Relationship of SYNTAX Score to Myocardial Ischemia as Assessed on Myocardial Perfusion Imaging

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Background: Although the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score is used to characterize coronary anatomy based on 9 anatomic criteria such as lesion location and complexity, the relationship between SYNTAX score and myocardial ischemia has yet to be elucidated.

Methods and Results: A total of 158 consecutive patients with suspected or known coronary artery disease (CAD), who underwent both ^{99m}Tc -sestamibi single-photon emission computed tomography (SPECT) and coronary angiography, were evaluated. Stress SPECT was assessed using a 17-segment model, and the percentage of the myocardial defect scores (DS) was calculated. In 37 patients with intermediate-high SYNTAX scores (>22), the number of men and the prevalence of multi-vessel CAD were significantly higher, and the % stress and ischemic DS were significantly greater than in 121 patients with low SYNTAX scores (≤ 22). Coronary risk factors, however, were similar between the 2 groups. The % stress and ischemic DS significantly correlated with SYNTAX score. In patients with a low SYNTAX score, % stress and ischemic DS also significantly correlated with the SYNTAX score, whereas no such correlation was observed in the intermediate-high SYNTAX score group.

Conclusions: SYNTAX score correlated well with myocardial ischemia as assessed on stress SPECT in general. The higher the SYNTAX score, however, the less clear was the correlation with the extent of myocardial ischemia. (*Circ J* 2013; **77**: 2772–2777)

Key Words: Coronary artery disease; Myocardial ischemia; Myocardial perfusion imaging; SYNTAX score

The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score has recently been developed to characterize coronary anatomy based on 9 anatomic criteria, such as lesion location and complexity, and in connection with the SYNTAX trial.^{1,2} Based on the outcome of this trial, the European Society of Cardiology has newly produced the guidelines for coronary revascularization with the use of SYNTAX score to determine when to perform percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).³ Even in Japan, the Japanese Circulation Society (JCS) has finally updated the guidelines for coronary revascularization by incorporating SYNTAX score and documenting myocardial ischemia as the indications for PCI or CABG.⁴ The nature of the relationship between SYNTAX score and myocardial ischemia, however, has not yet been evaluated. Thus, the aim of the present study was to examine whether SYNTAX score had a significant relationship with myocardial ischemia as assessed on myocardial perfusion imaging.

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Methods

We retrospectively studied 158 consecutive patients with suspected or known coronary artery disease (CAD) who had undergone both ^{99m}Tc -sestamibi single-photon emission computed tomography (SPECT) and coronary angiography between January 2008 and June 2009. Clinical grounds for suspected or known CAD were based on clinical symptoms, coronary risk profiles, electrocardiographic findings or past medical history. Patients with acute coronary syndrome were not included. In addition, patients with previous myocardial infarction based on definite clinical history or CABG were also excluded. There were 123 men and 35 women, aged 64 ± 10 years (range, 33–88 years). Hypertension was observed in 108 patients, diabetes mellitus in 59, and dyslipidemia in 102. Written informed consent for invasive coronary angiography was obtained from all participants. The study was approved by the Ethics Committee of Tokyo Medical University.

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Figure 1. Assignment of myocardial segments for the scoring of single-photon emission computed tomography images.

Exercise myocardial perfusion imaging with ^{99m}Tc -sestamibi was performed in 94 patients using the 1-day protocol. Symptom-limited multi-step exercise using a bicycle ergometer was also performed.^{5,6} ^{99m}Tc -sestamibi (259 MBq) was given at 85% of age-adjusted predictive maximal heart rate (target heart rate), or when chest pain, or ST-segment depression ≥ 0.1 mV or leg fatigue developed. Exercise was then continued for 1 min at the previous level. Thirty minutes after this last exercise session, electrocardiogram-gated SPECT was performed. Four hours later, the patients were given ^{99m}Tc -sestamibi (777 MBq) while at rest. Thirty minutes later, electrocardiogram-gated SPECT image acquisition was started. Adenosine triphosphate stress myocardial perfusion imaging with ^{99m}Tc -sestamibi was performed in 64 patients using the 1-day protocol. Anti-ischemic agents were withdrawn 24 h before the scintigraphic examination. Patients were also requested not to take a beverage containing caffeine at least 12 h before the test. Adenosine triphosphate disodium ($0.16 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was given i.v. for 6 min,⁷ and then 3 min after this, ^{99m}Tc -sestamibi (259 MBq) was given i.v. Image acquisition was started 30 min after stress application. Delayed images were obtained 4 h later, and ^{99m}Tc -sestamibi (777 MBq) was given at rest. Data were acquired with a 3-detector gamma camera (Prism 3000XP; Picker, Cleveland, OH, USA) for 360° arcs (in 6° -wide directions, taking 30 s/direction, 20 times). A low-energy high-resolution parallel multi-hole collimator was used, with a maximum matrix size of 64×64 . When taking electrocardiogram-gated images, the R-R interval was divided by the R-wave trigger into 8 equal portions, and end-diastolic and end-systolic images were obtained. All patients were in sinus rhythm during image acquisition. SPECT images were reconstructed into conventional short axis, vertical long axis, and horizontal long axis slices with a dedicated nuclear data processor (Odyssey VP; Picker) combined with a Butterworth filter (order 8; cut-off frequency, 0.25 cycle/cm) and a ramp filter.

Each SPECT image was divided into 17 segments (Figure 1) and visually evaluated by 2 cardiologists who were blinded to clinical information using a 5-grade scale: 0, normal; 1, mild defect; 2, moderate defect; 3, severe defect; 4, no uptake.⁸ Disagreements in image interpretation were resolved by consensus. The total of the scores for all segments during stress and at rest was designated as the summed stress score (SSS) and the summed rest score (SRS), respectively. SSS minus SRS was defined as the summed difference score (SDS). Then, these indices were converted to a percentage of the total left ventricular (LV) myocardium involved with stress, rest, or ischemia, by dividing the summed scores by the maximum potential score of 68 (4×17), and multiplying the result by 100.⁹ These indices were named as % stress, rest, or ischemic defect score (DS).

Each reconstructed short-axis gated SPECT image was processed using a quantitative gated SPECT program developed

by Germano et al to calculate the LV end-diastolic volume, LV end-systolic volume and LV ejection fraction (LVEF).¹⁰ In addition, the absolute changes in LV volume and function were calculated as LV end-diastolic volume after stress minus LV end-diastolic volume at rest, LV end-systolic volume after stress minus LV end-systolic volume at rest, or LVEF after stress minus LVEF at rest.

All patients underwent coronary angiography within 3 months of SPECT. Multi-direction coronary angiography was performed according to Judkin's method. The degree of coronary artery stenosis was visually rated using calipers, and stenosis was considered significant when a diameter narrowing $\geq 75\%$ was noted.¹¹ Each coronary lesion that produced a luminal narrowing $\geq 50\%$ in vessels ≥ 1.5 mm was separately scored using the SYNTAX score calculator, and then summed to provide an overall SYNTAX score (measurement key available at <http://www.syntaxscore.com>).

The results are presented as mean $\pm$ SD, median (interquartile range), or number and frequency. Student's t-test or Mann-Whitney U-test, according to the distribution of the data, was used to compare the means of the continuous variables, and categorical variables were analyzed using the chi-squared or Fisher's exact test, as appropriate. Linear regression analysis was used to clarify the relationship between % stress or ischemic DS and SYNTAX scores. $P < 0.05$ was regarded as denoting a statistically significant difference. The computations were performed using SPSS version 11.0 (SPSS, Chicago, IL, USA).

Results

Among 158 patients, left main or 3-vessel CAD was observed in 42 patients (27%), 2-vessel CAD in 40 (25%), 1-vessel CAD in 25 (16%), and insignificant lesions in the remaining 51 (32%). In all patients, the mean SYNTAX score was 12.7 ± 10.6 (range, 0–39), while the mean SYNTAX score was 25.0 ± 7.3 (range, 11–39) in patients with left main or 3-vessel CAD. The mean SSS and SDS were 11.3 ± 6.5 (range, 0–31) and 7.3 ± 4.9 (range, 0–23) in all patients, and 16.0 ± 6.2 (range, 4–29) and 10.3 ± 4.9 (range, 0–22) in patients with left main or 3-vessel CAD, respectively. In addition, the average of the % stress and ischemic DS were $16.6 \pm 9.6\%$ (range, 0–45.6%) and $10.7 \pm 7.2\%$ (range, 0–33.8%) in all patients, and $23.3 \pm 9.0\%$ (range, 0–42.7%) and $15.0 \pm 7.2\%$ (range, 0–2.4%) in patients with left main or 3-vessel CAD, respectively.

In 37 patients with intermediate-high SYNTAX scores (> 22),² the prevalence of male gender (92% vs. 74%; $P = 0.016$), hemoglobin A1c (median 6.0% vs. 5.7%; $P = 0.008$) and multi-vessel CAD (100% vs. 37%; $P < 0.0001$) was significantly higher, while % stress DS ($24.6 \pm 9.0\%$ vs. $14.1 \pm 8.4\%$; $P < 0.0001$) and % ischemic DS ($16.7 \pm 7.0\%$ vs. $8.8 \pm 6.3\%$; $P < 0.0001$) were both significantly greater than in 121 patients

Table 1. Clinical Patient Characteristics vs. SYNTAX Score

	SYNTAX score		P-value
	≤22 (n=121)	>22 (n=37)	
Age (years)	64±11	67±7	0.129
Male	89 (74)	34 (92)	0.016
Hypertension	83 (69)	25 (68)	0.832
Diabetes mellitus	41 (34)	18 (49)	0.121
Dyslipidemia	75 (62)	27 (73)	0.207
Smoking	54 (45)	13 (35)	0.264
Chronic kidney disease†	37 (31)	9 (24)	0.304
Total cholesterol (mg/dl)	205±39	216±44	0.138
LDL-C (mg/dl)	117±34	129±36	0.067
HDL-C (mg/dl)	53±17	48±14	0.143
Triglyceride (mg/dl)	125 (90–191)	139 (102–236)	0.216
Hemoglobin A1c (%)	5.7 (5.2–6.7)	6.0 (5.5–8.0)	0.008
Medications			
β-blocker	37 (31)	15 (41)	0.183
Calcium channel blocker	51 (42)	12 (32)	0.138
Nitrates	35 (29)	15 (41)	0.126
Nicorandil	30 (25)	16 (43)	0.088
Statin	47 (39)	18 (49)	0.301
Exercise stress protocol	70 (58)	24 (65)	0.450
% stress DS	14.1±8.4	24.6±9.0	<0.0001
% rest DS	5.3±5.1	7.9±5.0	0.008
% ischemic DS	8.8±6.3	16.7±7.0	<0.0001
Multivessel CAD	45 (37)	37 (100)	<0.0001
SYNTAX score	7.5 (2.0–13.8)	26.0 (24.5–33.0)	<0.0001

Data given as mean±SD, median (interquartile range), or n (%). †Defined as calculated estimated glomerular filtration rate <60 ml·min⁻¹·1.73 m⁻². CAD, coronary artery disease; DS, defect score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SYNTAX, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

Table 2. LV Volume and Function vs. SYNTAX Score

Table 2. LV Volume and Function vs. SYNTAX Score			
	SYNTAX score		P-value
	≤22 (n=121)	>22 (n=37)	
At rest			
LVEDV (ml)	92±35	102±29	0.100
LVESV (ml)	38±25	46±22	0.082
LVEF (%)	61±11	56±9	0.021
After stress			
LVEDV (ml)	94±37	109±32	0.033
LVESV (ml)	43±27	55±28	0.018
LVEF (%)	57±12	52±10	0.007
Absolute change (stress-rest)			
LVEDV (ml)	2.6±8.3	6.6±7.9	0.012
LVESV (ml)	4.6±6.2	8.8±7.4	0.001
LVEF (%)	−3.8±5.5	−4.9±4.5	0.298

Data given as mean±SD. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricular. Other abbreviation as in Table 1.

with low SYNTAX scores (≤22).² Age (67±7 vs. 64±11 years), coronary risk factors, and the prevalence of achieved target heart rate during exercise stress (80% vs. 78%), however, were similar in both groups (Table 1).

On volumetric and functional analysis, LV end-diastolic volume (109±32 vs. 94±37 ml; P=0.033) and LV end-systolic volume (55±28 vs. 43±27 ml; P=0.018) after stress were greater, and LVEF (52±10 vs. 57±12 ml; P=0.007) after stress was significantly lower in patients with intermediate-high

SYNTAX scores than in those with low SYNTAX scores (Table 2). When comparing the absolute changes in LV function and volumes (stress-rest), the changes in LV end-diastolic volume and LV end-systolic volume were greater in the intermediate-high SYNTAX score group than in the low SYNTAX score group, while the changes in LVEF were similar in both groups (Table 2).

The % stress and ischemic DS significantly correlated with SYNTAX score in all patients (r=0.654, P<0.0001 and

Figure 2. Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score vs. (A) % stress defect score and (B) % ischemic defect score in all patients.

Figure 3. Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score vs. (A) % stress defect score and (B) % ischemic defect score in patients with low SYNTAX score (≤ 22).

$r=0.647$, $P<0.0001$, respectively; **Figure 2**). In patients with low SYNTAX scores, % stress and ischemic DS also significantly correlated with SYNTAX score ($r=0.530$, $P<0.0001$ and $r=0.580$, $P<0.0001$, respectively; **Figure 3**). In contrast, no such correlation was observed in the intermediate-high SYNTAX score group ($r=0.104$, $P=0.541$ and $r=-0.033$, $P=0.846$; **Figure 4**). Of note is that 4 of the 37 patients (11%) with an intermediate-high SYNTAX score had a % ischemic DS $<10\%$. In these 4 patients, coronary angiography showed left main CAD in 1 and 3-vessel CAD in 3 (**Table 3**). Three, however, had either an increase in LV end-systolic volume ≥ 5 ml or a decrease in LVEF $\geq 5\%$ after stress, which are both signs of stress-induced myocardial stunning as assessed by volumetric analysis.^{12,13}

Discussion

In the present study we have shown a modest correlation between SYNTAX scores and the extent of stress-induced myocardial ischemia as assessed on myocardial SPECT ($r=0.647$, $P<0.0001$) in 158 patients without previous myocardial infarction. These significant correlations were predominantly based on patients with a low SYNTAX score ($r=0.580$, $P<0.0001$), whereas such a correlation no longer existed in patients with an intermediate-high SYNTAX score ($r=-0.033$, $P=NS$). Because the purpose of the SYNTAX score is to grade lesion complexity for coronary revascularization, the presence of difficult-to-treat anatomies such as trifurcations, bifurcations, tortuosity and calcification are taken into account in the calculation.¹ The score also depends on lesion location and diameter reduction, which usually determines the extent of myocardial

Table 3. Patient Profiles: Intermediate-high SYNTAX Score and % ischemic DS <10%

No.	Age (years)	Sex	SYNTAX score	% stress DS	% ischemic DS	Changes in LV function with stress			No. diseased vessels	Coronary artery lesions as determined on coronary angiography
						EDV (ml)	ESV (ml)	EF (%)		
1	65	M	24	14.7	8.8	2	2	-1	3-vessel	(4) 90% (7) 99% (9) 90% (11) 90%
2	61	M	25	17.7	5.8	-3	7	-9	3-vessel	(4) 75% (7) 90% (9) 99% (12) 90% (13) 90%
3	71	M	30	14.7	8.8	10	9	-5	LM+3-vessel	(2) 100% (5) 75% (6) 90% (11) 90% (12) 90% (13) 100%
4	80	F	35	19.1	1.5	3	6	-6	3-vessel	(1) 75% (2) 90% (6) 75% (7) 90% (13) 90% (14) 99%

(1), proximal RCA; (2), mid-RCA; (4), posterior descending artery; (5), left main coronary artery; (6), proximal LAD; (7), mid-LAD; (9), first diagonal branch; (11), proximal circumflex artery; (12), obtuse marginal branch; (13), distal circumflex artery; (14), left posterolateral. LAD, left anterior descending coronary artery; LM, left main coronary artery; RCA, right coronary artery. Other abbreviations as in Tables 1,2.

ischemia. There was a modest correlation between SYNTAX score and the extent of myocardial ischemia observed in the present patients, particularly in the low SYNTAX group. In patients with an intermediate-high SYNTAX score, however, adding the scoring points related to tortuosity or calcification resulted in a high score, but without an increase in the extent of myocardial ischemia. This may underlie the absence of a significant correlation between SYNTAX score and the extent of myocardial ischemia in such patients.

Recent clinical studies and guidelines indicate that inducible myocardial ischemia in $\geq 10\%$ of the LV is regarded as the threshold for coronary revascularization, because the extent of residual myocardial ischemia is an important determinant of prognosis in patients with stable angina.^{3,14,15} In this regard, approximately 90% of the present patients with an intermediate-high SYNTAX score (>22) had inducible myocardial ischemia in $\geq 10\%$ of the LV, which is considerable. Even in patients with known CAD, it is preferable to assess the extent of myocardial ischemia before coronary revascularization using stress echocardiography, perfusion magnetic resonance imaging or myocardial SPECT, particularly in patients with previous myocardial infarction in whom viability assessment is indispensable.¹⁶⁻¹⁸ In patients without myocardial infarction, however, such as those in the present study, the location of

coronary lesions and the severity of narrowing are the major determinants of the extent of myocardial ischemia. When detailed angiographic assessment shows a SYNTAX score >22, the likelihood of stress-induced myocardial ischemia exceeding 10% of the LV is very high. This finding, therefore, may have a significant impact on decision-making in clinical practice. Nevertheless, it is prudent to assess coronary physiology in addition to anatomical configuration given that a recent registry consisting of >5,000 patients with multivessel CAD reported that ischemia-guided coronary revascularization as assessed with thallium-201 SPECT resulted in better prognosis than non-ischemia-guided revascularization even in those with a SYNTAX score ≥ 24 .¹⁹

In the current study, 4 of the 37 patients with an intermediate-high SYNTAX score had a % ischemic DS <10%, and all 4 had left main or 3-vessel CAD. These 4 patients may have had a lesser extent of myocardial ischemia. In contrast, the level of physiological abnormality in these patients with high-risk anatomy might have been underestimated on scintigraphic assessment, which relied only on perfusion analysis, because one of the major limitations of myocardial perfusion imaging is its spatial relativity in perfusion defect analysis.²⁰⁻²³ In addition, myocardial ischemia at rest might be present in these patients with severe CAD due to a chronic-total occlusion or a severe

99% stenotic lesion, which made the SDS score low because of reduced reversibility from stress to rest. To overcome this potential limitation of myocardial SPECT, LV functional analysis after stress and at rest is reported to have additional diagnostic value.^{13,23,24} In the current study, not all, but 3 of the 4 patients showed signs of stress-induced myocardial stunning on LV functional analysis.^{13,24} This scintigraphic marker is also reported as an indicator of worse prognosis in patients with known or suspected CAD.^{25,26} Thus, these results emphasize the importance of the incorporation of LV functional analysis into conventional assessment of myocardial perfusion on SPECT, to help better identify patients with extensive CAD and, consequently, those who require coronary revascularization.

Study Limitations

The present study was performed retrospectively with a limited number of patients in a single institute. Given that one of the limitations of myocardial perfusion analysis of SPECT is the underestimation of balanced ischemia in severe CAD, a further evaluation is necessary in such patients with a SYNTAX score >22. Therefore, a prospective approach that will examine the relation between the extent of myocardial perfusion abnormality on SPECT and the SYNTAX score in a large patient group and multicenter clinical study is necessary.

Conclusions

SYNTAX score correlated well with myocardial ischemia as assessed on stress SPECT in general. The higher the SYNTAX score, however, the less clear was the correlation with the extent of myocardial ischemia.

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Disclosures

Conflicts of interest: None declared.

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