ORIGINAL ARTICLE

Relationship between SYNTAX score and myocardial viability in ischemic cardiomyopathy

İskemik kardiyomiyopatide SYNTAX skoru ve miyokardiyal canlılık arasındaki ilişki

Semi Öztürk, M.D.,[1] Ahmet Seyfeddin Gürbüz, M.D.,[2] Cevat Kırma, M.D.[3]

[1]Department of Cardiology, Haseki Training and Research Hospital, İstanbul, Turkey
[2]Department of Cardiology, Necmettin Erbakan University Meram Faculty of Medicine, Konya, Turkey
[3]Department of Cardiology, Kartal Koşuyolu Heart Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Objective: The SYNTAX score (SS) is not just a measure of the severity of coronary artery disease, but also complexity. The aim of this study was to evaluate the relationship between the SS and myocardial viability/non-viability assessed by positron emission tomography (PET) in patients with ischemic cardiomyopathy (IC).

Methods: A total of 107 IC patients who had undergone PET were enrolled in the study. The patients were divided into two groups according to the presence or absence of viable myocardium. SS was analyzed from recorded conventional coronary angiographies.

Results: Patients with a non-viable myocardium (n=21; 19.6%) had a significantly higher SS compared to those with a viable myocardium (17.6±3.7 vs. 14.1±5.2, respectively; p=0.004). Point-biserial correlation coefficient analysis indicated that the presence of myocardial non-viability was mildly correlated with a higher SS (rpb=-0.28, p=0.004). In multivariate logistic regression analysis, the SS was identified as the sole independent predictor of myocardial non-viability (odds ratio [OR]: 1.164, 95% confidence interval [CI]: 1.044–1.297; p =0.006]. Receiver operating characteristic analysis revealed a cutoff point of 16 for predicting a non-viable myocardium (area under curve: 0.71, 95% CI: 0.61–0.82) with a sensitivity of 76.2% and a specificity of 61.6%.

Conclusion: The results of the present study indicates that a high SS is associated with the presence of a non-viable myocardium in IC patients.

ÖZET

Amaç: SYNTAX skoru (SS), koroner arter hastalığının yalnızca ciddiyetini değil aynı zamanda yaygınlığını da ölçmek için kullanılmaktadır. Çalışmamızda iskemik kardiyomiyopati hastalarında pozitron emisyon tomografisi (PET) ile tespit edilmiş miyokardiyal canlılık/cansızlığı ile SS arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: Pozitron emisyon tomografisi ile değerlendirilen 107 iskemik kardiyomiyopati hastası çalışmaya dahil edildi. Hastalar miyokart canlılığının varlığı/yokluğuna göre canlı doku saptanan ve saptanmayanlar olmak üzere iki gruba ayrıldı. SYNTAX skoru, koroner anjiyografi kayıtlarından analiz edildi.

Bulgular: Canlı dokusu olmayan hastalar (n=21, %19,6), canlı doku saptananlara göre daha yüksek SS değerine sahipti (sırasıyla, 17.6±3.7 ve 14.1±5.2, p=0.004). SS miyokardiyal canlılıkla hafif ilişkiliydi (rpb=-0.28, p=0.004). Lojistik regresyon analizinde, SS miyokart canlılığının tek ve bağımsız öngördürücüsü olarak belirlendi [odds oranı (OO)=1.162, %95 güven aralığı (GA) 1.044–1.294, p=0.006]. ROC analizinde, SS değerinin 16 ve üzeri olması canlı miyokart varlığını %76.2 duyarlılık ve %61.6 özgüllükle belirlemekteydi [eğri altında kalan alan (AUC)=0.71, %95 GA 0.61–0.82].

Sonuç: Çalışma bulguları, iskemik kardiyomiyopatide yüksek SYNTAX skorunun miyokardiyal cansızlıkla ilişkili olduğunu düşündürmektedir.

Percutaneous revascularization techniques have evolved enormously during the past two decades. Despite significant improvement in the outcome of percutaneous revascularization, the best revascularization modality to be applied for ischemic cardiomyopathy (IC) is still debatable. Several studies have reported that percutaneous revascularization might be as effective as coronary artery bypass grafting in cases

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Correspondence: Dr. Semi Öztürk. Haseki Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, İstanbul, Turkey.
Tel: +90 212 - 529 44 00 e-mail: semi_ozturk@yahoo.com

with IC.[1] However, revascularization of patients with IC remains a challenging area. Though successful full revascularization is achievable in many patients, the outcome relies on the presence of myocardial viability. Imaging modalities such as echocardiography, single photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI) can all detect a viable myocardium, albeit with different diagnostic accuracies. The high accuracy of PET has led to its wide use in clinical practice.[2]

The SYNTAX score I (SS), a measure of coronary artery complexity, has been shown to be a validated predictor of cardiovascular outcomes.[3] Despite wide use of the SS to evaluate the severity of coronary artery disease, it should be remembered that the SS is a weighted score. Chronic total occlusion (CTO) lesions have a greater weight (5 points) than non-CTO lesions (50%–99% diameter stenosis: 2 points) in the scoring algorithm. Tortuosity (1 point), thrombus (1 point), and calcification (2 points) have only a minor effect on the total sum. The SS is far greater in cases of IC with CTO lesions. Higher scores representing CTO lesions might be related to less viability. The aim of this study was to investigate the relationship between the SS and myocardial viability/non-viability in patients with IC.

METHODS

Study population

Patients with a diagnosis of IC who underwent myocardial PET imaging for the evaluation of myocardial viability between August 2011 and September 2013 were included in the study. All of the patients presented with stable angina or dyspnea, and were clinically stable. Patients with recent myocardial infarction and/or decompensated heart failure were not included in the study. PET imaging was performed after coronary angiography. Patients with non-ischemic cardiomyopathies and in whom SS calculation could not be performed reliably were excluded from the study. The study patients were separated into two groups on the presence or absence of viability. The medical history, demographic details, coronary angiogram results, and PET images of the participants were retrospectively evaluated and analyzed.

SYNTAX score I

Each lesion with >50% diameter stenosis in a vessel >1.5 mm in diameter was included in the SS. The calculation was performed by an experienced interventional cardiologist who was blind to the study using an online tool (www.SYNTAXscore.com).

Abbreviations:

CT	*Computed tomography*
CTO	*Chronic total occlusion*
DE-MRI	*Delayed-enhancement magnetic resonance imaging*
ECG	*Electrocardiogram*
FDG	*Fludeoxyglucose*
IC	*Ischemic cardiomyopathy*
MRI	*Magnetic resonance imaging*
PET	*Positron emission tomography*
SPECT	*Single photon emission computed tomography*
SS	*SYNTAX score*
Tc-99m MIBI	*Methoxy isobutyl isonitrile technetium 99m*

Myocardial perfusion SPECT imaging

Patients who underwent fludeoxyglucose F 18 (18F-FDG) PET/computed tomography (CT), also underwent myocardial perfusion imaging. A 2-day protocol of methoxy isobutyl isonitrile technetium 99m (Tc-99m MIBI, sestamibi) myocardial perfusion scintigraphy was implemented. A pharmacological stress test with dipyridamole or a treadmill exercise test was conducted, according to the initial assessment. The Bruce protocol was applied in treadmill testing. At peak exercise, 20 mCi Tc-99m MIBI was infused. Exercise continued for at least 1.5 minutes after infusion. The dipyridamole stress test was performed with a 0.56 mg/kg dipyridamole infusion administered intravenously over 4 minutes. Eight minutes after beginning the dipyridamole infusion, Tc-99m MIBI (20 mCi) was infused. One hour after the tracer injection, electrocardiogram (ECG)-gated SPECT images were taken at points of stress and at rest.

Myocardial F-18 FDG PET imaging

Baseline blood sugar was measured in the morning after a minimum of 6 hours of fasting. Glucose loading with 50 to 100 g was performed and blood glucose was measured 45 to 60 minutes later. When the blood glucose level was less than 140 mg/dL, 444 MBq (12 mCi) of 18F-FDG was injected. For blood glucose levels of 140–160 mg/dL, 160–180 mg/dL, and 180–200 mg/dL, 2 U, 3 U, and 5 U of insulin, respectively, was injected. FDG PET imaging was performed with a PET scanner in 3-dimensional mode (Biograph 2 LSO DUO PET/CT; Siemens Healthineers, Erlangen, Germany), 45 to 60 minutes after the 18F-FDG injection. The PET image acquisition parameters consisted

of one-bed position with a slice thickness of 5 mm, 10 minutes of emission time, 128 matrices, zoom 2.0, and iterative reconstruction (4 iterations, 8 subsets). A CT-based attenuation correction was performed.

Two nuclear medicine specialists analyzed the images together. The perfusion and 18F-FDG PET images were evaluated side-by-side using conventional Siemens cardiac display software. Comparison of myocardial perfusion and myocardial metabolism was performed at the same time. The 3 major patterns were a) a mismatch pattern (reduced myocardial perfusion with preserved FDG uptake), representing a hibernating myocardium; b) a match pattern (absent myocardial perfusion with absent FDG uptake), representing a transmural scar; and c) a non-transmural match (partially reduced myocardial perfusion with concordant FDG uptake) pattern, representing a non-transmural scar. Myocardial viability was defined as the presence of hibernation and/or non-transmural scar (patterns a and/or c). Figure 1 demonstrates an example of PET results demonstrating a viable myocardium. Due to the lack of ECG gating and additional quantification software, it was not possible to measure the extent or size of metabolic patterns in PET/CT images.

Statistical analysis

Statistical analysis was performed using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). Normality of the data was analyzed with the Kolmogorov-Smirnov test. Continuous data were expressed as median (interquartile range) and categorical data were expressed as the number of cases and percentages. Categorical variables were assessed between groups with a chi-square test. The Yates continuity correction was applied when required. The relationship between myocardial viability and SS was evaluated with point-biserial correlation coefficient analysis. Logistic regression analysis was used to identify independent predictors of a non-viable myocardium. Significant factors ($p<0.25$) of the univariate analysis, SS, and the presence of dyslipidemia were included in the multivariate analysis. Multiple logistic regression analysis using the backward logistic regression method was performed to determine the variables independently associated with a non-viable myocardium. Differences between patient subgroups were tested using the Mann-Whitney U test. A p value <0.05 was considered statistically significant.

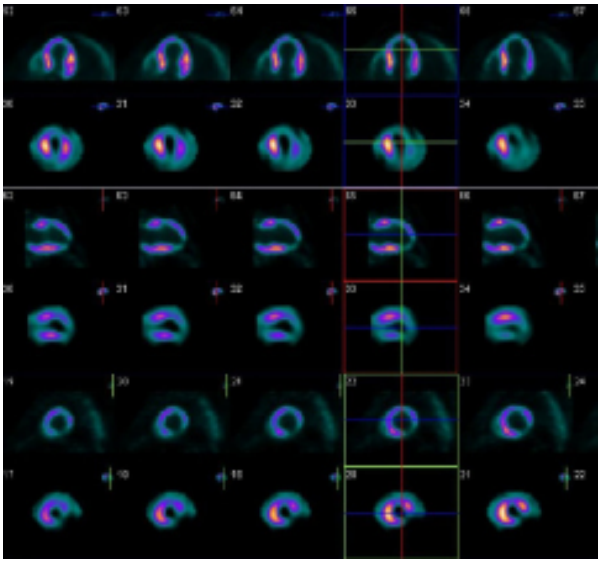

Figure 1. Reduced myocardial perfusion with preserved fludeoxyglucose (FDG) uptake in apical segment suggests a hibernating myocardium. Partially reduced myocardial perfusion with concordant FDG uptake in the anteroapical segment suggests a non-transmural scar. Absent myocardial perfusion with absent FDG uptake in the inferoapical segment suggests a transmural scar.

RESULTS

The study group consisted of 107 IC patients (95 males and 12 females). Among them, 86 patients (80.4%) with a non-transmural scar and/or hibernation made up the group with a viable myocardium. The group with a non-viable myocardium comprised 21 patients (19.6%) with a transmural scar. The baseline characteristics of the groups are presented in Table 1. There were no significant differences between the groups in terms of age, or the presence of hypertension, diabetes mellitus, or dyslipidemia. Furthermore, there was no significant difference between the two groups regarding the use of dual antiplatelet therapy, beta blockers, angiotensin-converting enzyme inhibitors, statins, or mineralocorticoid receptor antagonists.

The left anterior descending, circumflex, or right coronary artery was involved in 79.4%, 54.2%, and 57.9%, of the study patients, respectively. Significant left main coronary artery disease was present in 4.7% of the patients, whereas 3-vessel disease was present in 17.8%, and 23 (21.5%) patients had a single-vessel disease. In all, 27 (25.2%) patients were determined to have CTO. The frequency of CTO was greater in patients with a non-viable myocardium (47.6% vs 19.8%). Patients with a non-viable myocardium had

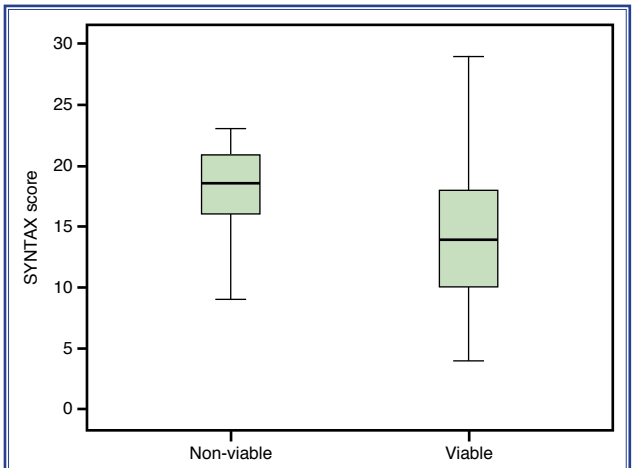

Figure 2. SYNTAX scores of the study groups.

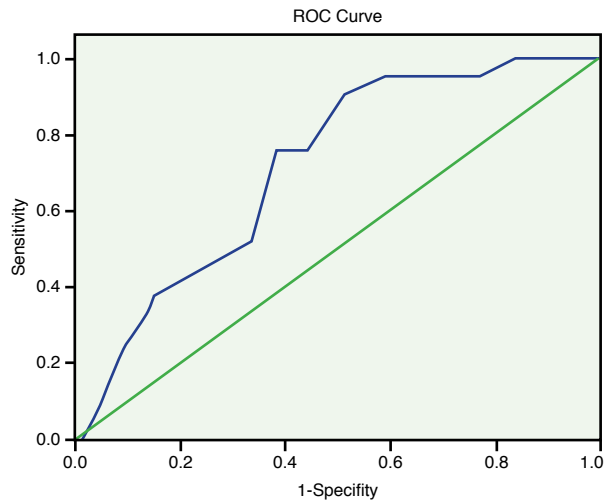

Figure 3. Diagnostic accuracy of SYNTAX score I in the prediction of a non-viable myocardium.

significantly higher SS values compared to those with viable myocardium [17 (15–21) vs. 14 (10–18), respectively; p<0.01] (Table 1, Fig. 2). Point-biserial correlation coefficient analysis showed that the presence of myocardial non-viability was mildly correlated with a higher SS (rpb=-0.28; p=0.004). In multivariate logistic regression analysis, the SS was identified as the sole independent predictor of myocardial non-viability [odds ratio (OR)=1.164, 95% confidence interval (CI): 1.044–1.297; p=0.006] (Table 2). Receiver op-

Table 1. Baseline characteristics

	Viable group (n=86)	Non-viable group (n=21)	*p*
Age (years)	59 (52–67.3)	51.5 (57–66)	0.36
Sex (male), n (%)	76 (88.4)	19 (90.5)	>0.99
Hypertension, n (%)	23 (26.7)	8 (38.1)	0.45
Diabetes mellitus, n (%)	31 (36)	8 (38.1)	>0.99
Dyslipidemia, n (%)	24 (27.9)	9 (42.9)	0.29
Ejection fraction (calculated with SPECT), (%)	25 (20–30.3)	25 (20–33.5)	0.84
Dual antiplatelet therapy, n (%)	21 (24.4)	4 (19)	0.78
Beta-blocker, n (%)	82 (95.3)	21 (100)	0.58
Angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker, n (%)	78 (90.7)	20 (95.2)	0.69
Mineralocorticoid receptor antagonist, n (%)	34 (39.5)	9 (42.9)	0.98
Statin, n (%)	64 (74.4)	14 (66.7)	0.66
SYNTAX score, n (%)	14 (10–18)	17 (15–21)	**<0.01**
Left anterior descending coronary artery, n (%)	69 (80.2)	16 (76.2)	0.76
Right coronary artery, n (%)	46 (53.5)	16 (76.2)	0.10
Circumflex artery, n (%)	45 (52.3)	13 (61.9)	0.45
Left main coronary artery, n (%)	3 (3.5)	2 (9.5)	0.55
3-vessel disease, n (%)	14 (16.3)	4 (19.0)	0.76
Chronic total occlusion, n (%)	17 (19.8)	10 (47.6)	**0.02**

SPECT: Single photon emission computed tomography.

Table 2. Univariate and multivariate logistic regression analysis for non-viable myocardium

	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Age (years)	0.978	0.933–1.025	0.353			
Sex (male)	1.250	0.253–6.187	0.781			
Hypertension	1.686	0.619–4.590	0.307			
Diabetes mellitus	1.092	0.408–2.923	0.861			
Dyslipidemia	1.937	0.724–5.185	0.188	1.961	0.699–5.502	0.201
EF (%)	1.018	0.967–1.071	0.502			
SYNTAX score	1.162	1.044–1.294	0.006	1.164	1.044–1.297	0.006

CI: Confidence interval; EF: Ejection fraction (calculated with single photon emission computed tomography).

erating characteristic analysis revealed that an SS of 16 was the cutoff point for a non-viable myocardium (area under the curve: 0.71, 95% CI: 0.61–0.82) (Fig. 3). An SS greater than 16 demonstrated a sensitivity of 76.2% and a specificity of 61.6% for myocardial non-viability (positive predictive value: 32.8%, negative predictive value: 91.0%).

DISCUSSION

These findings indicated, for the first time, that the SS appears to be associated with a viable myocardium. Though many studies have demonstrated an association between the SS and poor outcome in patients with acute coronary syndromes, to our knowledge, none have examined the relationship between SS and myocardial viability/non-viability.

Tanaka et al.[4] showed that SS was related to the extent of myocardial ischemia detected by perfusion imaging; however, the relationship was not significant in the high-SS group. Since SS takes multiple characteristics into account, including calcification and tortuosity, Tanaka et al.[4] reported that a high SS was related more to disease complexity than extent. The relatively low SS scores in our patient population were related to the low frequency of 3-vessel disease and the high frequency of single-vessel disease. A high SS in patients with non-viable myocardium would appear to be related to CTO lesions in our study population, rather than other minor characteristics included in the SS algorithm. Obviously, a CTO lesion decreases the viability of the myocardium and contributes to a marginally higher SS. A low SS in our study was associated with myocardial viability and suggested the presence of ischemia, which is consistent with the results reported by Tanaka et al.

Zhao et al.[5] demonstrated a relationship between the severity of coronary stenosis and the transmural extent of the myocardial infarction. They concluded that 64.71% of segments with transmural scars detected using delayed-enhancement magnetic resonance imaging (DE-MRI) were present in areas of blood supply which had >90% stenosis. Bexell et al.[6] found similar results to those of Zhao et al., and additionally, they found a relationship between the severity of coronary stenosis and the area of myocardial scarring observed with DE-MRI. Interestingly, a significant number of patients with mild to moderate stenosis had a transmural scar detected with DE-MRI. This finding was attributed to impaired flow reserve and recurrent thrombotic and embolic events, which result in a chronic myocardial scarring.

Myocardial ischemia-induced ventricular remodeling is a complex process. Sakai et al.[7] demonstrated that NT-proBNP release was associated with coronary artery disease assessed using the Gensini score, the left ventricular ejection fraction, and the end diastolic pressure. They speculated that NT-proBNP secretion might be stimulated by ischemia. Another study demonstrated that different ventricular remodeling patterns were associated with SS in hypertensive patients; however, the precise relationship between ischemic remodeling and SS remains unclear.[8]

SS has been associated with poor clinical and angiographic outcomes after primary percutaneous intervention.[9] Additionally, major adverse cardiac events have been found to be associated with SS, not only in patients with acute coronary syndromes, but also those with stable angina pectoris.[10,11] A recent study demonstrated a relationship between the extent of coronary artery disease assessed with SS and novel

markers of inflammation.[12] Akboga et al.[13] reported an increased level of serum YKL-40, a new marker of inflammation, that appeared to be related to poor collateral development and a high SYNTAX score in cases of stable coronary artery disease.[13] Extensive coronary artery disease is related to endothelial dysfunction, inflammation, poor collaterals, and consequently, with transmural infarction. Since SS is solely an angiographic score – not taking clinical factors into account- the utility and accuracy of SS in clinical practice have been questioned. The complex relationship between clinical outcomes and the SS remains to be further elucidated. Nonetheless, our study demonstrated that poor cardiovascular outcomes in patients with a high SS might be associated with a less viable myocardium. Although the SS is an angiographic scoring system, it does not simply reflect extent, but rather reflects a final measure of complex atherosclerotic process. Further studies must be performed in order to clarify the relationship between the SS and myocardial viability. Additionally, studies investigating the SS and cardiovascular outcomes must take the relationship between the SS and myocardial viability into account when making definitive inferences.

Study limitations

The primary limitation of this research is the unavailability of PET pattern quantitative data. The retrospective nature of the study and the small study population are additional limitations. Minor characteristics of the SS algorithm that represent small increases in the score were not taken into account. A minority of the patients had 3-vessel disease and only few had more than a single CTO lesion, thus most of the CTO studied was related to a high SS associated with the ischemia/infarct location; the use of an assessment of total SS constitutes a limitation. A larger study group and a specific SS calculation attributed to specific ischemia/infarct location might provide a better clarification of causality.

Conclusion

The present study demonstrated that the SS is related to the presence of a viable myocardium in IC. The SS may be helpful in the prediction of non-viability in cases of IC.

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Haseki Training and Research Hospital (268/11.11.2015).

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

Authorship contributions: Concept: SÖ; Design: SÖ, AG; Supervision: CK; Materials: SÖ, AG Data: SÖ, AG; Analysis: SÖ; Literature search: AG; Writing: SÖ Critical revision: CK.

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Keywords: Cardiomyopathy; positron emission tomography; SYNTAX score; viability

Anahtar sözcükler: Kardiyomiyopati; pozitron emisyon tomografisi; SYNTAX skoru; canlılık.