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Short communication

Longitudinal 2D strain can help diagnose coronary artery disease in patients with suspected non-ST-elevation acute coronary syndrome but apparent normal global and segmental systolic function

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ABSTRACT

Background: The clinical work-up of patients presenting with chest pain is a diagnostic challenge. We investigated the diagnostic performance of global (GLS) and territorial (TLS) longitudinal strain to predict coronary artery disease (CAD) in patients presenting with suspected non-ST-segment elevation acute coronary syndrome (NSTE-ACS) but apparent normal global and regional systolic function.
Methods: 150 consecutive suspected NSTE-ACS patients were initially screened for inclusion ; 58 patients with normal LVEF (≥55%) and WMSI (=1) were prospectively enrolled. Speckle-tracking echocardiography was performed on admission and all the patients underwent coronary angiography. CAD was defined as the presence of stenosis of >50%.
Results: CAD was present in 33 patients (57%). LVEF was 60.7 ± 4.6% in group 1 (CAD) and 61.1 ± 5.0% in group 2 (no CAD). Global longitudinal strain (GLS) was altered in group 1 (−16.7 ± 3.4%) as compared to group 2 (−22.4 ± 2.9%, $p < 0.001$). ROC curve analysis showed a high diagnostic value of GLS for the prediction of CAD (AUC = 0.92 [0.84–1.00], $p = 0.0001$). TLS was able to discriminate between coronary stenosis in the LAD, LCX or RCA.
Conclusions: Longitudinal 2D strain has a good diagnostic value and can efficiently localize the culprit lesion in patients presenting with NSTE-ACS but apparent normal global and regional systolic function.

1. Introduction

The positive diagnosis of acute coronary syndrome (ACS) is often a difficult challenge, particularly in patients with an inconclusive initial clinical and paraclinical examination. Echocardiography plays an important role in the clinical work-up of patients with chest pain by permitting evaluation of the global and segmental systolic function and by excluding differential diagnosis [1].

However, since the left ventricular ejection fraction (LVEF) and regional kinetics as assessed by the wall motion score index (WMSI) are normal in 25 to 76% of cases [2–4], transthoracic echocardiography is not informative for the diagnosis in about half of the patients presenting with suspected non-ST-elevation acute coronary syndrome (NSTE-ACS). Recently, 2D strain speckle-tracking has emerged as a new echocardiographic imaging mode which allows one to detect subtle left ventricular global and segmental kinetic alterations. In ACS, speckle-tracking echocardiography has been reported to be of help to predict significant coronary stenosis [5] or coronary occlusion [6,7]. However, the diagnostic value of 2D strain in suspected ACS patients without global or regional wall motion abnormality has not yet been reported.

The main objective of this study was to determine the diagnostic value of longitudinal strain as assessed by speckle-tracking in patients presenting with suspected acute NSTE-ACS but apparent normal LV global and regional function.

2. Methods

This study was conducted in a single tertiary coronary care center. A total of 150 consecutive suspected NSTE-ACS patients were initially screened for inclusion (January–April 2014). Those with left ventricular systolic dysfunction ($n = 70$) or poor visual analysis of LV wall motion (≥2 uninterpratable LV segments) ($n = 22$) were excluded. Eventually, fifty-eight patients admitted to the cardiac intensive care unit with suspected NSTE-ACS but apparent normal left ventricular systolic function as assessed by LVEF (≥55%) and WMSI (=1.0) were prospectively enrolled. All patients had experienced an episode of acute chest pain

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Table 1
Characteristics of the study population.

	Total patients ($n = 58$)	CAD ($n = 33$)	no CAD ($n = 25$)	p
Age - years	58.4 ± 12.8	57.8 ± 11.5	59.2 ± 14.5	0.69
Gender - Male sex	35 (60.3)	26 (78.8)	8 (36)	0.001
Risk factors				
Hypertension	35 (60.3)	21 (63.6)	14 (56)	0.60
Diabetes mellitus	19 (32.8)	12 (36.4)	7 (28)	0.60
Dyslipidemia	33 (56.9)	22 (66.7)	11 (44)	0.11
BMI > 25 kg/m^2	37 (63.8)	19 (57.6)	18 (72)	0.28
Current smoker	27 (46.6)	16 (48.5)	11 (44)	0.80
Family history	16 (27.6)	13 (39.4)	3 (12)	0.04
Medication				
Beta-blocker	19 (32.8)	12 (36.4)	7 (28)	0.60
ACE inhib./ARB	25 (43.1)	16 (48.5)	9 (36)	0.43
Thiazide diuretics	8 (13.8)	5 (15.2)	3 (12)	1.00
Thienopyridine	7 (12.1)	4 (12.1)	3 (12)	1.00
Antiplatelet drug	19 (32.8)	14 (42.4)	5 (20)	0.09
Statin	26 (44.8)	18 (54.5)	8 (32)	0.11
Troponine Ic > 0.03 ng/mL	39 (67.2)	27 (81.8)	12 (48)	0.01
Ischemic ECG findings	16 (28.6)	13 (39.4)	3 (12)	0.04
GRACE score[a]	3.19 ± 3.05	3.06 ± 2.55	3.36 ± 3.68	0.72
LVTDV[b]	43.3 ± 10.3	44.2 ± 8.6	42.2 ± 12.3	0.47
LVEF[c]	60.9 ± 4.8	61.0 ± 5.0	60.7 ± 4.7	0.85
Final diagnosis				
NSTEMI		27 (81.8)		
Unstable angina		6 (18.2)		
Type 2 MI[d]			7 (28)	
Non cardiac pain			18 (72)	
Angiography				
0 VD[e]			25 (43.1)	
1 VD	21 (36.2)			
2 VD	5 (8.6)			
3 VD	7 (12.1)			
LAD[f] stenosis	20 (34.5)			
LCX[g] stenosis	15 (25.9)			
RCA[h] stenosis	17 (29.3)			

Values are n (%) or mean ± SD.
[a] GRACE score expressed as the risk (%) of death at one year.
[b] LVTDV: left ventricular telediastolic volume (mL/m^2).
[c] LVEF: left ventricular ejection fraction.
[d] MI: myocardial infarction.
[e] VD: vessel disease.
[f] LAD: left anterior descending.
[g] LCX: left circumflex.
[h] RCA: right coronary artery.

lasting at least 10 min over the past 3 days and were under treatment with invasive care for ACS including coronary angiography, according to current guidelines [1]. Exclusion criteria were: prior known LV dysfunction, age <18 years, left bundle branch block, history of myocardial infarction, severe valvular dysfunction or atrial fibrillation. All patients gave their written informed consent to participate in the study. The study was approved by the regional ethics committee.

Electrocardiograms (ECGs) were performed on admission and repeated every day during hospitalization stay. They were evaluated by experienced cardiologists and were considered to be abnormal in the presence of >1 mm ST depression, T-wave changes or dynamic repolarization abnormalities in at least two consecutive leads. Troponin I (TnI) assays (TnI–Ultra assay on the ADVIA Centaur immunoanalyzer, Siemens®) were performed on admission and at 3 h. Elevated troponin I was based on at least one assay above the uper limit of normal (99th percentile) defined by the laboratory (≥0.04 ng/mL).

Echocardiography was performed in the hour following the admission to the acute coronary care unit, and prior to coronary angiography, using a Vivid S5 Ultrasound Machine and a 3Sc-RS transducer (GE Vingmed Ultrasound AS, Horten, Norway). Echocardiographic recordings were analyzed offline by two experienced observers blinded to patients' data, using commercially available software (EchoPAC version 113, GE Vingmed Ultrasound AS). LV volumes and ejection fractions (EF) were assessed by the biplane Simpson method. Wall motion was visually assessed in a 17-segment model by two observers (each segment was assigned a score of 1 for normal wall motion, 2 for hypokinetic motion, 3 for akinetic motion or 4 for dyskinetic motion) and the wall motion score index (WMSI) was calculated by averaging the segmental values. The peak negative systolic longitudinal strain was assessed in all 17 longitudinal LV segments and the segmental values were averaged to give the global longitudinal strain (GLS). The territorial longitudinal strain (TLS) was calculated for each major coronary artery (left anterior descending artery (LAD), left circumflex artery (LCX) and right coronary artery (RCA) as the average peak systolic strain in segments belonging to the theoretical perfusion territory of the artery [8]. The reproducibility of the echocardiographic analyses was evaluated by determining the intraclass correlations for intraobserver and interobserver variability. These were respectively 0.96 and 0.95 for GLS, 0.97 and 0.95 for LAD TLS, 0.96 and 0.81 for LCX TLS, 0.93 and 0.90 for RCA TLS.

All the patients underwent coronary angiography in average within 27 ± 20 h of admission and CAD was assessed by visual estimation in multiple projections. Significant coronary artery stenosis was defined as a 50% reduction of vessel diameter in at least one major coronary artery. The patients were finally classified in two groups according to the presence (group 1) or absence (group 2) of significant CAD.

3. Results

The patients' mean age was 58.4 ± 12.8 years, with a majority of males (60.3%) and 33 patients (56.9%) with significant CAD. The clinical characteristics of the patients are reported in Table 1.

All patients had a normal LVEF and WMSI, as was required for inclusion in the study. LVEF was 61.0 ± 5.0 in group 1 and 60.7 ± 4.7 in group 2 ($p = 0.85$), while WMSI was 1 in both groups. The global peak systolic longitudinal strain measured on admission was more significantly altered in patients with than in those without CAD (−16.7 ± 3.4 vs −22.4 ± 2.9%, $p < 0.001$). GLS was numerically more strongly altered in patients with 3-vessel disease (−15.0 ± 2.3%) than in those with 1-vessel (−17.3 ± 3.7%) or 2-vessel disease (−16.6 ± 2.8%), but these differences were not statistically significant ($p = 0.75$ and $p =$

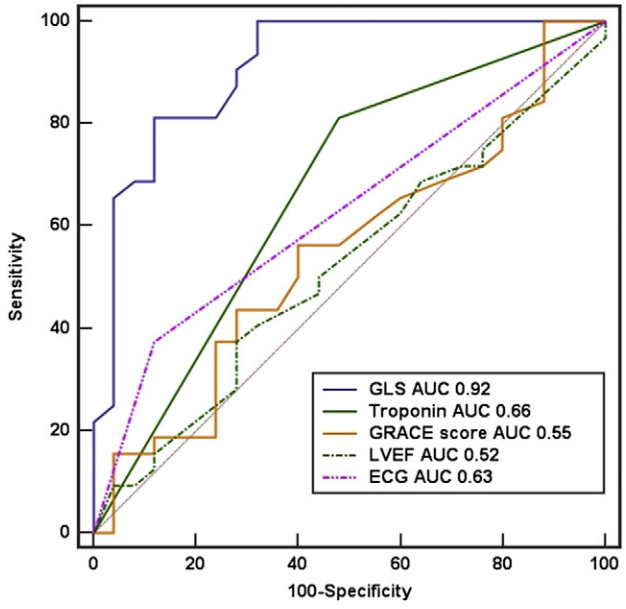

Fig. 1. Diagnostic performance of GLS compared to Troponin, Grace SCORE, LVEF and ECG. ROC curve analysis showing the comparative diagnostic performance of GLS (blue line), troponin (green line), GRACE score (yellow line), LVEF (green dotted line) and ECG (pink line) to identify patients with CAD. Differences between the AUC values: GLS vs troponin $p = 0.0002$, GLS vs ECG $p < 0.0001$, GLS vs LVEF and GRACE score $p < 0.0001$.

1.00, respectively). ROC curve analysis showed that GLS displayed good diagnostic performance for the prediction of CAD (AUC = 0.92) with a sensitivity of 81% and a specificity of 88% at the optimal cut-off of −19.7%. When the cut-off value of GLS was increased to −21%, the sensitivity reached 100% with a specificity of 68%. Comparing ROC curve areas for the prediction of CAD, the diagnostic value of GLS (AUC = 0.92) was significantly higher than that of LVEF (AUC = 0.52, $p < 0.0001$ vs GLS), GRACE score (AUC = 0.55, $p < 0.0001$ vs GLS), ECG (AUC = 0.55, $p < 0.0001$ vs GLS) or troponin (AUC = 0.66, $p < 0.0002$ vs GLS) (Fig. 1). Interestingly, the diagnostic value of GLS for CAD in the study population was significant whether troponin was positive (AUC = 0.87 [0.74–1.00], $p < 0.001$) or negative (AUC = 0.96 [0.88–1.00], $p < 0.01$). A ROC curve analysis of the diagnostic performance of TLS to predict coronary stenosis in the LAD, LCX or RCA is presented in Fig. 2. In patients with LAD stenosis, the average TLS in LAD segments had a significantly higher diagnostic value (AUC = 0.93) than TLS in LCX (AUC = 0.81) or RCA territories (AUC = 0.70) ($p = 0.047$ LAD vs LCX and $p < 0.0001$ LAD vs RCA). The optimal threshold for the average TLS in LAD segments to predict LAD stenosis was −19.4%, yielding a sensitivity of 91% and a specificity of 86%. In patients with LCX stenosis, the average TLS in LCX segments had a significantly higher diagnostic value (AUC = 0.88) than TLS in LAD (AUC = 0.67) or RCA segments

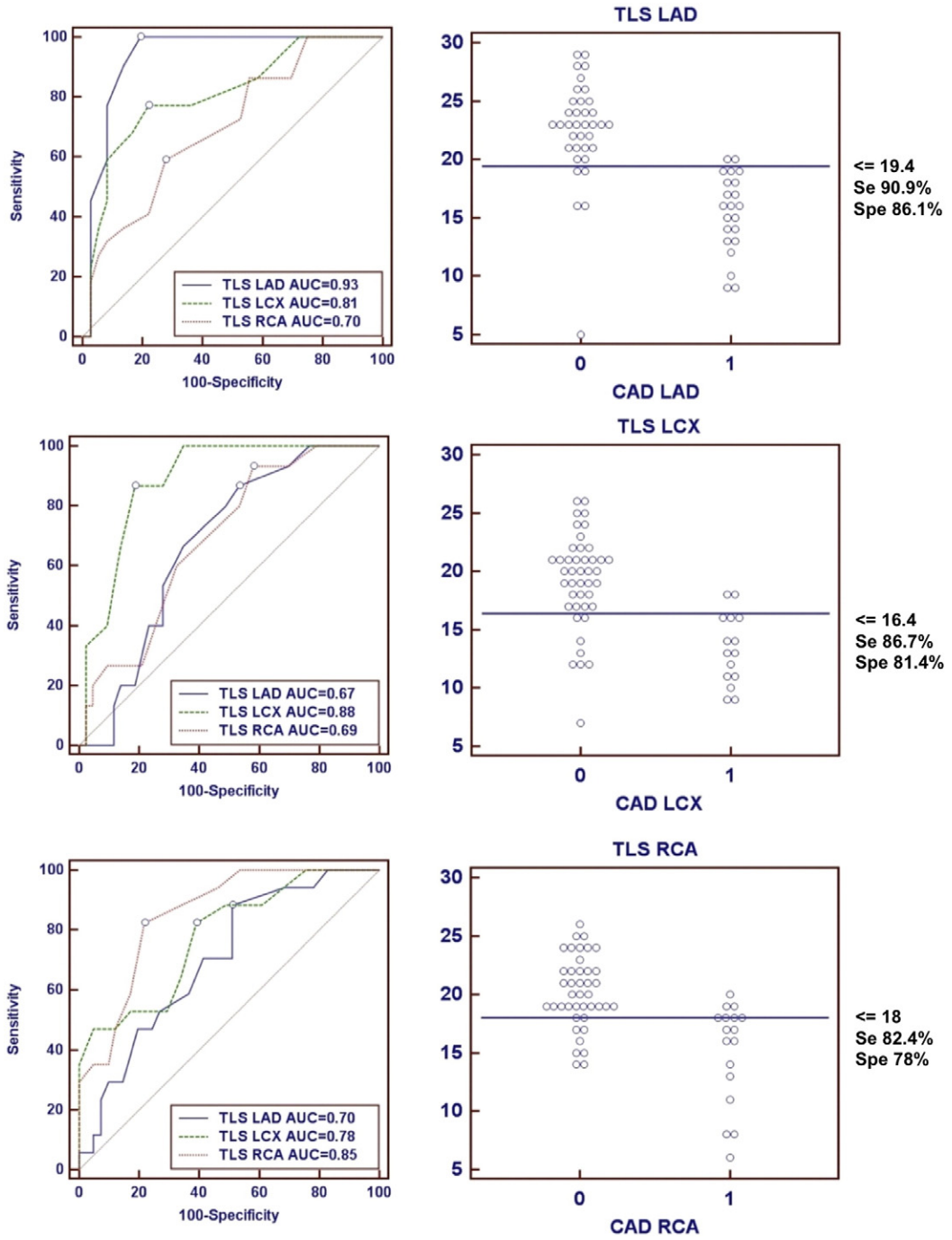

Fig. 2. Diagnostic performance of TLS in LAD, LCX and RCA territories in case of significant stenosis in LAD, LCX and RCA respectively. ROC curve analyses (left panels) and interactive diagrams (right panels) with the optimal thresholds comparing the diagnostic performance of the average TLS in LAD segments (blue line), LCX segments (green line) and RCA segments (red line) to identify patients with CAD in patients with LAD stenosis (upper panels), LCX stenosis (middle panels) and RCA stenosis (lower panels).

(AUC = 0.69) ($p = 0.0005$ LCX vs LAD and $p = 0.0074$ LCX vs RCA). The optimal threshold for the average TLS in LCX segments to predict LCX stenosis was −16.36%, giving a sensitivity of 87% and a specificity of 81.4%. In patients with RCA stenosis, the average TLS in RCA segments had a significantly higher diagnostic value (AUC = 0.85) than TLS in LAD (AUC = 0.70) or LCX territories (AUC = 0.70) ($p = 0.015$ RCA vs LAD and $p = 0.30$ RCA vs CD). The optimal threshold for the average TLS in RCA segments to predict RCA stenosis was −18%, yielding a sensitivity of 82% and a specificity of 78%.

4. Discussion

The principal findings of this study of 2D strain speckle-tracking in patients admitted to the coronary care unit with chest pain and suspected NSTEMI but apparent normal global and regional systolic function are as follows: i) GLS was significantly altered in patients with CAD with respect to patients without CAD, ii) the diagnostic performance of GLS to predict CAD was high (AUC = 0.92) and seemed to be higher than for ECG, troponin, or GRACE score, iii) TLS was of significant value to discriminate the myocardial territory involved in CAD. The main result of our study is the good diagnostic performance of global longitudinal strain to predict CAD in patients presenting with suspected NSTE-ACS. To the best of our knowledge, this is the first study reporting longitudinal 2D strain in the setting of NSTE-ACS patients without wall motion abnormalities (LVEF > 55%, WMSI = 1). A cut-off of −19.7% for GLS yielded a sensitivity of 81% and a specificity of 88% to detect the presence of CAD (AUC = 0.92). At a cut-off of −21%, GLS was able to rule out significant coronary artery stenosis in 100% of patients. The potential clinical applications of these results are important. Thus, GLS might be of help to rule out CAD and allow early discharge, avoiding in some cases useless coronary angiography. For example, if a cut-off value of −21% for GLS had been applied to our patients, a total of 16 (28%) normal coronary angiographies could have been avoided. These results are in line with previous studies of GLS in ACS. However, these earlier studies included patients with global and/or regional systolic dysfunction [5,6]. The present work extends the usefulness of GLS to patients with normal LVEF and WMSI and suggests an incremental diagnostic value of GLS over the visual assessment of wall motion in patients whose initial conventional echocardiography does not suggest CAD with regard to the global or regional LVEF kinetics. It supports the inclusion of 2D strain speckle-tracking in the diagnostic stratification of patients presenting with acute chest pain, as a complementary tool to ECG and troponin.

We observed in our study population that the diagnostic performance of GLS was superior to high-sensitvity troponins, ECG, or GRACE score to identify patients with CAD. Several hypotheses might explain this result: (i) in the paradigm of the ischemic cascade, left ventricular systolic dysfunction occurs prior to ECG modifications and symptoms; (ii) the endocardium is the first layer affected by ischemia and since the subendocardial myocardial fibres are mainly oriented in a longitudinal direction, longitudinal myocardial function might be affected primarily; (iii) conventional echocardiographic parameters including LEVF and WMSI are based on a visual assessment of the ventricular wall motion and in the case of moderate ischemia leading to longitudinal dysfunction, these subtle abnormalities might be undetectable to the naked eye due to compensatory mechanisms of circumferential and radial contraction.

A normal conventional echocardiograph at rest is an important marker of low clinical risk in patients presenting with acute chest pain and a non-ischemic ECG. Nevertheless, a visual assessment of wall motion abnormalities and calculation of a wall motion score is insufficient to detect subtle contractility defects and thus to rule out significant CAD, especially in patients with unstable angina pectoris. Our study indicates that GLS is effective to distinguish between patients with and without CAD, regardless of the positivity or negativity of cardiac biomarkers. Although the number of patients is low in this sub-group analysis, it suggests that GLS seems to be accurate to identify CAD in patients with (AUC = 0.87 ± 0.07) as well as in patients without troponin elevation (AUC = 0.96 ± 0.04), indicating a particular utility of 2D-strain in such patients. This result might be related to the very high sensitivity of novel HS troponin assays, to the detriment of the specificity of the test, leading to the detection of more patients with non specific troponin elevation, especially type 2 myocardial infarction.

In addition to GLS, the longitudinal strain can be analyzed regionally using TLS. Our results indicate a good localizing value of the territorial longitudinal strain to predict significant coronary artery stenosis in a given perfusion territory.

5. Conclusions

The present study suggests that myocardial longitudinal strain imaging by 2D speckle-tracking might be of help in the diagnostic work-up of CAD in patients with apparent normal global and regional systolic function but suspected NSTE-ACS. In this setting, GLS displayed a higher diagnostic performance than troponin or ECG. In addition, TLS may be helpful to localize coronary artery stenosis. Similar studies with an increased sample size will need to be conducted to confirm these results.

Conflicts of interest

None.

Acknowledgments

None.

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