CLINICAL STUDY

Comparison of Archival Angiographic Findings in Patients Later Developing Acute Coronary Syndrome or Stable Angina

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Summary

Acute coronary syndrome (ACS) can develop in patients with mildly to moderately stenotic lesions. However, the angiographic characteristics of lesions in patients who will later develop ACS have not been systematically investigated. For this reason, we examined the earlier angiographic findings of such patients in a retrospective study.

The study population consisted of 45 consecutive ACS and 45 stable angina (SA) patients who require revascularization. All of them had received cardiac catheterization within 5 years prior to onset, for different reasons. The detailed parameters of the earlier coronary angiographies at the culprit site the whole culprit vessel, and all three vessels were compared between the two groups.

Mild-to-moderate stenosis was present exclusively at the culprit site in the earlier angiographies, both in ACS and SA patients. Lesions associated with ACS progression were significantly shorter in length than those associated with SA progression (11.5 ± 5.5 versus 16.1 ± 10.5 mm, $P = 0.02$) and were more eccentric (eccentricity index: 0.5 ± 0.3 versus 0.7 ± 0.3, $P = 0.04$). Percent diameter stenosis was similar (42.2 ± 14.5 versus 44.0 ± 13.8%, $P = 0.5$). The mean grading scores for plaque extension and size (1-3) were significantly lower in ACS than in SA (1.4 ± 0.6 versus 1.8 ± 0.6, $P = 0.01$, and 1.3 ± 0.6 versus 1.7 ± 0.7, $P = 0.01$, respectively). Residual SYNTAX scores were significantly lower in ACS (12.5 ± 7.4 versus 16.4 ± 8.6, $P = 0.03$).

Despite equivalent degrees of stenosis in previous angiographies, ACS occurred more frequently in patients with more focal and eccentric lesions but with less diseased coronary arteries than SA.

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Key words: Coronary angiography, Quantitative coronary angiography, Eccentric plaque, Lesion length, Statin

Acute coronary syndrome (ACS) is a disease concept which includes acute myocardial infarction, unstable angina, and sudden cardiac death, manifesting as acute myocardial ischemia with a common basis of coronary atheroma rupture and thrombosis usually occurring at lesions with vulnerable plaques.[1-3] The characteristics of the latter have been established in several published studies using intracoronary imaging[4-6] and computed tomography.[7,8] In addition, well-known clinical risk factors, such as diabetes, hypertension, and dyslipidemia, are associated with ACS. Importantly, coronary plaques can regress and be stabilized by intensive hypolipidemic therapy combining statins, ezetimibe, and PCSK-9 inhibitors, thus reducing cardiovascular events.[9-11] However, to establish more "cost-effective" preventive care for identifying patients with the highest risk of developing ACS, maximum utilization of routine imaging tests, such as coronary angiography (CAG), would be valuable.

Many patients will have undergone CAG several times for various reasons over a specified period prior to developing ACS or SA. Therefore, focusing on such patients, we designed a retrospective study to examine angiographic data in an effort to identify findings that predict future ACS events. This study targeted detailed investigations of previous angiographies at 1) culprit site 2) the whole culprit vessel; and 3) all three vessels, including non-culprit vessels; as well as 4) consideration of clinical characteristics at onset.

Methods

Study patients: Study patients were exclusively recruited from the catheterization database of Iwate Memorial Heart Center. Between January 2007 and December 2017, a total of 2,759 patients with ACS underwent emergent percutaneous coronary intervention (PCI) or CABG at our center. Among these patients, a total of 45 underwent CAG in our center within 5 years prior to ACS onset; these patients are the subjects of the present study. Controls consisted of 45 consecutive patients with SA who underwent PCI or CABG at our center and who had previously received CAG in a similar manner. They were selected from

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1,688 patients with SA observed between January 2011 and December 2017.

Accordingly, a total of 90 patients were included in this study population. The culprit lesions had to be entirely *de novo* coronary artery diseases, and any restenotic lesions were excluded. If the patients had received cardiac catheterization several times within 5 years, the latest CAG prior to ACS or SA onset was selected for analysis. To elucidate potential selection bias in this study population, we surveyed consecutive patients undergoing PCI in our center during the most recent year as the reference population (January-December 2017). The clinical characteristics of the ACS and SA groups were then compared between the selected populations in this angiographic study and the reference population in 2017.

Definition: ACS was classified as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (uAP). STEMI was defined as clinical presentation consistent with an acute myocardial infarction, and detection of a rise and/or fall of cardiac biomarker values and an electrocardiogram with ST-segment elevation ≥ 0.1 mV in ≥ 2 contiguous leads or new left bundle branch block.[1] In contrast, patients who had a typical history of chest pain at rest without ST-segment elevation at presentation were designated as NSTEMI. In addition, uAP was defined as present in patients with worsening chest discomfort or other ischemic symptoms without elevated biomarker values.[1]

SA was defined as chest pain, such as discomfort or tightness, during exertion or under emotional stress, together with objective evidence of myocardial ischemia, including electrocardiogram changes, such as ST-segment depression or T-wave inversion at rest. Symptoms had to have been stable over a period of 1 to 4 months without worsening chest discomfort or other ischemic symptoms.[12,13]

Basis for quantitative and qualitative angiographic analysis: Quantitative and qualitative angiographic assessments were exclusively conducted by an expert physician for previous CAG prior to onset of ACS and SA. Angiographic analyses were separately conducted for 1) the culprit site, 2) the whole culprit vessel, and 3) all three vessels. The culprit sites of previous CAG (prior to onset) were determined by referring to coronary angiograms at the time of PCI. QAngio XA version 7.1 (Medis, Leiden, the Netherlands), which is a standard quantitative software package, was used. In addition to the established parameters, we measured specific parameters corresponding to each segment category in order to elucidate possible angiographic features that may be associated with ACS or SA progression within several years.

Angiographic assessments at the culprit lesion: Quantitative analyses at the culprit site included such standard QCA parameters as minimal lumen diameter, reference diameter, percent diameter stenosis, and lesion length. The eccentricity index was defined as the eccentricity of the plaque within the lesion and was calculated automatically. For the lesion angulation analysis, views were selected, in which the angulation in the target lesion was maximum from the various projections. In addition, Δangulation, defined as the difference (degree) of the angle between diastole and systole, was calculated to assess coronary artery movement during the cardiac cycle.[14] The distance to the culprit lesion was also measured, defined as the distance from the ostium of the coronary artery to the end of the culprit lesion.[15]

For qualitative analyses, the lesions were morphologically classified into three groups according to Ambrose's categories,[16] namely, 1) concentric stenosis defined as symmetric and smooth narrowing of the coronary artery; 2) eccentric stenosis, defined as asymmetric narrowing of the coronary artery, including asymmetric stenosis with smooth borders and a broad neck, or asymmetric stenosis in the form of a convex intraluminal obstruction with a narrow base due to one or more overhanging edges or extremely irregular or scalloped borders, or both; and 3) multiple irregularities, defined as three or more serial and closely spaced severe obstructions or severe diffuse irregularities in the coronary artery.

Coronary calcification was defined as positive if a mobile white spot or lineal tract in the angiogram was present, and calcification of the target lesion was scored with reference to Yamanaka's method from 0 to 2 (0: none, 1: barely observable, 2: clearly observable).[17]

Angiographic assessments of the whole culprit vessel: In order to assess the extent of atherosclerosis quantitatively throughout the culprit vessel, we calculated the "coefficient of variation" (CV) of angiographical diameter. CV is the established method to compare relative variation, calculated as standard deviation (SD) of diameter divided by mean diameter. We defined this as the percentage of lesion length calculated as the ratio of lesion length to the length of the coronary artery. Because the distal parts of the coronary artery appeared shortened in the angiographic view for culprit lesion assessment, we selected the proximal two-thirds of the whole coronary artery and then calculated CV as described above.

Furthermore, we have used a previously proposed classification method for grading diffuseness of coronary atherosclerosis, Hamsten's scoring system.[18] Accordingly, plaque was defined as protruding into the lumen, appearing, for example, as a sharp-edged or irregular indentation angiographically, and graded by the reduction of the whole culprit vessel diameter by the plaque and the number of plaques in the vessel. The scores for extension and plaque size were then multiplied to yield a segmental atherosclerosis score (0 to 9) presented in Table I as "diffuse extension × mean size."

Similarly, Yamanaka's method,[17] which grades vessel calcification from 0 to 4 (0: no calcification, 1: barely observable, 2: clearly observable, 3: more than half of the length calcified, 4: calcified overall), was applied to semiquantify the degree of calcification throughout the culprit vessel.

Angiographic assessments for all three vessels: For the evaluation of the extension of atherosclerotic changes through the entire coronary trees, a residual SYNTAX score was calculated for each patient. This score was determined using a publicly accessible web-based score calculator (http://www.syntaxscore.com), which corresponds to lesion complexity measured by the coronary tree char-

Table I. Baseline Clinical Characteristics

	ACS (n = 45)	SA (n = 45)	P-value
Age (years)	68.8 ± 10.2	67.7 ± 9.8	0.63
Body mass index (kg/m^2)	24.4 ± 3.5	24.9 ± 3.8	0.5
Male sex, n (%)	40 (88.9)	36 (80.0)	0.24
Diabetes mellitus, n (%)	18 (40.0)	18 (40.0)	0.82
Hypertension, n (%)	42 (93.3)	44 (97.8)	0.31
Hyperlipidemia, n (%)	35 (77.8)	42 (93.3)	0.04
Smoking History			0.87
Current, n (%)	9 (20.0)	8 (17.8)	
Former, n (%)	23 (51.1)	21 (46.7)	
Previous myocardial infarction, n (%)	23 (51.1)	21 (46.7)	0.67
Previous PCI, n (%)	34 (75.6)	42 (93.3)	0.03
Previous CABG, n (%)	3 (6.67)	1 (2.22)	0.31
Cholesterol (mg/dL) *			
TC	167.7 ± 37.3	162.2 ± 29.6	0.44
LDL-C	94.5 ± 31.0	86.1 ± 25.9	0.17
HDL-C	50.3 ± 11.2	46.9 ± 10.5	0.16
Triglycerides (mg/dL)	117.3 ± 86.9	163.5 ± 116.7	0.04
Glycated hemoglobin, n (%)	6.1 ± 1.1	6.4 ± 1.2	0.21
Medication			
Antiplatelet, n (%)	38 (84.4)	45 (100)	< 0.01
SAPT, n (%)	25 (56.8)	10 (22.2)	
DAPT, n (%)	13 (29.6)	35 (77.8)	
β-Blocker, n (%)	24 (54.6)	22 (48.9)	0.59
Statins, n (%)	25 (55.6)	40 (88.9)	< 0.01
Standard statins, n (%)	10 (22.7)	2 (4.4)	
Strong statins, n (%)	15 (34.1)	38 (84.4)	
Hypoglycemic agent, n (%)	14 (31.1)	15 (33.3)	0.88

TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SAPT, single antiplatelet therapy; and DAPT, dual antiplatelet therapy. Standard statins include pravastatin, simvastatin, and fluvastatin. Strong statins include atorvastatin, pitavastatin, and rosuvastatin. *Reference 18, Table I.

acteristics and the lesion locations and specifics.[19]

Statistical analysis: Categorical variables are expressed as percentages and continuous variables as mean values ± SD or median and interquartile range. The chi-squared test was applied to examine associations between categorical variables. Comparison of categorical and continuous variables was performed using independent t-tests or Mann-Whitney U tests as appropriate after testing for normality of distribution. If they were abnormally distributed, non-parametric test was applied for comparison. Statistical analysis was conducted using the JMP 14 software (SAS Institute Inc., Cary, USA). A two-tailed P value < 0.05 was considered statistically significant.

Results

Overall results: Table II presents a comparison of clinical characteristics between the study population and the reference population in 2017. Overall, for both ACS and SA groups, the prevalence of coronary risk factors was much higher in the study population than in the controls. Similarly, a previous history of PCI was significantly more frequent in the study population. Importantly, such underlying selection bias between the study population and reference population was similarly observed in the ACS and SA cohorts. Both groups consisted of almost equally biased patients.

Table I presents a comparison of baseline characteristics between the ACS and SA groups of this study population. The mean ages of patients with ACS and SA were similar (68.8 ± 10.2 and 67.7 ± 9.8 years, respectively). Male gender was dominant (ACS: 88.9%, SA: 80.0%). The mean observation period since undergoing pre-CAG and the onset of ACS was longer than for SA (942 ± 634 versus 585 ± 389 days, P < 0.01). Although there were no significant differences between the ACS group and SA group in known clinical characteristics, including smoking and diabetes, the incidence of hyperlipidemia was higher in the SA group. However, LDL cholesterol levels at onset were the same in both groups (94.5 ± 31.0 versus 86.1 ± 25.9 mg/dL, P = 0.17), but the rate of statin use was lower in the ACS group than in the SA group (55.6% versus 88.9%, P < 0.01).

Angiographic assessments at the culprit lesion: Mild-to-moderate stenosis was exclusively observed at the culprit site in previous angiographies, both in ACS and SA patients. Figure 1 presents a representative CAG examination for a patient in each group. Table III summarizes the results of quantitative and qualitative angiographic analyses. The locations of the culprit lesions were not significantly different in all three vessels between the two groups. The distance from the ostium to the lesion was similar. Overall, no significant differences were observed in the reference diameter, minimal lumen diameter, or per-

Table II. Comparison of Clinical Characteristics between Study Population and the Reference Population (2017)

	ACS (n = 45)	consecutive ACS-PCI in 2017 (n = 181)	P-value	SA (n = 45)	consecutive SA-PCI in 2017 (n = 222)	P-value
Age (years)	68.8 ± 10.2	68.5 ± 12.3	0.98	67.7 ± 9.8	69.7 ± 11.7	0.29
Body mass index (kg/m^2)	24.4 ± 3.5	23.8 ± 4.0	0.38	24.9 ± 3.8	24.5 ± 3.8	0.53
Male sex, n (%)	40 (88.9)	136 (75.1)	< 0.001	36 (80.0)	166 (74.8)	0.45
Diabetes mellitus, n (%)	18 (40.0)	45 (24.9)	0.04	18 (40.0)	90 (40.5)	0.89
Hypertension, n (%)	42 (93.3)	141 (77.9)	0.02	44 (97.8)	188 (84.7)	0.02
Hyperlipidemia, n (%)	35 (77.8)	97 (53.6)	0.004	42 (93.3)	154 (69.4)	0.001
Smoking History			0.01			0.06
Current, n (%)	9 (20.0)	41 (22.7)		8 (17.8)	37 (16.7)	
Former, n (%)	23 (51.1)	46 (25.4)		21 (46.7)	61 (27.5)	
Previous myocardial infarction, n (%)	23 (51.1)	23 (12.7)	< 0.001	21 (46.7)	40 (18.0)	< 0.001
Previous PCI, n (%)	34 (75.6)	26 (14.4)	< 0.001	42 (93.3)	61 (27.5)	< 0.001
Previous CABG, n (%)	3 (6.67)	5 (2.76)	0.21	1 (2.22)	9 (4.05)	0.52
Clinical presentation: ACS			0.01			
STEMI, n (%)	16 (35.5)	67 (37.0)		-	-	
NSTEMI, n (%)	9 (20.0)	40 (22.1)		-	-	
uAP, n (%)	20 (44.4)	30 (16.6)		-	-	
Clinical presentation: SA						0.47
AP, n (%)	-	-		15 (33.3)	68 (30.6)	
SMI, n (%)	-	-		30 (66.7)	106 (47.7)	

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass grafting; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; uAP, unstable angina pectoris; AP, angina pectoris; and SMI, silent myocardial ischemia.

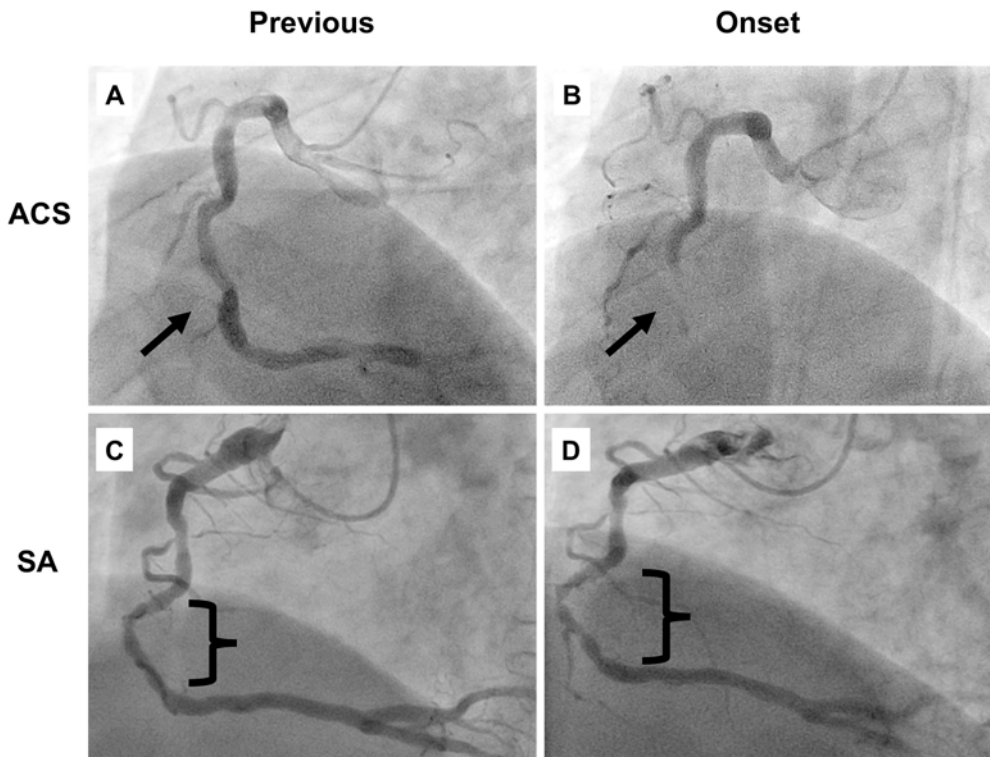

Figure 1. Changes in appearance at the culprit site between earlier angiography and at onset of ACS or SA. Coronary angiograms of a patient with ACS demonstrate slight stenosis in the mid-right coronary artery (arrow) (**A**), progressing to atheroma rupture and thrombosis (arrow) at the time of ACS onset 6 months later (**B**). In contrast, angiograms of a patient with SA reveal a diffuse irregular surface in the mid-portion of the right coronary artery (parenthesis) (**C**), which progressed to hemodynamically significant stenosis 2.5 years later (**D**).

cent diameter stenosis between the two groups prior to onset. Figure 2 presents a comparison of representative quantitative angiographic parameters for the two groups. Lesion length was significantly shorter in ACS (11.5 ± 5.5

Table III. Quantitative and Qualitative Angiographic Analysis

	ACS (n = 45)	SA (n = 45)	P-value
Localization of culprit lesion			0.76
RCA, n (%)	17 (37.8)	14 (31.1)	
LAD, n (%)	16 (35.6)	19 (42.2)	
LCX, n (%)	12 (26.7)	12 (26.7)	
			0.79
Proximal, n (%)	17 (37.8)	17 (37.8)	
Mid, n (%)	14 (31.1)	16 (35.6)	
Distal, n (%)	14 (31.1)	11 (24.4)	
Quantitative Analysis			
Culprit lesion			
Reference Diameter (mm)	2.9 ± 0.6	2.9 ± 0.6	0.87
Minimal Lumen Diameter (mm)	1.3 ± 0.4	1.3 ± 0.5	0.57
Percent Diameter Stenosis	42.2 ± 14.5	44.0 ± 13.8	0.50
Lesion Diameter (mm)	1.7 ± 0.6	1.6 ± 0.6	0.67
Lesion Length (mm)	11.5 ± 5.5	16.1 ± 10.5	0.02
Eccentricity index	0.5 ± 0.3	0.7 ± 0.3	0.04
Distance from ostium to lesion (mm)	45.1 ± 27.2	39.9 ± 21.9	0.32
Whole culprit vessel			
Coefficient of variation of diameter	0.2 ± 0.06	0.2 ± 0.07	0.18
Vessel Length (mm)	86.2 ± 19.8	83.4 ± 17.2	0.59
% Lesion Length (%)	12.8 ± 6.5	19.2 ± 11.9	< 0.01
Qualitative Analysis			
Culprit lesion			
Δangulation in target lesion (degree), median (interquartile range)	7.5 (3.2-15.4)	6.2 (3.0-10.6)	0.07
Plaque morphology			< 0.01
Concentric, n (%)	13 (28.9)	14 (31.1)	
Eccentric, n (%)	41 (91.1)	14 (31.1)	
Multiple irregularities, n (%)	4 (8.89)	17 (37.8)	
Calcification grade			0.12
None, n (%)	26 (57.8)	22 (48.9)	
Barely observable, n (%)	13 (28.9)	9 (20.0)	
Clearly observable, n (%)	6 (13.3)	14 (31.1)	
Whole culprit vessel			
Calcification grade			0.07
Low, n (%)	37 (82.2)	30 (66.7)	
Intermediate, n (%)	8 (17.8)	11 (24.4)	
High, n (%)	0 (0.0)	4 (8.89)	
Diffuse extension of plaque*			0.01
Normal vessel walls, n (%)	2 (4.44)	0 (0.0)	
1-2 plaques, n (%)	23 (51.1)	11 (24.4)	
> 2 plaques located as one or several groups, n (%)	19 (42.2)	30 (66.7)	
> 2 plaques producing continuous vessel wall irregularities, n (%)	1 (2.22)	4 (8.89)	
Score	1.4 ± 0.6	1.8 ± 0.6	0.01
Mean size of plaque*			0.01
Slight indentation, n (%)	32 (71.1)	19 (42.2)	
Intermediate size indentation, n (%)	11 (24.4)	19 (42.2)	
Large plaque, n (%)	2 (4.44)	7 (15.6)	
Score	1.3 ± 0.6	1.7 ± 0.6	0.01
Diffuse extension × mean size*	2.1 ± 1.7	3.4 ± 2.2	< 0.01
All three vessels			
Residual SYNTAX score	12.5 ± 7.4	16.4 ± 8.6	0.03

*Reference 18, Table I.

versus 16.1 ± 10.5 mm, P = 0.02), and the eccentricity index was significantly lower (0.5 ± 0.3 versus 0.7 ± 0.3, P = 0.04). Qualitatively, eccentric plaques were the most common form in the ACS group, whereas concentric plaques, including multiple irregularities, were more frequent in the SA group. Finally, the difference (degree) of the angle in target lesion between cardiac cycles, which was Δangulation, tended to be larger in ACS (median: 7.5, IQR: 3.2-15.4 versus median: 6.2, IQR: 3.0-10.6°, P = 0.07), and there was a suggestion that the motion of the lesion might be greater than in the SA group.

Whole culprit vessel and all three vessels: As presented in Table III and Figure 3, the ACS group had less plaques and a smaller mean plaque size relative to the SA group. In contrast, we detected no difference in CV, which had been our original parameter for differentiating the exten-

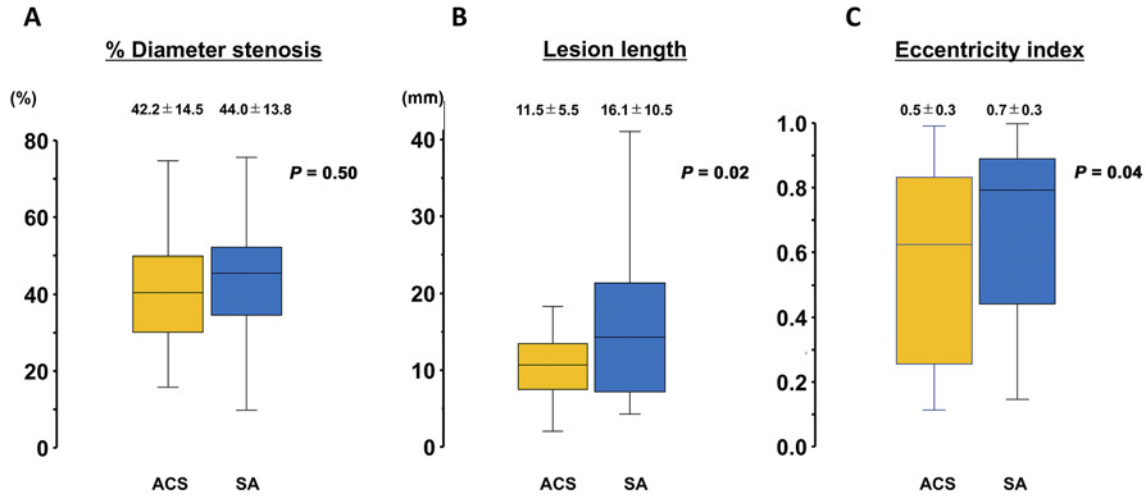

Figure 2. Comparison of representative angiographic parameters of the earlier angiographies at the culprit site. No significant difference in percent diameter stenosis between the 2 groups (**A**), but lesion length was significantly shorter in the ACS group (**B**). Eccentricity index of the ACS group was significantly different (more eccentric) (**C**).

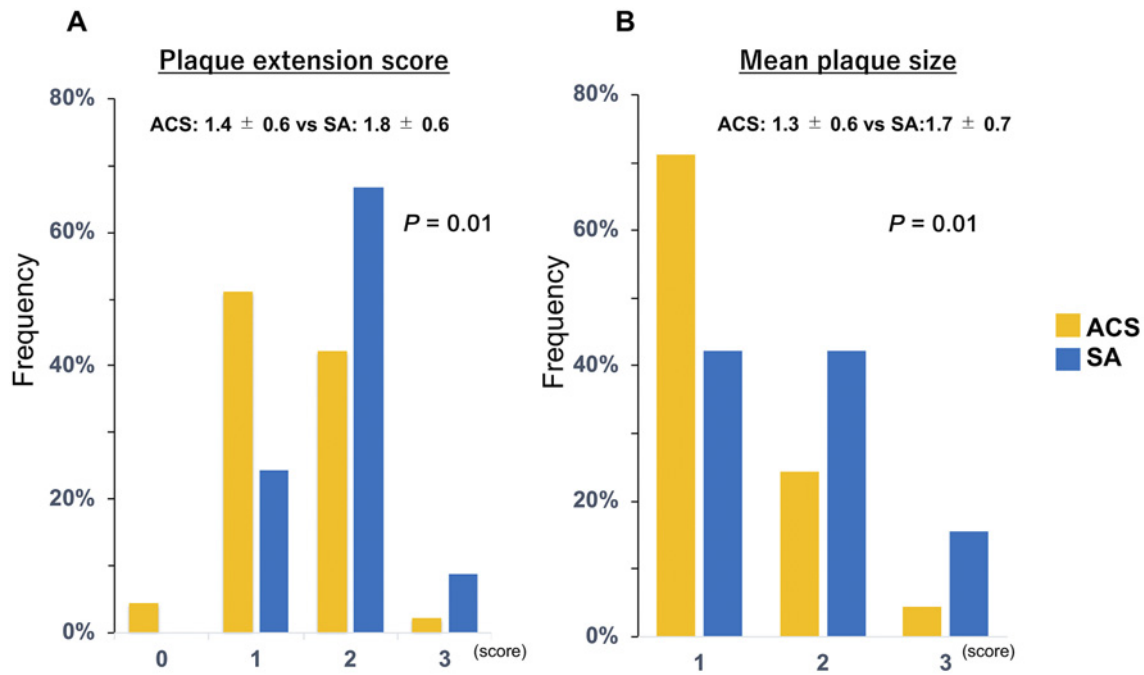

Figure 3. Distribution of indices of grade of diffuseness of atherosclerosis. Differences in distribution patterns between the ACS group with a lower plaque extension score (**A**) and smaller mean plaque size relative to the SA group (**B**).

sion of coronary atherosclerosis. However, no significant difference was observed between the two groups (0.2 ± 0.06 versus 0.2 ± 0.07, $P = 0.18$).

The length of the vessel with the culprit lesion was the same in both groups (86.2 ± 19.8 versus 83.4 ± 17.2 mm, $P = 0.59$). On the other hand, the percentage of the lesion length was shorter in ACS than in SA (12.8 ± 6.5 versus 19.2 ± 11.9%, $P < 0.01$). The residual SYNTAX score in the ACS group was also significantly lower than in the SA group (12.5 ± 7.4 versus 16.4 ± 8.6, $P = 0.03$).

Discussion

Summary of the results: This study clearly revealed that mildly atherosclerotic stenotic changes could already be observed in earlier angiographies several years before patients developed either ACS or SA. Moreover, the corresponding sites of the culprit lesions were exactly as later identified in CAG after onset. This would be expected, but to the best of our knowledge, this, in fact, had never been previously documented. The differences in the angiographic and clinical characteristics between the ACS and

SA groups in the present study can be summarized as follows: mildly stenotic lesions which progress to ACS 1) appeared to be shorter, 2) tended to be bigger in the Δangulation between cardiac cycles, 3) appeared to be more eccentric, but 4) tended to have similar calcification grades relative to those progressing to SA. According to culprit vessel assessments, they also had 5) lower numbers of and smaller-sized plaques, 6) less frequent multiple irregularities (Ambrose's categories), and 7) a tendency toward lower calcification grades throughout the culprit vessel. Furthermore, 8) they had significantly lower residual SYNTAX scores and 9) lower rates of statin use, despite similar serum LDL cholesterol levels. Accordingly, generally speaking, angiographic features of the lesions progressing to ACS appeared to be more focal and eccentric at the culprit site but less diseased in other, non-culprit sites, compared with SA. Such angiographic differences are very important for forecasting future clinical manifestations of mildly atherosclerotic coronary lesions and for considering potential mechanisms influencing the development of ACS or SA.

Characteristics of the lesions in patients progressing to ACS: Ambrose reported that ACS developed from mildly to moderately stenotic lesions,[20] the characteristics of which were well-known. However, "angiographic" characteristics of such progressive lesions prior to ACS onset have not been sufficiently systematically investigated. To the best of our knowledge, very few studies have ever been conducted, which focus on such angiographic features as those in our present study.[21-23] Therefore, we analyzed culprit lesions in detail.

Conventionally, many physicians presume that patients with short, mildly stenotic, and eccentric coronary lesions are less likely to be problematic in terms of the occurrence of future clinical events. In contrast, the present systematic study suggests quite the opposite in that such lesions are more likely to progress to ACS than diffuse coronary lesions. Furthermore, they are more likely to occur in patients with a lower residual SYNTAX score. This study motivates us to reconsider medical intervention and risk management in such circumstances.

Several intracoronary imaging studies[24,25] had demonstrated that eccentric plaques were associated with the development of ACS. Our findings from early angiography should be essentially similar to those from intravascular imaging modalities. It is possible that eccentric plaques identified from angiography may suggest the existence of underlying vulnerable plaques with positive remodeling and a necrotic core at the indent side. Such plaques may progress to TCFA[26,27] and later result in ACS occurrence due to plaque rupture or erosion. Therefore, angiographic eccentricity of the plaque may be equated with significant pathological signs of plaque vulnerability and a high risk of future clinical events. Additionally, "shortness" of the lesion is another important parameter in the results obtained here. Endothelial shear stress (ESS) at atherosclerotic lesions is well-known to be associated with ACS occurrence.[28,29] We suggest the following explanation for this: the shorter and more eccentric the extent of the plaque, the greater the changes of local ESS. A plaque protruding into the lumen, observed as an eccentric plaque, would be more exposed to high ESS. Because short lesions would have two plaque shoulders close together, ESS may be increased at such sites, which would promote plaque vulnerability.[30] Increased local ESS may be a plausible explanation for the association between lesion length and plaque vulnerability.

Clinical implications: Previous studies revealed that vulnerable plaques can be detected by intravascular ultrasound. Nonetheless, it is not realistic to routinely use such invasive modalities for diagnostic purposes in actual clinical practice. In contrast, because CAG remains a basic diagnostic tool, understanding the representative angiographic features predicting future disease development may be clinically highly meaningful. Therefore, when evaluating the coronary lesion angiographically, the fact that angiographically focal and eccentric lesions may more likely progress to ACS should be taken into account in daily practice. Furthermore, they could be applied to coronary CT angiography for less-invasive testing, superior at visualizing the underlying plaque.

Study limitations: There are several potential limitations to this study. First, a small population of patients was enrolled from a single center in a retrospective fashion. Due to the limited availability of the population in our datasets, we could not exactly match patients' characteristics in both the ACS and SA groups. However, we extracted consecutive patients from our database to minimize potential selection biases. Second, because angiographic analysis was conducted by a single experienced physician, potential measurement errors may exist. However, all coronary angiograms were exclusively overviewed by several collaborators (YM, TI, and TK), and the well-established QCA software was used; thus, we believe that potential measurement biases might be minimized in this study dataset. Third, all patients had previous CAG due to suspicion of ischemic heart disease. Hence, the majority of enrolled patients had a previous history of PCI to the other lesions. This is inevitable but is a significant limitation of this study. Accordingly, Table II was presented to elucidate the potential selection bias relative to the reference population in our institution. The selected populations in this study were truly high risk, but such bias may similarly distribute between patients with ACS and SA. In other words, this study dominantly included cases with nontarget lesion revascularization. Accordingly, this study can be interpreted as mainly targeting mild lesions with secondary prevention, which should be considered when applying the results to truly naive patients. Even when considering inevitable selection biases to some extent, there is no doubt that an absolute lesion length of 11.5 mm in earlier angiographies in the ACS group obtained by established QCA methods in this study is very short. Third, surveillance periods were longer in the ACS group due to lower rates of events than in the SA group. Motivation for the use of statins has been gradually increasing, and such a time difference could potentially influence the actual usage rates of statins in these two groups, in addition to the less-diseased appearance of the coronary artery in the index angiography of the ACS group. Fourth, all patients had had CAG previously, and patients with higher residual SYNTAX scores had already been excluded due

to CABG treatment, potentially influencing the average residual SYNTAX scores.

Conclusions

Mild-to-moderate stenosis could be observed exclusively at the culprit site detected on earlier angiographies in patients subsequently progressing to either ACS or SA. Despite equivalent degrees of stenosis in the previous angiogram, ACS more frequently occurred in patients with more focal and eccentric lesions and in those with a lesser extent of atherosclerotic changes than SA.

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Disclosure

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