Norway) with 1.5–4.6 MHz transducer was used. A 12-lead electrocardiogram, blood pressure, and standard two-dimensional echocardiograms were taken at baseline, low-dose, peak dobutamine levels and during recovery. The dobutamine infusion was terminated once 85% of the maximal predicted heart rate was achieved. Stress test was terminated prematurely and the patient was assigned to the pathologic group in the presence of severe chest pain or other intolerable symptoms, severe arrhythmia, >2 mm ST-segment elevation or depression, systolic blood pressure >230 mmHg, diastolic blood pressure >120 mmHg, or a drop in systolic blood pressure >20 mmHg.

Off-line speckle-tracking analysis (EchoPac, GE Healthcare) was performed using images obtained during DSE. Cardiac cycles associated with atrial or ventricular extrasystolic beats were excluded. The minimum frame rate used for analysis was 90 with an average being 101 ± 8.8. Conventional echocardiographic measurements were performed according to the American Association of Echocardiography recommendations [8]. LV ejection fraction was calculated using the modified Simpson's biplane method with manual tracing of the endocardial borders at end-diastole and end-systole in the apical 4- and 2-chamber views. All segmental analyses were based on the conventional American Society of Echocardiography 16-segment LV model [8]. Each segment was assigned a

wall motion score of 1–4, where 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic or aneurysmal. Wall motion score index was derived as the sum of individual segment scores divided by the number of segments visualized.

For strain, systolic and diastolic strain rate measurements, the endocardial borders were traced automatically with aid of manually marked reference points at the end-systolic frame. End-systole was identified as corresponding to the aortic valve closure measured by pulsed wave Doppler. In case of poor-tracking quality, the reference points were manually readjusted until satisfactory tracking was achieved. Patients with two or more segments with poor tracking even after manual correction were excluded from further analysis. After satisfactory tracking was obtained, numerical and graphical displays of myocardial deformation parameters were generated automatically for all six segments from each view. Longitudinal, circumferential, radial strain, systolic and diastolic longitudinal, circumferential, radial strain rate (SR) parameters and their changes from rest (BASE) to low stress (MIN), peak stress (MAX) and recovery (REC), were estimated. The majority (90%, $n = 878$) of the myocardial segments were suitable for STI analysis at BASE and REC, 83% ($n = 810$) during MIN, and 79% ($n = 771$) during MAX phases.

Peak radial and circumferential strain and SR (systolic and early diastolic) were measured from mid short-axis view at rest, low and high dobutamine doses. Peak longitudinal strain and SR were measured from apical 4-, 3-chamber and 2-chamber views. Global strain analysis was performed. According to the existing guidelines [9], GLS was calculated from loops acquired from 2-, 3- and 4-chamber views. Global radial and circumferential strain loops were acquired from the LV short axis view at the level of papillary muscles. Examples of 2-chamber of global longitudinal strain in the nonpathological and pathological groups at rest, low and high dobutamine dose are demonstrated in Figs. 1–3.

Before to AMRI, all patients were asked to refrain from caffeine-containing beverages or drugs for 24 h. Images were acquired using a dedicated 1.5 T scanner with an 18-channel phased-array receiver coil (Siemens Magnetom Aera, Siemens AG Healthcare Sector, Erlangen, Germany). A vector ECG and breathing motion were detected continuously. A retrospectively-gated balanced steady-state free-precession (bSSFP) sequence (repetition time 5.1 ms, echo time 1.3 ms, flip angle 80°, in-plane spatial resolution 0.9 mm × 0.9 mm with a slice thickness of 8 mm and 25 phases per cardiac cycle) was used to obtain cine images in three long-axis (2-, 3- and 4-chamber) views, followed by contiguous stack of short-axis slices. Perfusion imaging was planned using end-systolic frames of the long-axis cine images and performed in three short-axis slices corresponding basal, midventricular and apical segments of the left ventricle. For stress perfusion adenosine was infused at 140 μg/kg/min for a minimum 3 min to achieve hyperemia. In cases of inadequate hemodynamic response (heart rate increase <10 bpm or systolic blood pressure decrease <10 mmHg) adenosine dose was increased up to 210 μg/kg/min. Heart rate and blood pressure were monitored before and continuously during adenosine infusion. At peak stress gadolinium contrast (Gadovist, Bayer-Schering, Berlin,

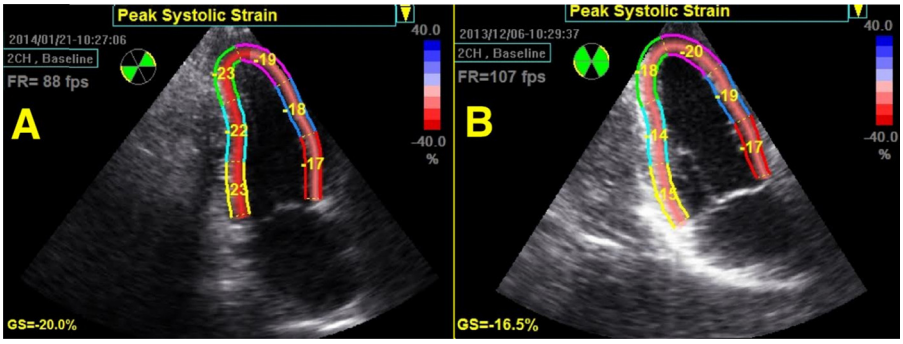

Fig. 1 – Comparison of global longitudinal strain of a nonpathological group subject (panel A) to a pathological group (panel B) at rest.

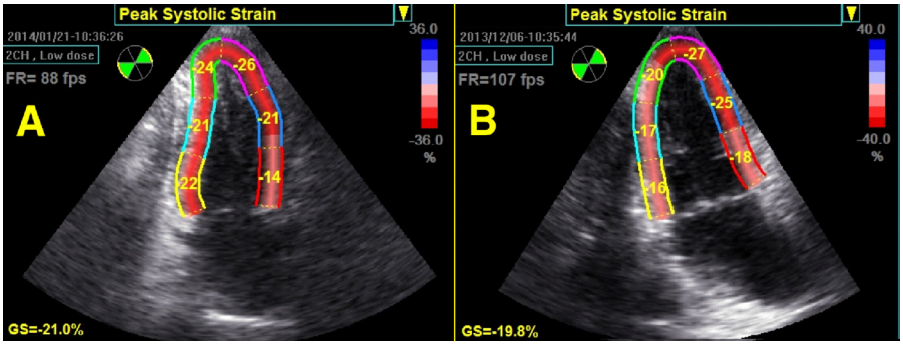

Fig. 2 – Comparison of global longitudinal strain of a nonpathological group subject (panel A) to a pathological group (panel B) at low dobutamine dose.

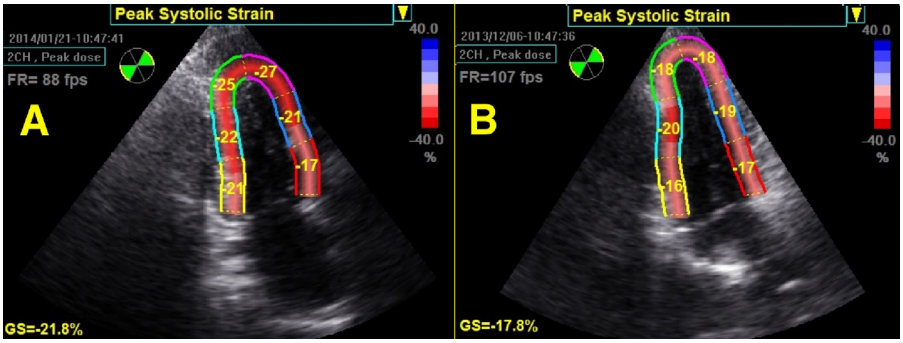

Fig. 3 – Comparison of global longitudinal strain of a nonpathological group subject (panel A) to a pathological group (panel B) at high dobutamine dose.

Germany, 0.1 mmol/kg) was rapidly injected at 4.0 m/s, followed by 20-mL saline flush using a power injector (Medrad UK, Ely, Cambridgeshire, UK). A saturation-recovery prepared bSSFP sequence (echo time 1.3 ms, flip angle 12°, in-plane resolution 2.4 × 2.4 with a slice thickness of 8 mm during 50 consecutive heart beats) was used for stress and rest perfusion imaging. After 10-min late gadolinium enhancement (LGE), images were acquired. Ventricular volumes, function, myocardial mass and ejection fraction were calculated using a manufacturer dedicated software (Syngo. via, Siemens AG Healthcare Sector, Erlangen, Germany). The rest and stress perfusion images were assessed by visual analysis. The true stress-induced perfusion defect was defined as a persistent hypoenhancement in subendocardial or transmural appearance with normal first-pass perfusion at rest. Patients with perfusion defects during stress were considered ischemia positive. Dark rim artifacts during perfusion imaging were noticed seldom and were defined as transient hypointense zone, usually seen in interventricular septum subendocardial layer, lasted for a several heart beats and in most cases were equally visible at rest and at stress. Patients with late gadolinium enhancement were excluded from the study.

After DSE and AMRI all patients underwent invasive coronary artery angiography. Significant coronary artery stenosis was defined as 75% or greater luminal narrowing of epicardial coronary vessel. DSE and AMRI investigators were blinded to coronary artery angiography results.

To describe the intra-observer variability the same investigator reevaluated systolic longitudinal strain and SR on two separate occasions of 20 randomly selected patients at REST and MIN. To evaluate inter-observer variability two echocardiographers, blinded to previously obtained data, performed the same measurements. Intra-observer and inter-observer variability values were calculated as the absolute difference between the corresponding two measurements as a percent of the mean.

2.3. *Statistical analysis*

Statistical analysis was performed using SPSS 20.0 software. For comparison of numerical variables Wilcoxon, Mann–Whitney *U* and Student *t* tests were used. For comparison of categorical variables χ^2 test was used. Discriminant function analysis was used for predictive value of strain ant strain rate parameters for predicting CAD. The value of $P < 0.05$ was considered as significant.

The strain and strain rate parameters as CAD indicators were evaluated by using ROC curves. A subject was assessed as positive or negative according to whether the parameter value was greater than, less than, or equal to a given cut-off value. Associated with any cut-off value was the probability of a true positive (sensitivity) and a true negative (specificity). A commonly used index of accuracy is the area under the ROC curve (AUC), with values close to 1.0 indicating high diagnostic accuracy.

3. Results

In studied patient population, moderate and high CAD likelihood was estimated in 63.7% and 36.3% patients, respectively. All patients were divided into two groups according to AMRI results: nonpathologic (41 patients) group, and pathologic group (40 patients). The same patients were also analyzed divided into two groups (nonpathologic 40 and pathologic 41) according to DSE result and additional analysis of STI parameters we done to see if AMRI grouping would be superior to DSE grouping.

Clinical characteristics of study population are shown in Table 1 and distribution of coronary artery lesions evaluated by angiography is presented in Table 2. Conventional echocardiographic parameters did not differ between AMRI and DSE groups and all parameters were within normal range (Table 3). Blood pressure and mean heart rate values during the stress test are provided in Table 4. There were no differences in longitudinal, circumferential, radial strain and SR parameters at rest between the groups (Table 5). The use of calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers did not differ significantly across groups.

3.1. *Changes of myocardial strain and strain rate*

Intra-observer variability of systolic longitudinal strain and SR at BASE was 5.5% and 5%, respectively; at MIN, 5.8% and 5% respectively; and at MAX, 6.8% and 6.2%, respectively. Inter-observer variability of systolic longitudinal strain and SR at

Table 1 – Clinical characteristics of study population.

Characteristics	Nonpathologic group	Pathologic group	P value
Men, *n* (%)	23 (56.1)	22 (55.0)	0.26
Age, years	63.0 ± 8.9	65.9 ± 7.5	0.41
History of hypertension, *n* (%)	21 (51.2)	20 (50.0)	0.10
History of smoking, *n* (%)	15 (36.5)	15 (37.5)	0.10
Obesity, *n* (%)	22 (53.6)	19 (47.5)	0.20
Diabetes, *n* (%)	7 (17.0)	4 (10.0)	0.32
Family history of CAD, *n* (%)	12 (29.2)	11 (27.5)	0.57
Systolic pressure, mmHg	139.3 ± 15.8	141.4 ± 16.3	0.66
Diastolic pressure, mmHg	78.2 ± 14.4	81.6 ± 14.8	0.45
Heart rate, beats per min	70.1 ± 7.4	69.0 ± 7.8	0.56
Moderate CAD risk[a]	23 (63.4)	22 (55.0)	0.26
High CAD risk[a]	15 (36.6)	18 (45.0)	0.32

Values are mean ± standard deviation unless otherwise indicated.
[a] CAD risk assessment by Diamond–Forrester classification (1979).

BASE was 6% and 5.5%; at MIN, 6.3% and 6% respectively; and MAX, 7.2% and 6.6% respectively.

Systolic longitudinal strain and systolic circumferential strain increased significantly from BASE to MIN in the AMRI and DSE nonpathologic groups, but not in the pathologic groups (Fig. 1). Radial strain remained significantly unchanged (Table 5).

A significant increase in systolic SR was observed in all three planes from BASE to MIN in the AMRI nonpathologic group, but not in the pathologic group. In the pathologic group a tendency of systolic longitudinal SR to decrease was noted. A significant increase in circumferential systolic SR was seen in both DSE groups while no other changes were significant.

Diastolic longitudinal, radial and circumferential SR significantly increased from BASE to MIN in nonpathologic group. In the pathologic group, diastolic SR significantly increased only in the longitudinal plane (Table 5). No significant diastolic radial SR change was noted in DSE nonpathologic group while longitudinal SR did not change significantly in neither of groups.

Longitudinal, circumferential and radial strain decreased in both AMRI and DSE groups from MIN to MAX (Table 5).

A significant increase in systolic SR was observed in all three planes from MIN to MAX in the AMRI nonpathologic group, but only in longitudinal plane in the pathologic group. Radial and circumferential systolic SR failed to increase significantly in DSE nonpathologic group. A tendency of decrease in systolic radial SR from MIN to MAX was observed only in the pathologic group (Table 5).

Diastolic SR had tendency to increase from MIN to MAX in all planes in both groups except for radial strain in pathologic group (Table 5).

Table 2 – Characteristics of coronary angiography findings.[*]

Characteristics	Nonpathologic group	Pathologic group
Single vessel disease	0 (0)	20 (50.0)
Two vessel disease	0 (0)	8 (20.0)
Three vessel disease	0 (0)	12 (30.0)
Diseased vessel left main coronary artery	0 (0)	7 (17.5)
Diseased vessel right coronary artery	0 (0)	20 (50.0)
Diseased vessel left circumflex artery	0 (0)	14 (35.5)
Diseased vessel left anterior descending artery	0 (0)	30 (75.0)

Values are number (percentage).
[*] Significant coronary artery stenosis was defined as 75% or greater luminal narrowing of epicardial coronary vessel.

Table 3 – Two-dimensional and tissue Doppler echocardiography parameters.

Parameter	Nonpathologic group	Pathologic group	P value
LVEDD, mm	46.4 ± 5.9	46.8 ± 6.7	0.84
LVEDD index, mm/m^2	23.2 ± 2.7	23.4 ± 3.9	0.87
LVESD, median (Q1;Q3), mm	33.4 ± 6.2	30.8 ± 8.7	0.17
LVESD index, mm/m^2	16.1 ± 3.5	15.9 ± 3.4	0.89
LVEDV, mL	93.5 ± 25.3	88.1 ± 25.1	0.36
LVEDV index, mL/m^2	45.8 ± 10.2	44.9 ± 13.1	0.94
LVESV, mL	39.5 ± 14.4	37.5 ± 15.6	0.64
LVESV index, mL/m^2	19.7 ± 6.6	18.6 ± 7.7	0.63
LVEF, %	59.7 ± 6.5	60.7 ± 6.9	0.80
E/A ratio, median (Q1;Q3)	0.9 ± 0.2	0.8 ± 0.2	0.68
E peak rate, m/s	59.8 ± 14.5	64.9 ± 18.5	0.40
A peak rate, m/s	70.5 ± 25.3	74.4 ± 11.8	0.16
e′ lateral, m/s	9.2 ± 1.8	9.2 ± 2.2	0.68
e′ septal, m/s	7.7 ± 1.7	9.1 ± 5.6	0.86
E/E′	3.4 ± 1.1	4.2 ± 2.6	0.12
DT, ms	272.6 ± 56.4	269.4 ± 99.5	0.44

Values are mean ± standard deviation unless otherwise indicated. LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LA, left atrium; LA vol, left atrium volume; LA vol. index, left atrium volume index; E/A, early diastolic transmitral flow velocity (E) and atrial systolic velocity (A) ratio; E, early diastolic transmitral flow velocity; A, atrial systolic velocity; e′, early diastolic mitral annular velocity; E/e′, early diastolic transmitral flow velocity and early diastolic mitral annular velocity; DT, deceleration time.

Table 4 – Heart rate and blood pressure during dobutamine stress echocardiography.

Strain, strain rate parameters	Nonpathologic group				Pathologic group				P value
	Rest	Low dobutamine doses	High dobutamine doses	Recovery	Rest	Low dobutamine doses	High dobutamine doses	Recovery	
Heart rate, beats/min	68.3 ± 6.6	101.4 ± 10.4	152.6 ± 13.3	69.4 ± 7.2	67.2 ± 6.7	103.4 ± 10.6	155.6 ± 13.0	72.3 ± 7.7	0.54
Systolic blood pressure, mmHg	134 ± 14.2	144 ± 15.6	156 ± 17.8	133 ± 13.8	132 ± 14.0	147 ± 17.2	158 ± 17.6	135 ± 14.3	0.32
Diastolic blood pressure, mmHg	84.3 ± 8.2	98.7 ± 9.3	94.7 ± 8.8	83.3 ± 8.6	83.6 ± 8.8	99 ± 9.6	96 ± 7.8	85 ± 6.5	0.29

Values are mean ± standard deviation.

Table 5 – Systolic and early diastolic longitudinal, circumferential and radial strain and strain rate parameters in nonpathologic and pathologic groups during dobutamine stress echocardiography.

Strain, strain rate parameters	Nonpathologic group				Pathologic group			
	Rest	Low dobutamine doses	High dobutamine doses	Recovery	Rest	Low dobutamine doses	High dobutamine doses	Recovery
Strain								
Systolic longitudinal strain, %	−18.9 ± 3.6	−20.9 ± 3.1*	−17.7 ± 4.8†	−18.7 ± 4.3	−18.3 ± 3.2	−19.2 ± 3.8	−16.4 ± 4.3†	−18.3 ± 1.8
Systolic circumferential strain, %	−17.2 ± 4.8	−19.5 ± 6.2*	−19.2 ± 7.0	−17.5 ± 6.8‡	−15.7 ± 5.2	−18.6 ± 6.0	−17.4 ± 10.3	−18.1 ± 7.9
Systolic radial strain, %	37.8 ± 28.4	33.4 ± 28.0	28.6 ± 14.8	35.0 ± 19.7	30.9 ± 20.1	40.6 ± 21.7	20.3 ± 14.7	20.5 ± 19.0
Systolic strain rate								
Systolic longitudinal strain rate, 1/s	−2.4 ± 3.7	−2.6 ± 0.4*	−2.1 ± 0.5†	−1.4 ± 0.3‡	−2.1 ± 2.6	−1.8 ± 0.4	−2.3 ± 0.3†	−1.4 ± 0.2
Systolic circumferential strain rate, 1/s	−1.7 ± 0.4	−2.6 ± 0.7*	−3.0 ± 0.6†	−1.9 ± 0.5‡	−1.7 ± 0.4	−2.7 ± 0.9	−2.8 ± 0.6	−1.7 ± 0.6
Systolic radial strain rate, 1/s	2.1 ± 1.1	3.0 ± 1.3*	4.3 ± 1.9†	2.3 ± 0.9	2.2 ± 0.8	4.6 ± 2.8	3.5 ± 0.8	1.8 ± 0.8
Diastolic strain rate								
Early diastolic longitudinal strain rate, 1/s	0.2 ± 0.2	1.7 ± 0.6*	2.2 ± 0.5	1.5 ± 0.5‡	0.5 ± 3.1	1.7 ± 0.2	2.2 ± 0.3	1.6 ± 0.2
Early diastolic circumferential strain rate, 1/s	1.8 ± 0.7	2.2 ± 0.8*	3.0 ± 0.7	2.0 ± 0.8‡	1.8 ± 0.6	2.1 ± 0.6	2.7 ± 0.5	2.1 ± 0.8
Early diastolic radial strain rate, 1/s	−2.2 ± 1.2	−2.3 ± 1.1*	−4.3 ± 2.5	−2.0 ± 1.2	−1.9 ± 0.8	−2.9 ± 1.4	−3.5 ± 1.4	−2.3 ± 1.3

Values are mean ± standard deviation.
* $P < 0.05$ from baseline to low dobutamine doses.
† $P < 0.05$ from low to high dobutamine doses.
‡ $P < 0.05$ from high dobutamine doses to recovery.

Longitudinal systolic strain had tendency to increase in both AMRI groups from MAX to REC. Radial strain had a tendency to increase in the nonpathologic group, but did not change in the pathologic group. However, circumferential strain decreased significantly in nonpathologic group, but not in the pathologic group (Table 5). The same tendencies were observed for DSE groups.

Longitudinal and circumferential diastolic SR decreased significantly from MAX to REC in the AMRI nonpathologic group. No changes were significant in pathologic group or both DSE groups (Table 5).

Discriminant function analysis revealed that radial strain at MAX, difference of systolic radial strain rate from BASE to MIN and difference of circumferential strain from BASE to MIN best classified patients into predefined AMRI groups (pathologic and nonpathologic). The accuracy of classifying to the pathologic and nonpathologic groups was 90.9% and 83.3%, respectively.

3.2. *ROC analysis*

According to ROC analysis these myocardial deformation parameters had the greatest predictive value of significant coronary artery stenoses: longitudinal strain at high dose (AUC 0.811, sensitivity 89.4%, specificity 64.7%), longitudinal strain rate at high dose (AUC 0.855, sensitivity 88.1%, specificity 71.0% at high doses); circumferential strain at high dose (AUC 0.749 sensitivity 86%, specificity 58.3% at high doses), circumferential SR at high dose (AUC 0.767 sensitivity 88.9%, specificity 62.3%). The sensitivity and specificity of wall motion analysis were 74.0% and 85.0% (AUC 0.798), respectively.

4. Discussion

In the present study, we found that strain and SR, especially longitudinal, during DSE may indicate the presence of myocardial ischemia in patients with moderate and high risk for CAD.

The severity and degree of coronary artery stenosis could be evaluated visually during coronary angiography; however, hemodynamic significance of it cannot be measured without FFR, which is additional expensive interventional diagnostic procedure. AMRI is useful in determining whether an angiographically moderate stenosis is functionally important. Real sensitivity and specificity of AMRI remains debatable. CE-MARC study [10] which was the largest, prospective, real world evaluation of CMR with 752 patients has established a high diagnostic accuracy of CMR in coronary heart disease and CMR's superiority over SPECT. Study results showed higher sensitivity and negative prognostic value of multiparametric CMR in comparison with SPECT (86.5% vs. 66.5% and 90.5% vs. 79.1% respectively, $P < 0.0001$ for both), but specificity and positive prognostic value were not significantly different (83.4% vs. 83.6%, $P = 0.916$ and 77.2% vs. 71.4%, $P = 0.061$, respectively) [10]. The results showed that CMR offers an accurate assessment of single-vessel and multivessel coronary disease, irrespective of the cut-off used for severity of clinically significant angiographic stenosis.

In order to determine the diagnostic value of strain and SR parameters during DSE we have chosen to investigate its associations with AMRI since it has been validated that fractional flow reserve results corresponds well to AMRI. Previous studies have shown that advanced echocardiographic techniques such as STI, which is widely used in resting echocardiograms, may be applied also in stress studies [4–6]. It has been reported that reduced left ventricle global longitudinal strain and SR can be associated with the extent of coronary artery lesions [4]. A progressive dysfunction of relaxation has been observed in relation to severity of coronary artery stenosis and number of involved vessels [5,6].

We did not observe any differences in echocardiographic parameters between the groups at rest, although longitudinal strain was shown to be useful for detecting CAD at rest in several previous studies [4,11–13]. It should be noted that patients in our study have been stratified to pathologic and nonpathologic group not only according to results of coronary angiography, but also noninvasive AMRI was used to determine the hemodynamic significance of CAD. It has been shown that scale of stenosis is not always equal to perfusions defects. Moreover, in the mentioned study [4], patients with lower longitudinal systolic SR were older and had greater myocardial mass index comparing to our patients. Increased left ventricle mass index is associated with abnormalities of systolic longitudinal strain and the proportion of systolic longitudinal impairment depends on the extent of left ventricle hypertrophy [14].

We observed that during dobutamine stress from rest to low dose, longitudinal and circumferential strain increased significantly in nonpathologic group, but not in the pathologic group. Longitudinal and circumferential strains were also analyzed by Weidemann et al., who found that these parameters tend to decrease or not to increase enough in ischemic myocardium [6]. In our study, we observed a similar trend in both longitudinal and circumferential strain. It is suggested that longitudinal strain and SR are the most sensitive markers for ischemia [15–18]. The rationale is explained by subendocardial myocardial fibers that are oriented mainly along the stems, and as a result, are affected in the earliest stages of ischemia [17]. Our findings also suggest that longitudinal strain and SR are important in distinguishing ischemic and healthy myocardium, however, our results indicate that sensitivity of longitudinal strain and SR to ischemia varies in different stages of DSE. Larger studies are needed to determine which phase of DSE is most important in this aspect, while it appears that the most important changes are at high and even at low dobutamine dose.

Strain follows a biphasic pattern, initially increasing at low stress, but remaining constant or even decreasing slightly as heart rate increases [18]. Meanwhile SR is increasing during all the period of stress. We observed longitudinal, circumferential and radial strain significant decrease from low to high dobutamine dose in both groups. However, SR changes from low to high dobutamine dose were different in both groups: a significant increase in systolic SR was observed in all three planes from MIN to high dobutamine dose – longitudinal, radial and circumferential in the nonpathologic group, but only in longitudinal plane in the pathologic group. A tendency of decrease in systolic radial SR from MIN to MAX was observed only in the pathologic group. This could reflect a reduction in stroke volume at higher heart rates due to reduced left ventricle filling time, and suggests that SR rather than strain itself may be a more sensitive marker of changes in myocardial function during stress [19]. Our results confirm this trend and correspond to the findings from previous studies, i.e. in ischemic myocardium strain decreased with stress while SR stayed the same, while in the nonischemic myocardium strain did not change with stress although SR increased [18]. Moreover, SR changes in nonpathologic group were more often significant than in pathologic, suggesting that ischemic myocardium has lower capabilities to adapt to stress because of lower contractile reserves. Reduction in myocardial adaptation abilities has been previously explored in animal models [20]. This raises idea that not only the cut-offs of absolute SR but the change of SR might be also valuable in detecting myocardial ischemia. What is more, two out of three discriminating parameters to classify patients into groups are based on strain and SR changes and not on absolute values. It should be noted that grouping according to

DSE results frequently failed to show difference of systolic or diastolic SR across groups while AMRI grouping proved to be superior.

It is also important to remember the significance of the change in diastolic SR. In the ischemic cascade, changes in diastolic strain occur first. The authors of previous studies agree that diastolic left ventricular abnormalities are sensitive early signs of myocardial ischemia and have the additional advantage of persisting longer than ischemic-induced systolic dysfunction [21–23]. In our study, diastolic SR changes were most important in the first phase of dobutamine echocardiography, i.e. from rest to low dobutamine dose. Significant increase in all three echocardiographic planes was only noted in the nonpathologic group. However, this needs to be confirmed in a larger sample.

It has been shown that regional strain and SR have correlations to a specific diseased coronary artery [24,25]. However, these changes are not always superior to global longitudinal strain [26,27]. Strain and SRs are homogenously distributed across the myocardium; the detection of even subtle changes in either measure suggests myocardial dysfunction [16]. That is why changes in global strain and SR caused by even single diseased vessel could be noticed. That is of practical use in a real world scenario where a screening for a significant disease is of most importance.

DSE sensitivity to detect myocardial ischemia with wall motion abnormality index is 79%–83% [28]. Discriminant function analysis suggests that strain and SR analysis during DSE is a promising diagnostic method that can allow increasing sensitivity up to 90.9%. What is more, as it can be validated against AMRI while being less expensive. It has incremental value of detected hemodynamically significant coronary artery stenosis, which may allow to apply an appropriate revascularization technique in everyday clinical practice. ROC analysis also confirmed that strain and strain rate (especially longitudinal) analysis could be valuable in detecting significant coronary artery stenosis in patients with moderate and high possibility of CAD. Future studies are needed to assess the diagnostic value of regional and global myocardial deformation parameters in large population.

There are some limitations in this study to be mentioned. One of the most important limitations of our study is that our protocol did not include fractional flow reserve (FFR) as part of the functional assessment of coronary stenosis during coronary angiography. The second important limitation of this study was the absence of contrast imaging during DSE, which could improve the diagnostic value of DSE. Small sample size with predominance of LAD disease can also be a limitation since other CAD pathomorphological types are not reflected sufficiently.

5. Conclusions

Left ventricular strain and strain rate analyses during DSE can be used in the assessment of hemodynamic significance of coronary artery stenosis in patients with moderate and high risk for CAD. We will focus on further myocardial strain and SR cut-off value research.

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