

ORIGINAL PAPERS

Two-Dimensional Speckle Tracking Echocardiography - a Useful Non-Invasive Method in Predicting Significant Coronary Artery Disease in Low Risk Acute Coronary Syndrome

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Abstract

Objectives: To evaluate if global and regional longitudinal strain (LS) using two-dimensional speckle tracking echocardiography (2DSTE) could be useful to predict significant coronary artery disease (CAD) in patients with low risk acute coronary syndrome (ACS). We also assessed if LS is compensatory augmented in nonischemic segments and whether the gradient of LS between segments (LSD) would be higher in this category of patients. **Methods:** 117 consecutive patients presenting with low risk ACS, without wall motion abnormalities on conventional echocardiography underwent LS analysis by 2DSTE and coronary angiography. Global peak systolic longitudinal strain (GLS) of the 18 segments of left ventricle (LV), GLS of 12 segments of LV, LSD and longitudinal strain ratio (LSR), defined as the ratio of LSD to GLS were calculated. Territorial correlation between the segmental LS and angiography was also assessed. **Results:** GLS18 and GLS12 were significantly decreased, while LSD and LSR were increased in patients with CAD comparative with those without CAD. Moreover GLS18, GLS12, LSD and LSR had moderate predictive value for CAD (AUC 0.631, 0.67, 0.617 and 0.665 respectively). The regional predefined LS had moderate predictive value for left anterior descending artery disease (AUC=0.718) and right coronary artery disease (AUC=0.627), but not for circumflex disease (AUC=0,555). **Conclusions:** In low-risk ACS, global and regional LS could be a powerful noninvasive diagnostic tool for significant CAD. LSD and LSR are also valuable parameters, and together with standard strain parameters could improve the accuracy of rest echocardiography in the diagnosis of CAD.

Keywords: Two-dimensional longitudinal strain, myocardial ischaemia, ventricular function, acute coronary syndrome

Rezumat

Obiective: Evaluarea utilității strainului longitudinal (SL) global și segmentar, derivat din ecocardiografia speckle tracking (2DSTE), în diagnosticul bolii coronariene semnificative (BCI), la pacienții cu sindrom coronarian acut (SCA) la risc scăzut. De asemenea, am investigat dacă SL și gradientul strainului (GSL) sunt crescute compensator în segmentele non-ischemice la pacienții cu BCI. **Metode:** Strainul longitudinal a fost evaluat prin 2DSTE la 117 pacienți cu SCA la risc scăzut investigați coronarografic. Deformarea mecanică a ventriculului stâng (VS) a fost analizată prin următorii parametri: strainul global longitudinal (SLG) calculat pe 18 respectiv 12 segmente, GSL și RSL (definit ca raportul dintre GSL și SLG). Am evaluat corelația dintre SL segmentar corespunzător teritoriului de distribuție

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coronariană și leziunile coronariene semnificative decelate angiografic. **Rezultate:** La pacienții cu BCI am observat reducerea semnificativă a SLG18 și SLG 12 comparativ cu cei fără BCI, în timp ce valorile GSL și RSL au fost crescute semnificativ la pacienții cu BCI. Atât SLG18, SLG12, GSL cât și RSL au valoare predictivă moderată pentru BCI (AUC 0.631, 0.67, 0.617 respectiv 0.665). Strainul longitudinal segmentar corespunzător teritoriilor de distribuție coronariană are valoare predictivă moderată pentru artera descendentă anterioară (AUC=0.718) și artera coronară dreaptă (AUC=0.627), dar nu și pentru artera circumflexă (AUC=0.555). **Concluzii:** Evaluarea SL global și regional poate fi o metodă utilă pentru diagnosticul BCI la pacienții cu SCA la risc scăzut. Noi parametri derivați din imagistica de strain precum SLG și RSL ar putea îmbunătăți acuratețea diagnostică a ecocardiografiei la pacienții cu BCI.

Cuvinte cheie: Strain longitudinal bi-dimensional, ischemie miocardică, funcție ventriculară, sindrom coronarian acut

INTRODUCTION

Echocardiography is the first cardiac imaging technique used to evaluate patients presenting with acute coronary syndrome (ACS). However, in the absence of wall motion abnormalities, conventional echocardiography at rest provides little information. Patients presenting with low risk ACS usually have normal wall motion and left ventricle ejection fraction (LVEF) at rest.

The subendocardial layer of the myocardium is known to be the first affected by ischemia^{1,2}. The myocardial fibers of this layer are disposed longitudinally, and for this reason measurements of longitudinal deformation could be the most sensitive marker of coronary artery disease (CAD)^{3,4}.

In patients with acute myocardial ischemia longitudinal strain has been demonstrated to have better sensibility than tissue velocity and displacement for the quantification of regional myocardial function⁵. Two dimensional longitudinal strain (LS) assessed by 2D speckle tracking echocardiography (2DSTE) was validated for the evaluation of longitudinal LV function^{6,7}. It has the advantage of being angle-independent unlike strain Doppler imaging.

The objective of the study

In this study we aimed to evaluate if global and regional LS, using 2DSTE, could be useful to detect, in a non-invasive manner, significant CAD in patients with low risk ACS. We also wanted to evaluate if LS could be improved in nonischemic segments secondary to a compensatory response, and whether the gradient of LS between segments would be higher in this category of patients.

Methods

Study subjects

We evaluated 129 consecutive patients presenting with low risk ACS who underwent coronary angio-

graphy in our institution between August 2014 and August 2015. The indication of coronarography was established by the attending physician. Twelve patients were excluded because of inadequate quality of the echocardiographic examination. ACS was defined as typical angina with one of the following criteria of instability: prolonged angina at rest, de novo angina CCS II/III, crescendo angina CCS III⁸. Low risk was defined as the absence of all of the following: ongoing ischemia, ischemic ECG changes, cardiomyocyte necrosis (cardiac troponin above 99th percentile of the upper reference limit, wall motion abnormalities on conventional 2D echocardiography. We also excluded patients with significant heart valve disease (defined as more than mild mitral, aortic, tricuspid and pulmonary valve disease).

The study was approved by the human research committee of our hospital, and informed consent was obtained from all subjects.

Echocardiography examination

Standard 2D echocardiography acquisitions were performed at rest using a VIVID E9 system (GE Vingmed; Horten, Norway) with a 3.5 Mhz multiphase-array probe. Cardiac chamber diameters were measured according to the latest guidelines, Left ventricular (LV) volumes and LV ejection fraction were assessed using the biplane Simpson's method⁹. For evaluation of LV LS we acquired two-dimensional LV focused apical four-chamber (4C), two-chamber (2C) and long-axis views. All images were obtained at a rate of 50-70 frames/s and three consecutive cardiac cycles were saved in digital format. Strain analysis was performed offline by an experienced observer (OR) using Q-Analysis package (EchoPAC BT12, GE Vingmed). LV peak systolic LS was assessed using the STE method, a semi-automated algorithm for automated function imaging (AFI)^{10,11}. Briefly, the software automatically detected the endocardium and tracked the end-systolic LV endocardial border in each of the three apical views, the region of interest (ROI) was adjusted to include the

whole myocardial wall but to exclude the pericardium. The reference point of each cardiac cycle was placed at the beginning of the QRS complex. Aortic valve closure was identified on the pulse-wave Doppler tracing of the LV outflow tract. The software automatically divided the LV walls in 6 segments for each view, resulting in a 18 segment model. In case of poor tracking, the region of interest was readjusted and the segments with inadequate tracking were excluded from analysis. The automated algorithm provided the segmental peak systolic longitudinal strain in bull's eye display. The global peak systolic longitudinal strain (GLS) of the 18 segments was defined as an average value of these peak systolic longitudinal strains (GLS18). We also calculated the GLS12, as an average value of the 6 basal and 6 midventricular segments, thereby excluding the apical segments, as recommended in previous studies¹²⁻¹⁴. The automated algorithm provided the value of regional strain for the 3 views (apical 4C, 2C and long-axis). Longitudinal strain difference (LSD) was defined as the difference of longitudinal strain between the highest and the lowest strain among all of the segments, and the longitudinal strain ratio (LSR) was defined as the ratio between LSD and GLS.

Coronary angiography

Coronary angiography was performed by two experienced operators who were unaware of the echocardiographic results. Significant CAD was defined as the presence of $\geq 70\%$ stenosis of the epicardial coronary arteries, all coronary lesions being assessed in two orthogonal planes.

Statistical analysis

Normal distribution of variables was assessed by Kolmogorov-Smirnov test. Accordingly, continuous variables were summarized as mean \pm SD if normally distributed and as median (interquartile range [IQR]) otherwise, scalar variables were reported as percentages. LV strain parameters were interpreted as absolute values, and comparisons were based on strain magnitude

(with lower strain values indicating worse deformation and higher strain values better deformation, independent of mathematical sign).

Differences between the patients with significant CAD and controls (patients without CAD) were assessed using independent T test for continuous variables and chi-square test for categorical variables. Nonparametric ROC (receiver operating characteristic) curve analyses were performed to assess the discriminatory capacity of AUC of the different LS parameters to predict significant CAD.

To examine intra-observer variability, strain measurements were repeated in 15 data sets 5 weeks after the first analysis by the same observer (OR) who was blinded to the initial values. To investigate inter-observer variability, measurements were performed offline by two investigators on 40 randomly selected data sets. The Bland-Altman analysis demonstrated a good intra- and inter-observer agreement for GLS. For GLS the intra-observer difference was $-0.1 \pm 1.7\%$; and $0.2 \pm 2.0\%$ for inter-observer. The analysis showed reasonable reproducibility for the measurements of segmental LS.

All analyses were performed using SPSS version 20.0 (SPSS, Inc, Chicago, IL). P-values < 0.05 were considered significant.

RESULTS

One hundred seventeen patients enrolled in the study. The mean age was 61.4 ± 12.07 years, and 55 (47%) of these had CAD. The clinical characteristics according to study group are shown in Table 1. Compared to patients without significant CAD, patients with significant CAD were older, and higher percentage of them were male (69% versus 43.5% control group). No significant differences were found between the two groups regarding the distribution of traditional CV risk factors: smoking; obesity; family history of premature CVD; dyslipidemia; hypertension or diabetes mellitus.

Table 1. Comparison of clinical characteristics between patients with significant CAD and patients without significant CAD.

	Patient with significant CAD	Patient without significant CAD	P-value
n	55	62	
Age (year)	62,6 \pm 11.2	60 \pm 12.4	.029
Male, n(%)	38 (69.0%)	27(43.5%)	.006
Hypertension, n(%)	46(83.6%)	50(80.6%)	.460
Diabetes mellitus, n(%)	17(30.9 %)	20 (32%)	.876
Dislypidemia, n(%)	48(87.2%)	48(77.4%)	.166
Obesity, n(%)	12(21.8 %)	11(17.7%)	.58
Smoker, n(%)	28(50.9 %)	23(37.09%)	.133
Family history of CAD, n(%)	5 (9.0%)	4 (6.45%)	.593

Table 2. Comparison of echocardiographic parameters between patients with significant CAD and patients without significant CAD

	Patient with significant CAD	Patient without significant CAD	P-value
LV EF (%)	57± 5.4	60±5.2	.167
GLS 18 (%)	-16.4±3.2	-18±2.4	.002
GLS 12 (%)	-15±3.4	-17±2.5	.001
LSD (%)	17.85±6.8.	15±6.1	.02
LSR	1.158±0.558	0.850±0.375	.001

Table 3. Angiographic data

Diseased vessel	
LAD	39 (33.3%)
RCA	21 (17.9%)
LCx	21(17.9%)
Number of diseased vessel	
3-vessel disease	3 (5.5%)
2-vessel disease	20 (36%)
1-vessel disease	31 (58%)

The echocardiographic and angiographic data are presented in table 2 and 3. All patients had normal rest kinetics, and no significant differences were found between the two groups in terms of LV ejection fraction. All patients had normal rest kinetics, and no significant differences were found between the two groups in terms of LV ejection fraction.

GLS (18 and 12) were significantly lower in patients with CAD (GLS 18= -16.4±3.2 versus -18±2.4, p=0.002, GLS 12 = -15±3.4 versus -17±2.5, p=0.001). Both of them showed predictive value for CAD, AUC= 0.631, p=0.015 for GLS 18 and AUC=0.652, p=0.005 for GLS 12 (Fig. 1). A cutoff value of -17.5 for GLS predicted CAD with 62% sensitivity and 63% specificity for GLS 18; and 71 % sensitivity and 42% specificity for GLS12.LSD and LSR were increased in patients with CAD, and both of them predicted CAD, AUC= 0.617; p=0.03 for LSD, and AUC=0.665; p=0.02 for LSR (Figure 1). A cut-off value of 0.85 for LSR predicted CAD with a sensitivity of 71% and a specificity of 55%.

In the evaluation of the territorial correlation between the 18 segments of left ventricle obtained by AFI and angiography, we defined LAD territory as the next segments: basal, middle and apical anterior, basal, middle and apical anteroseptal, middle and apical septal. For RC territory we defined the following segments: basal, middle and apical inferior, basal septal. Cx artery was considered: basal, middle and apical lateral, basal, middle and apical posterior. For the above mentioned coronary territory, we calculated the regional peak systolic LS as an average of the peak systolic

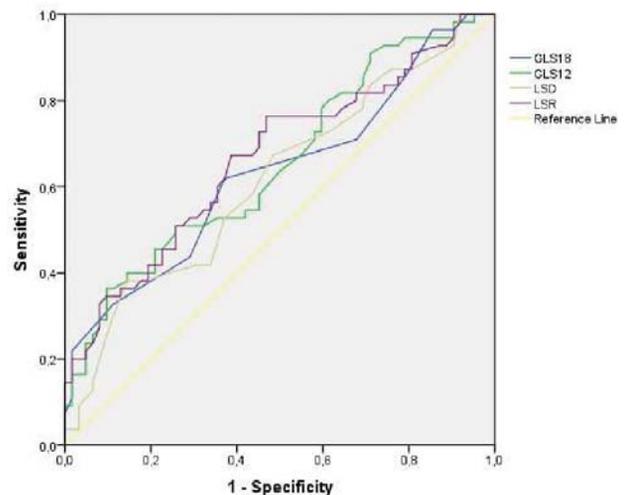


Figure 1. ROC curves for predicting significant CAD.

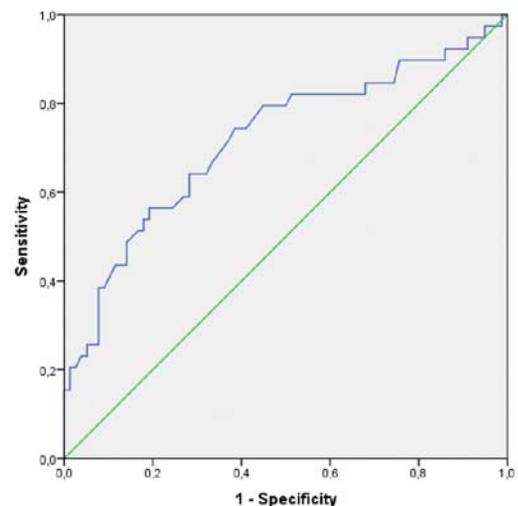


Figure 2. ROC curves for predicting significant LAD disease.

segmental LS of the segments included in that coronary territory.

Regional LS for LAD territory (8 segments) predicted LAD disease with 72% sensitivity and 63% specificity for a cutoff value of -18 of the regional LS, AUC=0.718, p=0.000 (Figure 2). Regional LS for RC territory (4 segments) had predictive value for RC disease: AUC=0.627, p=0.068 (Figure 3). For the Cx ar-

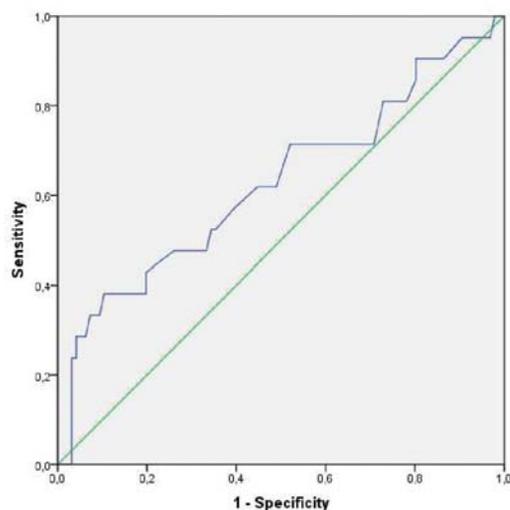


Figure 3. ROC curves for predicting RC disease.

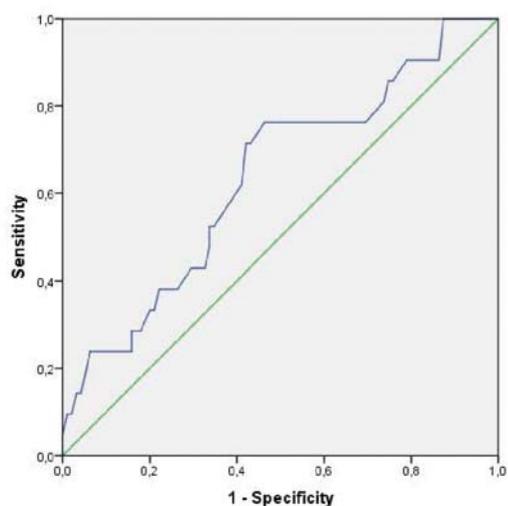


Figure 4. ROC curves for predicting significant Cx disease.

tery disease, the regional predefined LS (6 segments) could not predict disease in that territory, $AUC=0.585$, $p=0.226$; but we found that the regional LS of the lateral wall could predict Cx disease, with 72% sensitivity and 57% sensibility, for a cut off value of -16.5 , $AUC=0.64$, $p=0.052$ (Figure 4).

DISCUSSION

Previous studies have shown that GLS and segmental LS, measured by 2DSTE method are promising parameters for diagnosing ischaemic heart disease. Choi et al.¹³ evaluated patients with stable and unstable angina and normal resting wall motion and ejection fraction. They showed that GLS and segmental LS were significantly reduced in patients with severe ischaemic heart disease (left main CAD or three-vessel CAD). They also reported a better accuracy of strain in the mid and basal segments in the detection of high-risk CAD compared with the strain of the apical segments. Biering-Sorensen et al.¹⁴ demonstrated that GLS was significantly lower in patients with CAD compared with patients without CAD. GLS12 was an independent predictor of significant CAD in patients with suspected stable angina pectoris, and it significantly improved the diagnostic performance of exercise test. Another study of W. Tsai et al.¹⁵ found also, that the GLS measured by 2DSTE with AFI method was significantly decreased in patients with CAD. The LSD and the LSR were significantly higher in these patients. In W. Tsai's study LSR had the highest diagnostic value for CAD.

The present study demonstrated that in patients presenting with low risk ACS, GLS 12 or 18 segments have predictive value for CAD. The diagnostic perfor-

mance determined by the AUC was not significantly different for the two GLS. For the same cut off value of the GLS we observed a better sensitivity, but with a worse sensibility for GLS12 versus GLS18.

We also found a lower diagnostic rate for GLS than in the above mentioned studies. A possible explanation could be that only 3 patients (5.5%) from the CAD group had severe ischemic heart disease (3 coronary lesions). The incidence of severe coronary artery disease was higher in the above mentioned studies.

Another aspect we identified was a high prevalence of the cardiac risk factors in the study population, which is closer to a real-world situation. GLS is noted to be decreased not only in patients with CAD but also in patients with hypertension and hypertensive heart disease^{15,16}, diabetes¹⁷, hypertrophic cardiomyopathy¹⁸, or smokers¹⁵. In our study GLS was impaired by hypertension and diabetes, but strain parameters were still significantly different between the two groups. The prevalence of hypertension, diabetes and smoking did not differ significantly between the two groups. We found smaller values for the GLS in the control population than the normal ranges presented in literature¹⁹. This fact could be explained through the high prevalence of cardio-vascular risk factors in the control population (80.6% were hypertensive and one third had diabetes) and it could be another cause for the lower diagnostic rate of GLS found in our study. The basal LS was noted to be more affected in hypertensive heart disease, and this could be the reason for the small specificity observed for the GLS 12 in predicting CAD.

The regional predefined LS predicted CAD in LAD and RC territory. For the Cx artery we found that the regional LS of the lateral wall can predict Cx disea-

se. The regional predefined LS had the best diagnostic performance for LAD territory.

W. Tsai et al. were first to test the hypothesis that changes of segmental LS occur in both ischemic and nonischemic segments because of the LV remodeling response to chronic ischemia, with improvements to the LS in nonischemic segments¹¹. Their study showed that LSD and LSR were significantly higher in CAD group, and found that the LSR had the highest diagnostic value for CAD. There are also previous studies which have demonstrated a compensatory adaptive early response of the remote nonischemic myocardium during the acute phase of coronary occlusion²⁰⁻²². As in the above mentioned study we found a significantly increase in LSD and LSR in patients with CAD; both of them had the capacity to predict CAD. However, we did not find a significant difference regarding the diagnostic performance between GLS and LSR. These findings (increase in LSD or LSR) support the hypothesis of nonischemic segments remodeling as a response to chronic ischemia. Therefore, these two parameters together with regional and GLS could be useful in the diagnosis of CAD.

Our study has some limitations. Strain analysis is highly dependent on the quality of ultrasound window. We had to exclude 12 patients (9%) because of inadequate quality of the echocardiographic examination and impossibility for AFI analysis.

Also, in order to limit the influence of other factors on longitudinal strain we excluded patients with wall motion abnormalities on 2D echocardiography and significant heart valve disease. Another limitation was that we did not evaluate the extent of coronary lesions using intravascular ultrasound or functional studies-fractional flow reserve, which could have provided a more accurate measure on their severity and consequences, myocardial ischemia.

CONCLUSIONS

In low-risk ACS, global and regional LS could be a powerful noninvasive diagnostic tool for significant

CAD, despite not being CAD specific. LSD and LSR are also valuable parameters, and together with strain parameters could improve the accuracy of rest echocardiography in the diagnosis of CAD.

Further larger studies would be needed to determine the cut-off values for strain parameters which could best predict the CAD. The prognostic value of the above mentioned parameters should also be evaluated.

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Abbreviation

ACS	acute coronary syndrome
AFI	automated function imaging
AUC	area under the curve
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society
Cx artery	circumflex artery
2C	two-chamber
4C	four-chamber
GLS	global peak systolic longitudinal strain
2DSTE	two dimensional speckle tracking echocardiography
LAD artery	left anterior descending artery
LS	longitudinal strain
LSD	longitudinal strain difference
LSR	longitudinal strain ratio
LV	Left ventricular
LVES	left ventricle ejection fraction
RC	right coronary
ROC	receiver operating characteristic
ROI	region of interest

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