



# The duration of early systolic lengthening may predict ischemia from scar tissue in patients with chronic coronary total occlusion lesions

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## Abstract

In this study, we aimed to investigate the predictive value of early systolic lengthening duration in differentiating myocardial ischemia from scar tissue in patients with chronic coronary total occlusion. A total of 69 patients were included in the study. The participating patients were divided into two groups as 35 patients with ischemia and 34 patients with scar tissue based on the results of the myocardial perfusion scintigraphy. In the scar group compared to the ischemia group; LVEF, GLS, SRS<sup>1</sup>, and the duration of early systolic lengthening were significantly lower; whereas, EDV, ESV, and WMSI were significantly higher in the scar group compared to the ischemia group. In the multivariate logistic regression test, LVEF (OR 1.150, 95% CI 1.044–1.268,  $p=0.005$ ) and duration of early systolic lengthening (OR 1.021, 95% CI 1.004–1.039,  $p=0.016$ ) were determined as independent predictive parameters for ischemia detected by myocardial perfusion scintigraphy. Duration of early systolic lengthening obtained by speckle tracking echocardiography in patients with chronic total occlusion lesions may be useful in differentiating ischemia from scar tissue detected in myocardial perfusion scintigraphy. Prolonged duration of early systolic lengthening in patients with chronic total occlusion lesions was related to the presence of ischemia detected by myocardial perfusion scintigraphy.

**Keywords** Chronic total occlusion · Ischemia · Scar · Speckle tracking · Early systolic lengthening

## Introduction

Chronic total occlusions (CTOs) of the coronary arteries are found in 15–25% of patients with stable angina pectoris [1]. CTO is defined as a 100% occlusion in coronary arteries with a thrombolysis in myocardial infarction (TIMI) grade of 0 flow lasting for at least 3 months [2]. Although the benefits of revascularization of chronic totally occluded coronary arteries are still controversial, they remain to play an important role in interventional cardiology.

A decision of performing percutaneous revascularization in CTO is taken in patients with persistent symptoms despite optimal medical therapy (OMT) when myocardial viability

is observed in the area supplied by the occluded vessel [3]. Myocardial ischemia and viability can be assessed using selected diagnostic tests among several non-invasive imaging methods, which include single-photon emission computed tomography (SPECT), dobutamine stress echocardiography, cardiac magnetic resonance imaging (CMR), and PET imaging with F-18 Fluorodeoxyglucose [4]. Among these, CMR is considered as the gold standard imaging method for the evaluation of myocardial viability [4]. The option of performing a percutaneous intervention is considered when 10–12.5% myocardial ischemia or reversible perfusion defects are detected with these non-invasive imaging methods [5–8]. However, a percutaneous intervention is not recommended in the absence of myocardial viability since left ventricular ejection fraction (LVEF) will not improve in these cases even though the CTO is resolved [9, 10]. Therefore, it is important to distinguish between the presence of myocardial ischemia and scar formation in CTO lesions in patients with severe wall motion abnormalities.

The two-dimensional speckle tracking echocardiography (2D-STE) is a method for assessing the left ventricular (LV)

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function and the presence of ischemic changes, providing comprehensive information compared to conventional echocardiography [11–13]. Recent studies have shown that when the LV pressure starts rising during early systole, ischemic myocardium will tend to lengthen before the onset of systolic shortening, probably because its ability to generate active force is reduced [14, 15]. This phenomenon is defined as early systolic lengthening. A previous study reported that the duration of early systolic lengthening (DESL) measured with 2D-STE was a predictor of significant coronary artery disease in the patients with stable angina pectoris [15]. A study by Zahid W. et al. reported that DESL might be associated with the infarct size in patients with non-ST-segment-elevation acute coronary syndrome (NSTEMI) [16]. Lyseggen et al. reported that the ratio of the systolic lengthening to total shortening measured with 2D-STE might predict ischemic but viable myocardium in patients with ST-segment elevation myocardial infarction (STEMI) [14]. Based on these studies, we aimed to investigate the predictive value of DESL in differentiating myocardial ischemia from scar tissue in patients with CTO.

## Methods

This study was designed as a prospective single-center, non-randomized observational study. A total of 69 patients, who had a single vessel CTO without any significant findings in the remaining coronary arteries, were examined in the dates between June 2017 and January 2018. Exclusion criteria were the presence of an acute coronary syndrome, a history of myocardial infarction (MI) or previous heart surgery, a CTO involving other coronary arteries ( $\geq 50\%$ ), a severe valvular disease, atrial fibrillation, and the presence of bundle branch block with QRS  $> 120$  ms. All patients with persistent symptoms despite OMT, who were decided to be evaluated for performing a percutaneous intervention, underwent a  $^{99m}\text{Tc}$ -sestamibi stress/rest MPI-SPECT.

## Blood tests and clinical features

Blood samples, hemogram, and other biochemical parameters were examined at admission of the patients to the hospital. A fasting plasma glucose level  $\geq 126$  mg/dl or a random plasma glucose level  $\geq 200$  mg/dl plus diabetic symptoms, or the second-hour plasma glucose level  $\geq 200$  mg/dl in oral glucose tolerance test, or a HbA1C level  $\geq 6.5$  were accepted in favor of a diabetes mellitus (DM) diagnosis. Arterial hypertension (HT) was diagnosed in patients with a blood pressure value  $> 140/90$  mmHg or in patients receiving anti-hypertensive therapy.

Body mass index (BMI) was calculated by dividing the body weight by the square meter of the patient height (kg/

m<sup>2</sup>). Body surface area was calculated with the Mosteller formula ( $\text{m}^2 = [\text{height (cm)} \times \text{weight (kg)} / 3600]^{1/2}$ ).

Glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease formula as follows:  $\text{GFR} = 186 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if women}) \times (1.21 \text{ if black})$  [17].

The study was approved by the local institutional ethics committee. Oral and written informed consents were obtained from all participants.

## Echocardiography

### Two-dimensional echocardiography

All echocardiographic examinations were performed with the help of the Vivid 7 machine (GE Vingmed Ultrasound AS, Horten, Norway), which was equipped with a 3.5 MHz transducer. A total of three cardiac cycles were recorded at the end of the expiration phase. Settings were manually adjusted in order to obtain optimal images. All data were transferred to a workstation for further offline analysis (EchoPAC PC; GE Vingmed Ultrasound AS).

Conventional two-dimensional (2D) echocardiographic examinations were performed according to the recommendations of the American Society of Echocardiography [18]. LVEF was calculated using the biplane Simpson's method [19]. The wall motion score index (WMSI) was calculated with the 17-segment model for the LV. The contractility of the individual segments was scored as follows: 1 = normal or hypercontractile; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia. The WMSI was calculated by dividing the sum of the score of each segment by the number of visualized segments [20].

### Doppler imaging

The LV inflow was evaluated with the tissue Doppler imaging. Early (E) and late (A) wave ventricular filling velocities, and E/A ratio were measured with the mitral inflow profile [21]. The Nyquist limit was set at 15–20 cm/s in order to acquire tissue Doppler imaging data and the minimal optimal gain was used. The frame rate was set in the range of 135–145 frames per second for TDI techniques. The myocardial systolic (Sm), early diastolic (Em), and late diastolic (Am) velocities were obtained at the septal and lateral mitral annulus by placing a sample volume. The E/Em ratio was subsequently calculated with the help of the septal and lateral measurements and the mean values were determined.

## Speckle tracking echocardiography

All measurements used in this analysis were performed offline and by one investigator, blinded to the clinical data. Using a dedicated software package (Echopac, GE Vingmed) 2D strain and strain rate (SR) were measured as previously described, to obtain information about the local myocardial function and velocity [22].

For speckle tracking analysis, three cycles were recorded at a frame rate of  $\geq 45$  fps, and the mean value was calculated for the strain analysis. The aortic valve opening and closing times were measured with the LV outflow Doppler profile and they were integrated into the speckle tracking strain profile in order to exclude post-systolic components. LV endocardial borders were automatically detected by the software in apical views with the help of three manually selected landmark points (lateral and septal mitral annulus and LV apex). Finally, automatic tracking of the myocardial speckles was performed throughout the cardiac cycle. Manual correction of the border tracings was avoided as far as possible. Global longitudinal strains (GLS) were obtained for apical 4-chamber, 3-chamber, and 2-chamber views, including all LV myocardial segments (six segments per view). Similarly, LV strain rate during systole (LV SRS), early diastole (LV SRE), and late diastole (LV SRA) were calculated.

The duration of LV early systolic lengthening was defined as the time starting from the onset of the Q wave on ECG (or onset of the R wave if the Q wave was absent) until the time of maximum myocardial systolic lengthening. For each segment, the duration of early systolic lengthening was recorded by fully automated software. Values for all analyzed segments were then averaged to obtain a mean value.

## Coronary angiography

Coronary angiography was performed via the femoral percutaneous approach using a Siemens Angiocore (Germany) device by experienced interventional cardiologists. Chronic total occlusions were diagnosed on the basis of visual angiographic characteristics.

## Myocardial perfusion scintigraphy

Studies were performed using 2-day protocols of  $^{99m}\text{Tc}$ -sestamibi stress and  $^{99m}\text{Tc}$ -sestamibi rest. Patients fasted  $> 6$  h before the study. Patients underwent exercise treadmill testing for the stress study. During the exercise treadmill test, they received an intravenous injection of 10 to 12 mCi (370–444 MBq)  $^{99m}\text{Tc}$ -sestamibi at peak exercise. Then, the patients continued the exercise testing for 1 min. The following day, the rest study was performed with the same

dose administered for the stress study. SPECT images were acquired 15–60 min after the tracer injection using the IQ-SPECT Symbia S system (Siemens, USA) gamma camera system with dedicated multifocal SMARTZOOM™ collimators performing cardiocentric acquisition. SPECT tomograms were reconstructed and reoriented by using an automated algorithm system as described in previous studies [23, 24]. Images were processed using Cedars–Sinai quantitative perfusion SPECT (QPS) software.

The presence of redistribution or reversibility in resting images in a myocardial perfusion defect was defined as ischemia. The absence of a significant redistribution or reversibility was defined as scar [25].

## Statistical analysis

All values were expressed as mean  $\pm$  standard deviation, median (25th–75th percentile) or as percentages. The normal distribution of each type of variables was assessed using the Kolmogorov–Smirnov test. For the non-normally distributed variables, the comparison of the groups was performed using nonparametric tests. Comparisons of the continuous variables in the two groups were performed using the Student's *t*-test or Mann–Whitney *U* test. Distributions of the categorical variables were compared with the chi-square or Fisher's exact tests. Pearson's correlation analysis was used for comparing the correlation between the continuous variables. Highly inter-correlated variables were identified by Pearson's correlation coefficient; however, only one of these variables was entered into the multivariate regression model. Significant parameters in the univariate analysis ( $p \leq 0.05$ ) were included in the multivariate analysis.

Finally, a multiple logistic regression analysis was performed to determine independent predictors of myocardial ischemia detected by myocardial perfusion scintigraphy and the receiver operator characteristic (ROC) curve analysis was performed to test the diagnostic accuracy of DESL. All statistical analyses were performed with SPSS v16.0 (SPSS, Inc., Chicago, IL). A *p*-value  $< 0.05$  was considered statistically significant.

## Results

A total of sixty-nine patients were included in the study. The mean age of the patients was  $63.79 \pm 9.61$  years. Of the included patients, 54 (78%) were males and 24 (34.8%) had diabetes mellitus. The participating patients were divided into two groups as 35 patients with ischemia and 34 patients with scar tissue based on the results of the myocardial perfusion scintigraphy. Clinical and demographic characteristics and laboratory findings of the patients were summarized in Table 1. There were no statistically significant differences

**Table 1** Clinical characteristics, demographic, laboratory and angiographic finding of the study population

	All (n:69)	Ischemia (n:35)	Scar (n:34)	p
Age (years)	63.79 ± 9.61	62.8 ± 9	64.7 ± 10.2	0.429
Sex (male)	54 (78%)	28 (80%)	28 (82.3%)	0.523
DM	24 (34.8%)	13 (37.1%)	11 (32.3%)	0.537
HT	35 (50.7%)	17 (48.6%)	18 (52.9%)	0.811
BMI (kg/m <sup>2</sup> )	27.74 ± 3.49	27.4 ± 3.7	28 ± 3.2	0.5
BSA (m <sup>2</sup> )	1.9 [1.8–2]	1.9 [1.75–2]	1.9 [1.8–2.02]	0.68
Hemoglobin (mg/dl)	13.69 ± 1.61	13.8 ± 1.6	13.4 ± 1.5	0.32
Creatinine (mg/dl)	1 ± 0.43	0.95 ± 0.19	1.05 ± 0.58	0.35
GFR ( ml/min/1.73 m <sup>2</sup> )	82.04 ± 20.85	85.54 ± 19.31	78.43 ± 22.03	0.15
Diseased vessel				
LAD	28 (40.6%)	13 (37.1%)	15 (41.1%)	
Cx	10 (14.5%)	5 (14.3%)	5 (14.7%)	0.811
RCA	31 (44.9%)	17 (48.6%)	14 (41.2%)	

*BMI* Body mass index, *BSA* Body surface area, *DM* Diabetes mellitus, *GFR* Glomerular filtration rate, *HT* Hypertension, *LAD* Left anterior descending coronary artery, *CX* Circumflex coronary artery, *RCA* Right coronary artery

between the two groups with respect to the clinical, demographic, laboratory and angiographic findings.

The echocardiographic parameters by the ischemia and scar tissue groups are presented in Table 2. In the scar group compared to the ischemia group; LVEF (54.73 ± 8.15 vs. 43.89 ± 8.58,  $p < 0.001$ ), GLS (− 15.27 [− 17.6 to − 12.9] vs. − 10.84 [− 13.5 to − 7.7],  $p < 0.001$ ), SRS' (− 0.71 ± 0.18 vs. − 0.61 ± 0.18,  $p = 0.03$ ), and the duration of early systolic lengthening (80.6 [49–96] vs. 34 [23.37–40.31],  $p < 0.001$ ) were significantly lower; whereas, EDV (118 [107–130] vs. 130 [119.5–140],  $p = 0.01$ ), ESV (48.17 [4.41–61.9] vs. 68 [58.77–84.4],  $p < 0.001$ ), and WMSI (1.1 [1–1.3] vs. 1.48 [1.34–1.88],  $p < 0.001$ ) were significantly higher in the scar group compared to the ischemia group (the values in the

parentheses represent the values for the ischemia and scar groups respectively).

In the univariate correlation analysis, a close relationship was observed between LVEF, ESV and WMSI values. Therefore, ESV and WMSI values were excluded from the multivariate analysis. The correlation coefficients in Pearson's and Spearman's correlation analyses are presented in Table 3.

The statistically significant LVEF, SRS', EDV, GLS and DESL values found in the univariate analyses were evaluated with the multivariate logistic regression analysis. Based on the results of the multivariate logistic regression test, LVEF (OR 1.150, 95% CI 1.044–1.268,  $p = 0.005$ ) and DESL (OR 1.021, 95% CI 1.004–1.039,  $p = 0.016$ ) were determined as

**Table 2** Conventional and speckle tracking echocardiographic characteristic of the study population

	All (n:69)	Ischemia (n:35)	Scar (n:34)	p
EF (%)	49.39 ± 9.94	54.73 ± 8.15	43.89 ± 8.58	<0.001
EDV (ml)	128.24 [110–135]	118 [107–130]	130 [119.5–140]	0.01
ESV (ml)	61 [47.4–71]	48.17 [4.41–61.9]	68 [58.77–84.4]	<0.001
E/Em	7.53 [5.4–9.25]	7.8 [5.2–10]	7.51 [7.17–8.17]	0.947
WMSI	1.31 [1.05–1.51]	1.1 [1–1.3]	1.48 [1.34–1.88]	<0.001
GLS (%)	− 13.4 [− 16.05 to − 9.95]	− 15.27 [− 17.6 to − 12.9]	− 10.84 [− 13.5 to − 7.7]	<0.001
SRS' (s <sup>−1</sup> )	− 0.66 ± 0.18	− 0.71 ± 0.18	− 0.61 ± 0.18	0.03
SRE' (s <sup>−1</sup> )	0.69 [0.54–0.79]	0.7 [0.58–0.80]	0.66 [0.47–0.73]	0.352
SRA' (s <sup>−1</sup> )	0.73 ± 0.204	0.78 ± 0.2	0.68 ± 0.19	0.054
Duration of early systolic lengthening (ms)	42 [26.2–87]	80.6 [49–96]	34 [23.37–40.31]	<0.001

*EF* left ventricular ejection fraction, *EDV* end-diastolic volume, *ESV* end-systolic volume, *E* early ventricular filling velocity, *Em* ventricular tissue doppler early diastolic velocity, *WMSI* wall motion score index, *GLS* global longitudinal strain, *SRS'* systolic strain rate, *SRE'* early diastolic strain rate, *SRA'* late diastolic strain rate

**Table 3** Correlation of left ventricle ejection fraction with echocardiographic measurements

	r	P
SRS' (s <sup>-1</sup> )	-0.410	<0.001
EDV (ml)	-0.524	<0.001
ESV (ml)	-0.870	<0.001
WMSI	-0.841	<0.001
GLS (%)	-0.189	0.119
DESL (ms)	0.225	0.63

*DESL* duration of early systolic lengthening, *EDV* end-diastolic volume, *ESV* end-systolic volume, *GLS* global longitudinal strain, *SRS'* systolic strain rate, *WMSI* wall motion score index

**Table 4** The result of multivariate logistic regression analysis for the prediction of ischemia detected by MPS

Variables	OR	CI	p
EF (%)	1.150	1.044–1.268	0.005
SRS' (s <sup>-1</sup> )	0.423	0.010–17.842	0.652
EDV (ml)	1.001	0.963–1.041	0.960
GLS (%)	0.940	0.865–1.023	0.153
DESL (ms)	1.021	1.004–1.039	0.016

*DESL* duration of early systolic lengthening, *EDV* end-diastolic volume, *EF* left ventricular ejection fraction, *GLS* global longitudinal strain, *SRS'* systolic strain rate

independent predictive parameters for ischemia detected by MPS (Table 4).

In the ROC analysis, DESL > 51 ms predicted myocardial ischemia detected by MPS with 74% sensitivity and 80% specificity (AUC = 0.741, p = 0.001).

## Discussion

In this study, we found out that LVEF and DESL had a predictive value for ischemia in chronic total occlusion. DESL was determined to be significantly prolonged in the ischemia group compared to scarring detected in myocardial perfusion scintigraphy. LVEF was significantly higher in the ischemia group. CTO is still an important issue in interventional cardiology since identification of prospective patients, who may benefit from revascularization, remains to be an important point. The documentation of myocardial viability and ischemia in the CTO territory are of great importance during the decision-making process for performing a percutaneous intervention [26]. Various imaging methods such as SPECT, dobutamine stress echocardiography, PET with FDG and CMR are utilized to determine the myocardial viability since only a viable myocardial tissue can recover contractile functions after revascularization [4]. Our study

showed that DESL can help distinguish ischemic myocardium from scar tissues.

DESL was previously studied in acute anterior MI, NSTEMI, and stable angina pectoris based on the hypothesis that early systolic lengthening occurs in the ischemic myocardium before the onset of systolic shortening during the increase in the LV pressure [15, 16, 27]. This finding was associated with the reduced ability of the ischemic myocardium to generate force actively. In a study on patients with stable angina pectoris by Smedrud et al., duration of early systolic lengthening was shown to predict a significant coronary artery disease [15]. The study found the duration of early systolic lengthening longer in patients with a significant coronary artery disease (CAD) compared to those with non-significant CAD. Based on the results of the ROC curve analysis, Smedrud et al. determined that duration of early systolic lengthening > 58 ms (95% CI by bootstrapping: 38–58 ms) distinguished a patient with significant CAD from a patient with patent coronary arteries. However, Smedrud et al. excluded patients with CTO lesions. In another study, Vartdal et al. measured DESL with tissue Doppler strain in acute anterior MI patients, demonstrating that DESL was a useful parameter in distinguishing ischemic but viable myocardium [27]. Vartdal et al. reported that the percentage of systolic lengthening increased in these patients with the increased percentage of infarcted tissue detected with magnetic resonance imaging. Similarly, another study on NSTEMI patients reported that the duration of early systolic lengthening increased as the infarct size increased [16]. In our study, the duration of early systolic lengthening was shorter in the scar group compared to the ischemia group. We observed that DESL was associated with an independent predictive value in differentiating myocardial ischemia from scar tissue. Previous studies reported DESL longer in the presence of a larger infarct area or in the presence of significant coronary artery stenosis; however, our study provided different findings. We think that, compared to the ischemic but viable myocardium, a relatively shorter DESL occurs in scar tissue due to the inability of generating active force. Therefore, we suggest that scar tissue will be associated with a shorter DESL, whereas, ischemia will be associated with a prolonged DESL.

Supporting our findings, a study on dogs by Lyseggen et al. reported that the ratio of systolic lengthening to total shortening (L–S ratio) increased in ischemia and decreased after reperfusion in viable segments in acute coronary occlusion [14]. Also, there were no further changes in the L–S ratio after reperfusion when the myocardium underwent necrosis. With the development of necrosis, a significant decrease occurs in systolic lengthening due to decreased myocardial compliance. The L–S ratio in dyskinetic segments has been shown to be capable of identifying a viable myocardium that may generate active force. Since previous

studies on ESL were performed on different patient groups such as on patients with stable angina pectoris and acute coronary syndrome, it may not be accurate to compare their results with the results of our study on patients with CTO lesions.

## Study limitations

First, a relatively small number of patients were included in this study. Second, two-dimensional speckle tracking echocardiography measurement has the advantage of being relatively angle independent. It is, however, like all echocardiographic methods, dependent on image quality. Thirdly, we did not evaluate the values of 2D-STE indices after PCI, which would have indicated that revascularization occurred in the ischemia group. If the duration of ESL after revascularization had been evaluated in the group with ischemia, it could have provided more meaningful information. Fourth, CMR or myocardial PET was not performed in our center, and ischemia/scar assessment was performed with MPS.

## Conclusion

The duration of ESL obtained by speckle tracking echocardiography in patients with CTO lesions may be useful in differentiating ischemia from scar tissue detected in myocardial perfusion scintigraphy. Prolonged duration of early systolic lengthening in patients with CTO lesions was related to the presence of ischemia detected by MPS.

## Compliance with ethical standards

**Conflict of interest** The authors have no conflicts of interest to disclose.

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