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NEW RESEARCH PAPERS

CORONARY

Prognostic Links Between OCT-Delineated Coronary Morphologies and Coronary Functional Abnormalities in Patients With INOCA

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ABSTRACT

OBJECTIVES Whether there are prognostic links between coronary morphologies and coronary functional abnormalities was examined in ischemia and nonobstructive coronary artery disease (INOCA) patients.

BACKGROUND Although INOCA has attracted much attention, little is known about the prognostic impact of coronary morphologies in this disorder.

METHODS A total of 329 consecutive INOCA patients were enrolled and underwent spasm provocation testing combined with lactate sampling for diagnosis of epicardial and microvascular spasm (MVS). On the basis of the functional tests, the patients were classified into 4 groups: a control group without epicardial spasm or MVS (n = 32), MVS alone (n = 51), diffuse spasm in ≥2 coronary segments (n = 204), and focal spasm in 1 segment (n = 42). In this population, optical coherence tomography imaging of the left anterior descending coronary artery was performed for evaluation of adventitial vasa vasorum (AVV) and intraplaque neovessels (IPN). Index of microcirculatory resistance was also measured.

RESULTS MVS frequently coexisted with diffuse (70%) and focal spasm (68%) with a good correlation between AVV and index of microcirculatory resistance (R = 0.353; p = 0.022). For a median follow-up of 1,043 days, focal spasm showed the worst prognosis (log rank p = 0.005), for which IPN was a significant prognostic factor. By contrast, diffuse spasm showed the greatest AVV with an intermediate prognosis. The prognostic value of INOCA was significantly enhanced by adding AVV and IPN to the physiological indices (area under the curve = 0.88 vs. 0.76; p = 0.048).

CONCLUSIONS These results provide the first evidence that there are important prognostic links between coronary morphologies (evaluated by optical coherence tomography) and coronary functional abnormalities in patients with INOCA, indicating the importance of both evaluations in this population. (J Am Coll Cardiol Intv 2021;14:606–18)

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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For decades, attention has been paid to technology developments in interventional cardiology, particularly for resolving flow-limiting coronary stenosis. Meanwhile, the importance of ischemia and nonobstructive coronary artery disease (INOCA) has been emerging for its poor prognosis as documented in several cohorts (1,2). INOCA is diagnosed when patients are suspected to have myocardial ischemia but with <50% coronary stenosis (1,2). Coronary microvascular dysfunction (CMD) and epicardial spasm have been proposed as relevant causes of INOCA (1,2) that are hardly identified by routine coronary angiography (3). The interventional diagnostic approach to INOCA includes the measurement of index of microcirculatory resistance (IMR) for CMD and pharmacological spasm provocation testing (4,5). In this regard, we previously demonstrated the usefulness and safety of pharmacological spasm provocation testing (6) combined with lactate sampling in the coronary sinus for diagnosis of microvascular spasm (MVS) (7). Most recently, we also have demonstrated that IMR ≥18 is a prognostic marker for major adverse cardiovascular events (MACE) in patients with epicardial spasm (8). However, the prognostic links between coronary morphologies and coronary functional abnormalities in INOCA patients remain to be fully elucidated.

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Optical coherence tomography (OCT) allows the precise plaque type categorization with clear delineation of morphological features (9). We have established an OCT method for quantification of adventitial vasa vasorum (AVV) (10) that corresponds well to adventitial inflammatory changes (11). Importantly, patients with epicardial spasm showed a profound increase in AVV as compared with those without the spasm (10,11). Furthermore, intraplaque neovessels that often arise from AVV are likely to cause rapid plaque progression and disruption as a consequence of intramural hemorrhage (12). However, little is known about the prognostic impacts of AVV, intraplaque neovessels, or other atherosclerotic features in INOCA. Epicardial spasm generally comprises 2 phenotypes: focal and diffuse spasm (13,14). Focal spasm showed a poorer prognosis compared with diffuse spasm (13), which was confounded by significant coronary stenosis that is frequently noted at the site of focal spasm (15).

The aims of the study were to determine whether there are distinct coronary morphological features as evaluated by OCT in several endotypes of INOCA, and if so, to examine whether there are prognostic links between coronary morphologies and coronary functional abnormalities in INOCA patients.

METHODS

The study protocol was approved by the ethics committee of Tohoku University Graduate School of Medicine (2013-2-31) and was performed in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients before study entry.

STUDY FLOW CHART. The study flow chart is shown in **Figure 1**. From April 2013 to December 2018, patients who underwent diagnostic cardiac catheterization for evaluation of chest pain determined by their doctor's discretion and/or electrocardiogram abnormalities were initially enrolled. INOCA was then defined as ischemia with no significant organic coronary stenosis, defined as luminal narrowing <50% on coronary angiography and/or fractional flow reserve (FFR) >0.80 (16). Among 451 consecutive patients with INOCA, 372 who underwent pharmacological spasm provocation testing with lactate sampling and OCT imaging over the left anterior descending coronary arteries (LAD) were prospectively enrolled. Interventional diagnostic approaches for INOCA during baseline cardiac catheterization were detailed thereafter. Among the 372 INOCA patients, 43 were excluded for spasm documented in the left circumflex and/or right coronary arteries, but not in the LAD, for insufficient OCT data due to incomplete blood clearance during OCT imaging, or for ergometrine use. Lactate sampling was performed at each step of spasm provocation testing for diagnosis of MVS (Supplemental Figure 1A). The control group with noncardiac chest pain was defined as negative for both spasm provocation testing and lactate sampling. Diffuse spasm was defined as epicardial spasm induced in more than 2 coronary segments in the LAD, and focal spasm as spasm in 1 segment of the artery (13,14). Finally, a total of 329 patients were classified into 4 groups: a control group without spasm, and with MVS, diffuse spasm, and focal spasm.

DATA COLLECTION FOR BASELINE CHARACTERISTICS. Details are available in the Supplemental Appendix. Results are shown in **Table 1** and Supplemental Table 1.

SPASM PROVOCATION TESTING. Interventional diagnostic approaches are detailed in Supplemental Figure 1A. Coronary angiography at baseline was

ABBREVIATIONS AND ACRONYMS

AVV = adventitial vasa vasorum

CMD = coronary microvascular dysfunction

FFR = fractional flow reserve

LAD = left anterior descending coronary artery

IMR = index of microcirculatory resistance

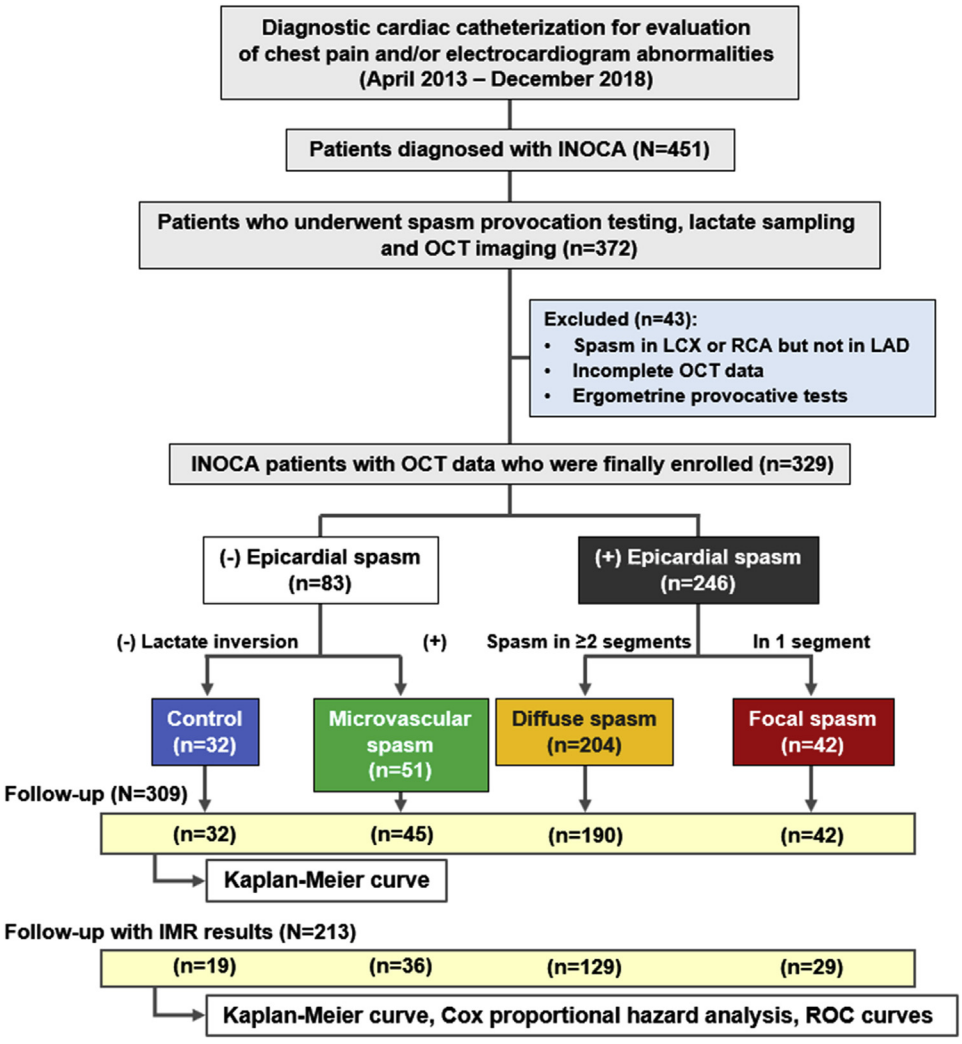
INOCA = ischemia and no obstructive coronary artery disease

MACE = major adverse cardiac event(s)

MVS = microvascular spasm

OCT = optical coherence tomography

FIGURE 1 Study Flow Chart



IMR = index of microcirculatory resistance; INOCA = ischemia and nonobstructive coronary artery disease; LAD = left anterior descending; LCX = left circumflex coronary artery; OCT = optical coherence tomography; RCA = right coronary arteries; ROC = receiver-operating characteristic.

followed by pharmacological spasm provocation testing for diagnosis of epicardial spasm. Acetylcholine was administered in an incremental manner into the left coronary artery (20, 50, and 100 μg), and if negative for the test in the left, administered to the right coronary artery (20 and 50 μg) over a period of 20 s with a 3- to 5-min interval (Supplemental Table 2). We performed serial coronary angiography at 1 min after acetylcholine administration, or when chest pain with or without ischemic electrocardiogram changes were documented. To resolve the spasm, isosorbide dinitrate (2 mg) was administrated into the left or right coronary arteries. The spasm provocation test was performed after a washout period of at least 24 h for calcium-channel blockers or nitrates. The diagnosis of epicardial spasm was made when a total or subtotal (>90%) coronary artery narrowing was accompanied by chest pain and/or was documented in accordance with the Japanese Circulation Society guidelines (17) and the COVADIS (Coronary Vasomotor Disorders International Study group) consensus document (18). The presence of myocardial bridging was assessed on coronary angiography (19).

TABLE 1 Clinical Characteristics and Treatments (N = 329)

	Control (n = 32)	Microvascular Spasm (n = 51)	Diffuse Spasm (n = 204)	Focal Spasm (n = 42)	p Value
Age, yrs	59 ± 3	61 ± 2	62 ± 1	61 ± 2	0.46
Female	11 (34)	27 (53)	91 (45)	24 (57)	0.18
SAQ					
Physical limitation	68 ± 8	79 ± 4	82 ± 2	83 ± 5	0.17
Angina stability	53 ± 7	58 ± 5	54 ± 3	50 ± 7	0.76
Angina frequency	62 ± 8	76 ± 5	77 ± 3	78 ± 5	0.31
Treatment satisfaction	63 ± 9	72 ± 4	69 ± 3	74 ± 7	0.76
Disease perception (quality of life)	42 ± 10	47 ± 4	47 ± 2	42 ± 7	0.78
Hypertension	13 (40)	24 (47)	103 (50)	21 (50)	0.76
Diabetes mellitus	7 (22)	10 (20)	40 (20)	4 (10)	0.44
Dyslipidemia	9 (28)	23 (45)	92 (45)	18 (43)	0.33
Smoking behavior	13 (40)	16 (31)	63 (31)	11 (26)	0.61
LVEF, %	62 ± 2	66 ± 2	65 ± 1	68 ± 1	0.10
BNP, pg/ml	50.3 ± 13.5	70.4 ± 17.5	53.8 ± 9.3	22.4 ± 3.0	0.26
hs-cTnT	0.03 ± 0.01	0.04 ± 0.02	0.01 ± 0.00	0.04 ± 0.03	0.13
hs-CRP, mg/dl	0.35 ± 0.14	0.34 ± 0.17	0.25 ± 0.06	0.12 ± 0.03	0.55
Medications					
Calcium-channel blocker	14 (44)	24 (47)	129 (63)	30 (71)	0.02
Long-acting nitrate	1 (3)	2 (4)	36 (18)	6 (14)	0.02
Potassium channel opener (nicorandil)	2 (6)	5 (10)	29 (14)	4 (10)	0.50
ACE inhibitor or ARB	7 (22)	16 (31)	70 (34)	16 (38)	0.48
Beta-blocker	6 (19)	11 (22)	41 (20)	2 (5)	0.11
Statin	8 (25)	16 (31)	77 (38)	20 (48)	0.19
Antiplatelet agent	6 (19)	9 (18)	58 (28)	9 (21)	0.29

Values are mean ± SEM or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers; BNP = B-type natriuretic peptide; hs-cTnT = high-sensitivity cardiac troponin-T; hs-CRP = high-sensitivity C-reactive protein; LVEF = left ventricular ejection fraction; SAQ = the Seattle Angina Questionnaire.

LACTATE SAMPLING IN THE CORONARY CIRCULATION. Details are available in the Supplemental Appendix. Apart from the degree of IMR, the diagnosis of MVS was made when patients were negative for epicardial spasm but positive for negative myocardial lactate extraction ratio during the spasm provocation testing (7). Coexistence of MVS in diffuse spasm and focal spasm was considered when showing a negative myocardial lactate extraction ratio before the appearance of epicardial coronary spasm during the provocation testing (7).

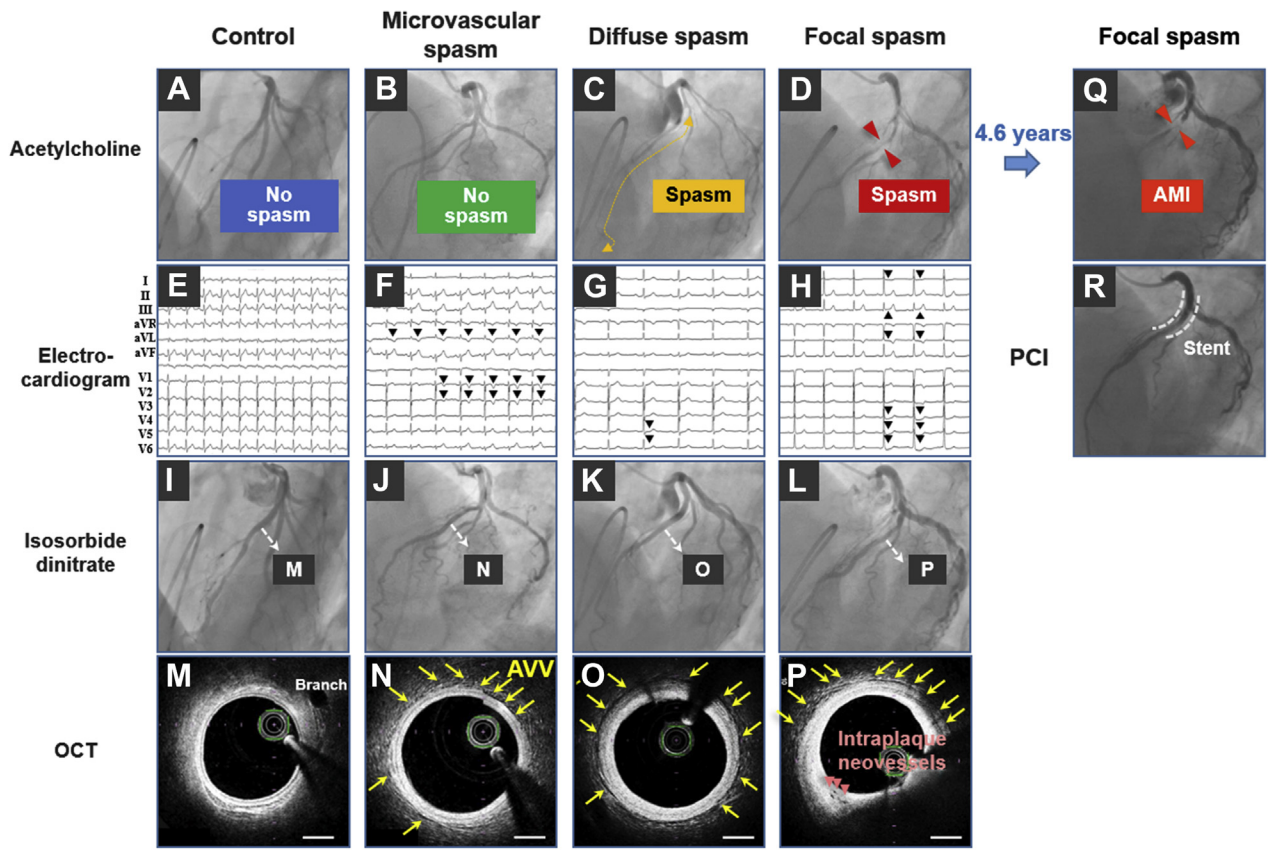
IMR AND FFR MEASUREMENTS. Details are available in the Supplemental Appendix. High IMR was defined as IMR ≥18 on the basis of its significant prognostic value for CMD with epicardial spasm (8), and not according to the recommended cutoff value of IMR ≥25 (20).

OCT IMAGING AND MORPHOMETRIC ANALYSIS. Details are available in the Supplemental Appendix. After IMR and FFR measurements, OCT imaging was performed over the entire length of the LAD. Lumen and vessel area, % intimal+medial area as plaque burden (9,21), adventitial area, and then AVV density (10,11,21) were calculated at the proximal, mid-, and distal LAD (segments 6, 7, and 8) of 329 patients (Supplemental Table 3).

OCT-DELINEATED CORONARY PLAQUE TYPE. In a total of 987 OCT cross sections, coronary plaque type was categorized as either normal, intimal thickening, fibrous plaque, lipid-rich fibroatheroma, or fibrocalcific plaque (22). The number of OCT frames with intraplaque neovessels or other atherosclerotic features, such as cholesterol crystals and superficial macrophage infiltration (9), was counted. Lipid arc and fibrous cap thickness (9) were measured in fibroatheroma. The appearance of intraplaque hemorrhage on OCT was referred to histological validation (23).

CLINICAL OUTCOME AND PATIENT FOLLOW-UP. Details are available in the Supplemental Appendix. MACE was defined as the composite of cardiac death, non-fatal myocardial infarction, and urgent

FIGURE 2 Representative Cases Showing Various Mechanisms in INOCA



(A to D) Representative coronary angiography during intracoronary acetylcholine administration, **(E to H)** electrocardiogram, **(I to L)** coronary angiography immediately after isosorbide dinitrate, and **(M to P)** OCT cross sections acquired at mid-LAD. The **dashed arrows in I to L** indicate the location of the OCT image in **M to P**, respectively. A control subject showed no changes in coronary angiography or electrocardiogram during spasm provocation testing, and almost normal lesion with sparse AVV on OCT **(I and M)**. A microvascular spasm patient showed no epicardial spasm in coronary angiography but ischemic electrocardiogram changes during spasm provocation testing, and intimal thickening with AVV augmentation **(yellow arrows) (J and N)**. A diffuse spasm patient showed epicardial spasm along the LAD accompanied by electrocardiogram changes during spasm provocation testing and intimal thickening with abundant AVV proliferation (**K and O**). A 64-year-old female patient showed focal spasm at mid-LAD accompanied by electrocardiogram changes during spasm provocation testing, and showed no stenotic fibroatheroma with AVV and IPN augmentation **(pink arrowheads)** (**L and P**). AMI occurred in this patient at exactly the same location of focal spasm, 4.6 years after the first examination (**Q and R**). Scale bars = 1 mm **(M to P)**. AMI = acute myocardial infarction; AVV = adventitial vasa vasorum; IPN = intraplaque neovessels; PCI = percutaneous coronary intervention; other abbreviations as in Figure 1.

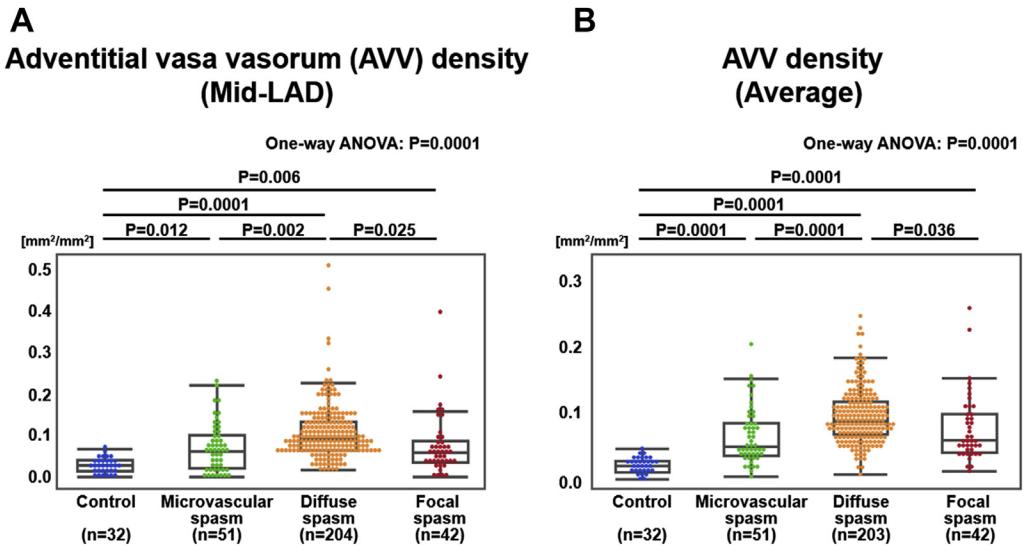
hospitalization due to either unstable angina pectoris or heart failure (8).

STATISTICAL ANALYSIS. Details are available in the Supplemental Appendix. Continuous variables are expressed as mean ± SEM, and categorical variables as number and percentages. A value of $p < 0.05$ was considered to be statistically significant. The statistical analysis was performed with SPSS Statistics 25 software (IBM Corp., Armonk, New York) and R version 3.1.1 software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PATIENT CHARACTERISTICS. We enrolled noncardiac control (n = 32), MVS (n = 51), diffuse spasm (n = 204), and focal spasm (n = 42) patients (Figure 1, Supplemental Figure 1A). Importantly, MVS frequently coexisted with diffuse spasm (70%) and focal spasm (68%) (Supplemental Figure 1B). More than one-half of patients with MVS and those with focal spasm were female, and the prevalence of female patients was significantly higher in the focal spasm group than in the control group (Table 1).

FIGURE 3 AVV Formation in INOCA



(A and B) AVV density (in mid-LAD and average) was compared among the 4 groups. AVV was significantly increased in microvascular spasm, diffuse spasm, and focal spasm as compared with the control subjects. Diffuse spasm exhibited the highest AVV density. The **central box** covers the interquartile range, with the median indicated by the **line within the box**. The **whiskers** extend to the most extreme values within 1.5 interquartile ranges. Outliers are plotted individually. ANOVA = analysis of variance; other abbreviations as in **Figures 1 and 2**.

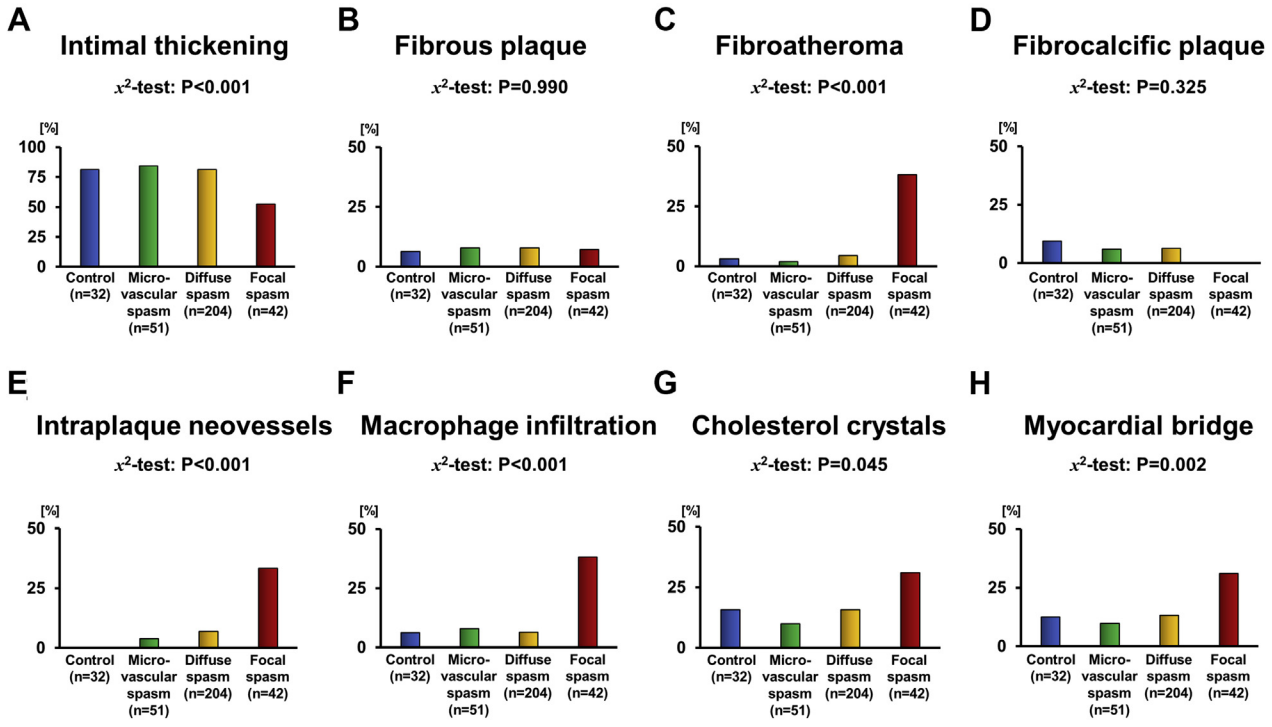
Coronary risk factors and laboratory data were comparable among the 4 groups (**Table 1**) except for lipid markers (Supplemental Table 1). Focal spasm was most commonly induced at mid-LAD compared with the proximal and distal LAD (proximal 16% vs. mid 75% vs. distal 9%), and thus, we examined coronary plaque morphology for the mid-LAD.

REPRESENTATIVE OCT IMAGES IN INOCA. Representative OCT images obtained at mid-LAD were visually compared (**Figure 2**). AVV formation was augmented in patients with MVS, diffuse spasm, and focal spasm, but not in the control patients (**Figure 2**). A 64-year-old woman with focal spasm showed fibroatheroma with AVV and intraplaque neovessel augmentation (**Figure 2**). After 4.6 years, she developed acute myocardial infarction at the spasm site (**Figure 2**). In the focal spasm group, AVV appeared to be increased from the distal to proximal portions, and importantly, all intraplaque neovessels had connections to AVV, and some caused intraplaque hemorrhage (Supplemental Figures 2 and 3). These findings suggest that adventitial inflammatory changes could be exacerbated in the MVS, diffuse spasm, and focal spasm groups, and that focal spasm could be a precipitating factor for MACE by causing coronary plaque progression and disruption due to hemorrhagic intraplaque neovessels.

AVV FORMATION IN INOCA. We then examined the involvement of adventitial inflammatory changes in INOCA. AVV density was significantly greater in the MVS, diffuse spasm, and focal spasm groups as compared with the control group (**Figure 3**, Supplemental Figure 4). Patients with diffuse spasm exhibited the highest AVV (**Figure 3**). Of note, AVV was enhanced more at the distal LAD than the proximal LAD in the MVS, diffuse spasm, or focal spasm groups (Supplemental Figure 5). Although the numerical value of IMR was statistically comparable (Supplemental Table 4), patients with high IMR were distributed with a steady increase from MVS, diffuse spasm, to focal spasm, but not in the control group (Supplemental Figure 6A). There were significant positive correlations between AVV density and the degree of IMR in the MVS and diffuse spasm groups (Supplemental Figures 6B and 6C).

PLAQUE BURDEN (% INTIMAL+MEDIAL AREA) IN INOCA. We further examined coronary atherosclerotic changes in INOCA. Lumen area, vessel area at mid-LAD, and the presence of coronary stenosis in the LAD were all comparable (Supplemental Tables 2 to 4). At mid-LAD, plaque burden, expressed as % intimal+medial area, was significantly greater in the focal spasm group as compared with the other 3 groups (Supplemental Figure 7). Plaque burden

FIGURE 4 Coronary Plaque Types in INOCA



(A to G) Coronary plaque type for mid-LAD was categorized as normal/intimal thickening, fibrous plaque, and lipid-rich fibroatheroma or fibrocalcific plaque. In the control, microvascular spasm, and diffuse spasm groups, more than 75% of plaques were categorized as intimal thickening **(A)**. By contrast, lipid-rich fibroatheroma was most prevalent in the focal spasm group **(C)**. **(E to G)** Intraplaque neovessels, cholesterol crystals, and macrophage infiltration were prominent in focal spasm. **(H)** The focal spasm group had the highest number of myocardial bridges in the LAD. Abbreviations as in Figures 1 and 2.

appeared to be expanded with aging (Supplemental Figure 8), and in particular, a sudden increase was noted in patients with focal spasm older than 50 years (Supplemental Figure 8).

CATEGORIZATION OF CORONARY PLAQUE TYPE IN INOCA. In the 3 groups, except for the focal spasm group, more than 75% of coronary plaques at mid-LAD were categorized as mild lesions with intimal thickening (Figure 4A), explaining their smaller plaque burden. Lipid-rich fibroatheroma was most prevalent in the focal spasm group (Figure 4C). Similarly, intraplaque neovessels, macrophage infiltration, cholesterol crystals, and myocardial bridging were evident in the focal spasm group (Figures 4E to 4H). The lipid arc of fibroatheroma was 112 ± 6.9°, and fibrous cap thickness was 267 ± 3 μm. The remaining plaques at mid-LAD were categorized as

TABLE 2 Clinical Events (Overall, N = 309)

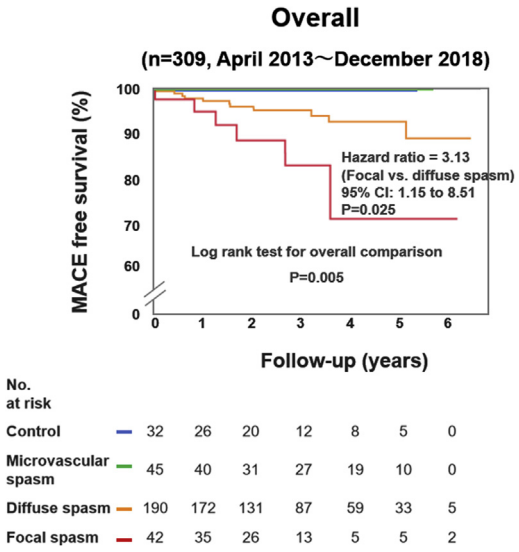
	Control (n = 32)	Microvascular Spasm (n = 45)	Diffuse Spasm (n = 190)	Focal Spasm (n = 42)
Median follow-up, days	879	1,329	1,063	904
Interquartile range	439–1,123	821–1,511	902–1,148	783–1,091
MACE	0 (0)	0 (0)	11 (6)	6 (14)
Cardiac death	0 (0)	0 (0)	0 (0)	0 (0)
Non-fatal MI	0 (0)	0 (0)	1 (1)	2 (5)
Hospitalization for UAP or HF	0 (0)	0 (0)	10 (5)	4 (10)

Values are n (%) unless otherwise indicated.
HF = heart failure; MACE = major adverse cardiovascular event(s); MI = myocardial infarction; UAP = unstable angina pectoris.

fibrous and fibrocalcific plaques (**Figures 4B and 4D**). The majority of the coronary plaques at the proximal and distal LAD were categorized as intimal thickening (Supplemental Figure 9).

MACE IN INOCA. A total of 309 patients were successfully followed for a median follow-up of 1,043 days (interquartile range: 904 to 1,119 days) (**Figure 1**). During the follow-up period, MACE occurred most frequently in the focal spasm group followed by the diffuse spasm group (**Table 2,** Supplemental Table 5). The Kaplan-Meier survival analysis showed that the focal spasm group had the worst outcome, followed by the diffuse spasm group (**Figure 5**). The result remained unchanged even when extracting 213 patients who underwent IMR measurements (Supplemental Figure 10). Cox analysis for the 213 patients with IMR measurements or for the 158 patients with diffuse or focal spasm showed that high IMR, AVV, and intraplaque neovessels were independently correlated with MACE (**Tables 3 and 4**). In fact, prognostic values were significantly improved when adding AVV and intraplaque neovessels to the physiological indices (**Figure 6**). Cox analysis and the receiver-operating characteristic curve for diffuse spasm showed that AVV was an independent prognostic factor for MACE, whereas the analysis for focal spasm indicated that a combination of IMR and intraplaque neovessels was significantly correlated with MACE (Supplemental Figure 11, Supplemental Tables 6 and 7).

FIGURE 5 Kaplan-Meier Curve in INOCA



The Kaplan-Meier curve in the overall population of 309 patients. Focal spasm had the worst prognosis, followed by diffuse spasm. CI = confidence interval; INOCA = ischemia and nonobstructive coronary artery disease; MACE = major adverse cardiovascular event(s).

DISCUSSION

Major findings of the present study were that: 1) compared with the control group, the MVS group had enhanced AVV formation associated with increased IMR; 2) the diffuse spasm group showed the highest AVV density associated with increased IMR, with a significant correlation with MACE; 3) the focal spasm group had a vulnerable atherosclerotic phenotype with the worst outcome, where IMR and intraplaque neovessels were significant prognostic factors; and 4) prognostic values were significantly enhanced by adding AVV and intraplaque neovessels to the known physiological indices (**Central Illustration**). To the best of our knowledge, this is the first study demonstrating the prognostic links between coronary morphologies and functional coronary abnormalities in patients with INOCA.

IMPORTANCE OF AN INVASIVE DIAGNOSTIC APPROACH FOR INOCA. INOCA has currently attracted much attention because this disorder has increased risk for worse prognosis (1,2). Although multiple mechanisms may be involved in the pathogenesis of INOCA, coronary vasomotion abnormalities, such as CMD and epicardial spasm, are the most possible causes of the disorder (2,4,5). In the present study, we were able to demonstrate that patients with MVS or high IMR were highly prevalent in the diffuse spasm and focal spasm groups. Focal spasm was then extracted as the highest-risk subset in INOCA, followed by diffuse spasm. Thus, it is important for cardiologists to consider interventional diagnostic approaches when no significant stenosis exists on coronary angiography. In this regard, we previously demonstrated the clinical usefulness of pharmacological spasm provocation testing (6). Indeed, no thrombus formation was noted even after the occurrence of severe epicardial spasm, ensuring the diagnostic safety of the testing.

PROGNOSTIC IMPACTS OF CORONARY MORPHOLOGIES IN INOCA. A recent OCT study reported the significance of plaque features at nonculprit sites for clinical events in obstructive coronary artery disease (24). However, the prognostic links between coronary morphologies and coronary functional abnormalities in INOCA remain to be fully elucidated. Using OCT for

TABLE 3 Cox Proportional Hazard Model for MACE in INOCA Patients With IMR Results (N = 213)

	Univariable Analysis			Multivariable Analysis With 4 Variables		
	HR	95% CI	p Value	HR	95% CI	p Value
Age	0.96	0.66–1.49	0.862			
Female	0.93	0.33–2.62	0.891			
Hypertension	1.52	0.54–4.27	0.429			
Diabetes mellitus	1.27	0.40–4.01	0.681			
Dyslipidemia	0.95	0.73–1.26	0.737			
Smoking	1.16	0.86–1.56	0.325			
eGFR	0.96	0.73–1.20	0.727			
Epicardial spasm with microvascular spasm	5.42	1.22–24.06	0.026	3.41	0.74–15.67	0.115
High IMR	4.53	1.44–14.26	0.010	2.74	0.82–9.10	0.100
AVV	2.29	1.35–3.43	0.004	2.09	1.21–3.26	0.011
Intraplaque neovessels	3.77	1.29–11.03	0.016	4.27	1.36–13.46	0.013

Unit for age is represented by age $\cdot 10^{-1}$; eGFR, ml/min/1.73 m^2 $\cdot 10^{-1}$; AVV, mm^2/mm^2 $\cdot$ 10. HR is for age per 10-yr increase; eGFR per 10 increase; AVV, mm^2/mm^2 per 0.1 increase.

AVV = adventitial vasa vasorum; CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; IMR = index of microcirculatory resistance; INOCA = ischemia and nonobstructive coronary artery disease; MACE = major adverse cardiovascular event(s).

in vivo AVV quantification, we previously examined coronary atherosclerotic changes and adventitial inflammatory changes, demonstrating that AVV was significantly increased in patients with epicardial spasm compared with control patients (10,11,19,21). Furthermore, in the present study, we were able to demonstrate that all intraplaque neovessels were increased at focal spasm sites, networking with augmented AVV. These microvasculature proliferations, but no other atherosclerotic features, showed excellent prognostic values for MACE. Thus, the present study underlines the significance of coronary morphology evaluation for risk assessment and elucidation of underlying mechanisms of INOCA.

TABLE 4 Cox Proportional Hazard Model for MACE in Diffuse Spasm and Focal Spasm Patients With IMR Results (N = 158)

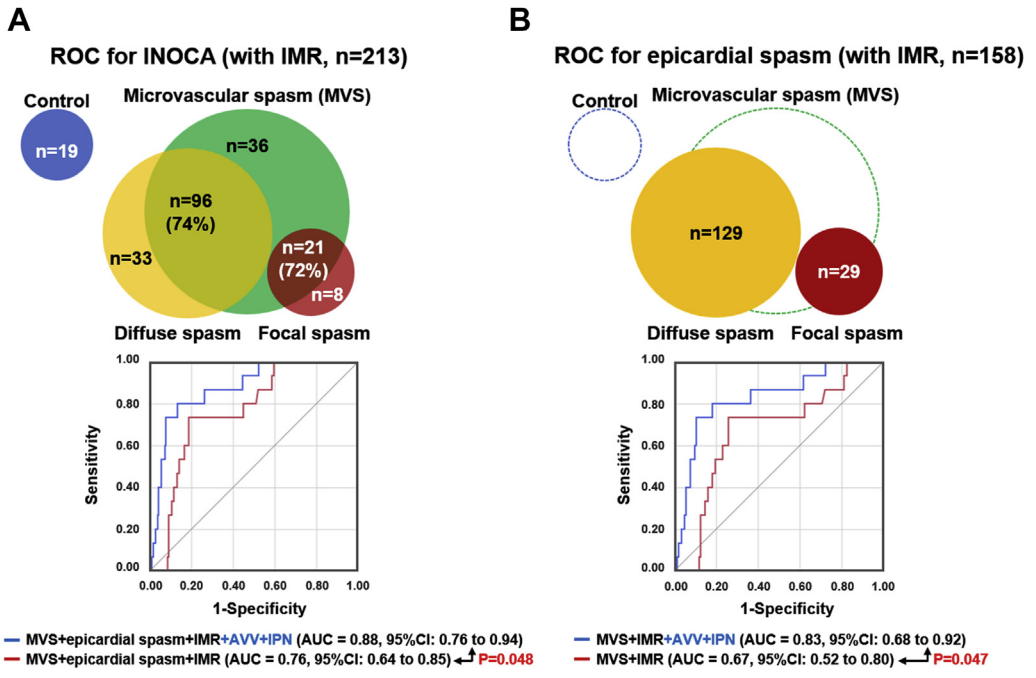
	Univariable Analysis			Multivariable Analysis With 3 Variables		
	HR	95% CI	p Value	HR	95% CI	p Value
Age	0.94	0.62–1.48	0.777			
Female	0.92	0.33–2.57	0.866			
Hypertension	1.54	0.55–4.35	0.408			
Diabetes mellitus	1.42	0.45–4.46	0.550			
Dyslipidemia	1.16	0.42–3.21	0.769			
Smoking	1.99	0.72–5.49	0.185			
eGFR	0.97	0.70–1.31	0.864			
Microvascular spasm	2.25	0.51–9.98	0.286			
High IMR	3.88	1.23–12.21	0.021	3.00	0.92–9.75	0.068
AVV	2.09	1.19–3.19	0.014	2.08	1.12–3.26	0.014
Intraplaque neovessels	3.00	1.02–8.80	0.045	3.79	1.20–11.93	0.023

Abbreviations are as in Table 3.

CORONARY MORPHOLOGIES IN MVS. In the present OCT analysis, AVV density was significantly greater in MVS patients as compared with the control patients, and was gradually increased from the distal to proximal ends of the coronary artery. Patients with high IMR were prevalent in the MVS group, but not in the control group. Of note, there was a significant positive correlation between AVV and IMR in MVS, a consistent finding with the previous study, demonstrating an association between vasa vasorum proliferation and CMD (25). This could be explained by several mechanisms, including turbulent blood flow due to hyperconstricting responses of coronary microvessels, altered local shear stress (26), and resultant AVV proliferation.

Regardless of the incidence of high IMR, MVS was diagnosed when a patient was positive for myocardial lactate production. Although coronary atherosclerosis and its preceding risks are common in CMD patients (2), the magnitude of atherosclerotic plaque burden in MVS was smaller than anticipated. In general, CMD variably involves 2 major pathophysiological mechanisms, including increased microvascular constriction (MVS) and impaired microvascular dilatation (27). Enhanced coronary vasoconstriction caused by medial vascular smooth muscle cell hypercontraction plays a crucial role in epicardial spasm (28,29). In the present study, we thus focused on MVS determined on the basis of lactate inversion, but not high IMR, so that we could compare this CMD subset with epicardial spasm. Indeed, MVS coexisted in more than one-

FIGURE 6 ROC Curves for INOCA



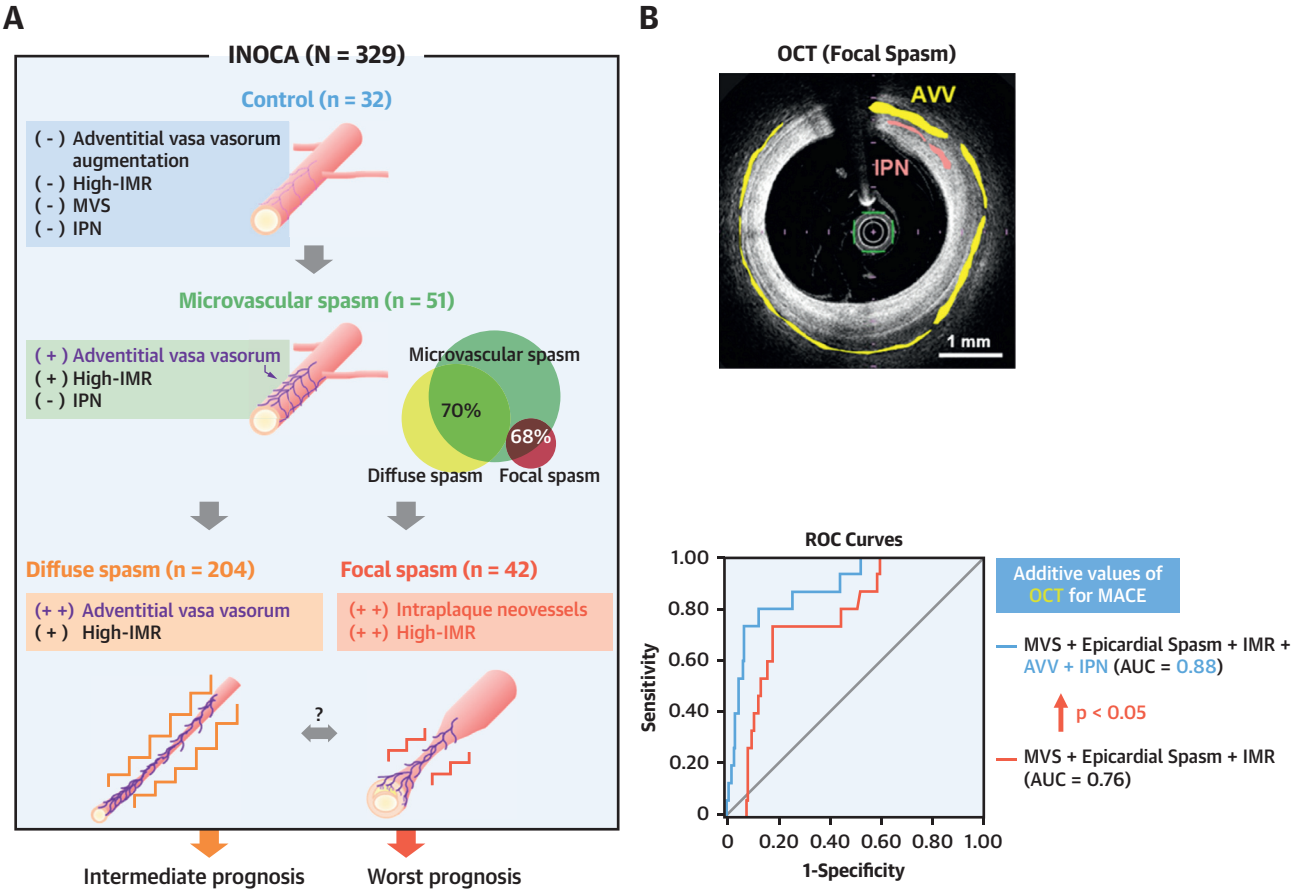
ROC curves for **(A)** INOCA patients with IMR measurements, and **(B)** diffuse spasm and focal spasm patients with IMR measurements. Prognostic values were significantly enhanced when adding OCT parameters (AVV and IPN) to the physiological indices of microvascular spasm (MVS), epicardial spasm, and IMR. AUC = area under the curve; MVS = microvascular spasm; other abbreviations as in Figures 1 and 2.

half of patients with diffuse spasm or focal spasm, suggesting that the MVS phenotype could be an early stage leading to epicardial spasm. Patients with high IMR were most prevalent in the focal spasm group characterized by the atherosclerotic phenotype. CMD determined by impaired coronary blood flow in response to acetylcholine was an independent predictor of virtual histology intravascular ultrasound-derived thin-cap fibroatheroma, supporting the present finding (30). Recently, we demonstrated that CMD, partly determined by high IMR, is a cardiac manifestation of systemic microvascular dysfunction caused by impairments of both nitric oxide- and endothelium-dependent hyperpolarization-mediated vasodilation (31,32).

CORONARY MORPHOLOGIES IN DIFFUSE SPASM. We have recently reported that diffuse spasm is more common than focal spasm in both Whites and Japanese (diffuse spasm 70% vs. focal spasm 20%) (33). Consistently, the present study shows that diffuse spasm is the leading subset of INOCA. The diffuse spasm group exhibited the greatest AVV density, positively associated with IMR. It is of note that diffuse spasm was with an intermediate prognosis in INOCA, where AVV density was the strong correlated factor. Given that AVV density in diffuse spasm is positively correlated with Rho-kinase activation (a molecular switch of the spasm) (10,11), preceding AVV proliferation in MVS could be further promoted by enhanced Rho-kinase activation (29) over the diffuse spastic segments. Thus, a Rho-kinase inhibitor (29) would hold promise for a risk-reduction strategy for diffuse spasm.

CORONARY MORPHOLOGIES IN FOCAL SPASM. Focal spasm has a poor prognosis compared with diffuse spasm partly due to the higher incidence of significant coronary stenosis (13,14). In the present study, even after screening significant organic stenosis based on coronary angiography or FFR, focal spasm remained as a poor prognostic factor compared with the other 3 groups. Albeit with a vulnerable atherosclerotic phenotype determined by OCT, coronary risk factors in the focal spasm group were comparable with the other groups, indicating the unveiled underlying mechanism in focal spasm in INOCA. In the present study, in addition to the excellent prognostic value of IMR ≥18 (8), intraplaque neovessels augmentation of focal spasm also showed

CENTRAL ILLUSTRATION **Coronary Artery Morphologies and Long-Term Prognosis in Ischemia and Nonobstructive Coronary Artery Disease Patients**



Nishimiya, K. et al. J Am Coll Cardiol Intv. 2021;14(6):606–18.

The present study demonstrates the prognostic links between optical coherence tomography (OCT)-delineated coronary morphologies and coronary functional abnormalities in patients with ischemia and nonobstructive coronary artery disease (INOCA). **(A)** A total of 329 INOCA patients were enrolled. They underwent pharmacological spasm provocation testing with lactate sampling for making diagnosis of microvascular spasm (MVS) and also intravascular OCT imaging over the left anterior descending coronary arteries. On the basis of the findings of the functional testing, they were classified into 4 groups: control group without epicardial spasm or microvascular spasm (n = 32), microvascular spasm alone (n = 51), diffuse spasm in ≥2 coronary segments (n = 204), and focal spasm in 1 segment (n = 42). Microvascular spasm, diffuse spasm, and focal spasm groups showed profound increases in OCT-derived adventitial vasa vasorum, but none in the controls. Patients with high index of microcirculatory resistance (IMR), a marker for coronary microvascular dysfunction, were prominent in microvascular spasm, diffuse spasm, and focal spasm, but none in the control subjects. Microvascular spasm co-existed in 70% of diffuse spasm and 68% of focal spasm, indicating that this subset is a precursor stage of epicardial spasm. Despite of increased adventitial vasa vasorum and IMR, microvascular spasm and diffuse spasm were characterized by less atherosclerotic phenotypes compared with focal spasm. Lipid-rich fibroatheroma with intraplaque neovessels (IPN) was prominent in focal spasm. **(B)** Receiver-operating characteristic (ROC) curves demonstrated that a prognostic value for major adverse cardiac events (MACE) in INOCA was significantly improved by adding OCT-derived morphological features of adventitial vasa vasorum (AVV) and intraplaque neovessels to the known physiological indices. AUC = area under the curve; IMR = index of microcirculatory resistance; INOCA = ischemia and nonobstructive coronary artery disease; MACE = major adverse cardiac event(s); MVS = microvascular spasm; OCT = optical coherence tomography; ROC = receiver-operating characteristic.

a significant link to MACE. It is conceivable that intraplaque hemorrhage due to intraplaque neovessels originating from AVV precipitates rapid plaque progression or disruption (12) and that progressive hypoxia due to rapid plaque expansion induces further proliferations of AVV and intraplaque neovessels. OCT with near-infrared autofluorescence for intraplaque hemorrhage (34) could provide the additive prognostic value for INOCA in the future. A sudden increase in plaque volume was noted in

patients older than 50 years of age in the focal spasm group, where rapid plaque progression related to the spasm (15) may be involved. Targeted treatments within the INOCA population merit further research, including a Rho-kinase inhibitor (29) and anti-inflammatory agents (35), targeting on microvasculature proliferation.

STUDY LIMITATIONS. First, OCT imaging was performed only in the LAD. Similar to the patients with myocardial infarction due to INOCA (36), the number of vessels with mild coronary lesions seemed to be relevant to MACE in INOCA (Supplemental Table 8). Second, we have incorporated IMR measurements into the routine procedure since November 2014 (8). OCT measurements could be influenced by vasodilating responses after adenosine triphosphate, even though considerably minor, which could also be compromised by signal attenuation at fibroatheroma (9). Third, it remains unclear whether or not diffuse spasm precedes the manifestation of focal spasm. Fourth, the limited number of MACE during follow-up may reduce the statistical power, which could make it difficult to perform multivariable Cox analysis for MACE in the focal spasm group. A higher MACE rate in a larger population during a longer follow-up period was reported (37). Possible ethnic differences in long-term prognosis of INOCA patients remains to be addressed in future studies. Fifth, because we excluded patients with obstructive coronary artery disease, IMR levels were lower than the previous study (38). The association between IMR and atherosclerotic changes in coronary microcirculation should be detailed in future studies. Sixth, although myocardial bridging was not predictive for MACE (hazard ratio: 0.43, 95% confidence interval: 0.08 to 2.42), the prognostic value of this anomaly depending on varying orientation (39) should be elucidated in future studies.

CONCLUSIONS

In the present study using OCT for comprehensive evaluation of coronary artery morphology in INOCA patients, we were able to provide the first evidence that there are important prognostic links between coronary morphologies (evaluated by OCT) and coronary functional abnormalities (epicardial and MVS) in patients with INOCA, indicating the potential utility of both examinations in future INOCA research studies.

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PERSPECTIVES

WHAT IS KNOWN? Ischemia and nonobstructive coronary artery disease (INOCA), including microvascular spasm and epicardial coronary spasm, has been emerging as an important cause of impaired prognosis.

WHAT IS NEW? We found that focal epicardial spasm was associated with worst outcome in INOCA, followed by diffuse epicardial spasm, where optical coherence tomography (OCT)-delineated intraplaque neovessels and adventitial vasa vasorum were strong prognostic factors. Furthermore, prognostic values were significantly improved by adding those OCT parameters to the known physiological markers (e.g., index of microcirculatory resistance), indicating the important prognostic links between coronary morphologies and functional abnormalities in INOCA.

WHAT IS NEXT? Because intraplaque neovessels and adventitial vasa vasorum play crucial roles in coronary inflammatory changes, a novel anti-inflammatory strategy targeting coronary microvascular inflammation may have promise for risk reduction in INOCA patients.

REFERENCES

1. Maddox TM, Stanislawski MA, Grunwald GK, et al. Non-obstructive coronary artery disease and risk of myocardial infarction. JAMA 2014;312:1754–63.

2. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade. Circulation 2017;135:1075–92.

3. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886–95.

4. Ford TJ, Rocchiccioli P, Good R, et al. 1-Year outcomes of angina management guided by invasive coronary function testing (CorMicA). J Am Coll Cardiol Intv 2020;13:33–45.

5. Ford TJ, Yii E, Sidik N, et al. Ischemia and no obstructive coronary artery disease: Prevalence and correlates of coronary vasomotion disorders. Circ Cardiovasc Interv 2019;12:e008126.

6. Takagi Y, Yasuda S, Takahashi J, et al. Clinical implications of provocation tests for coronary artery spasm: safety, arrhythmic complications, and prognostic impact: multicentre registry study of the Japanese Coronary Spasm Association. Eur Heart J 2013;34:258–67.

7. Odaka Y, Takahashi J, Tsuburaya R, et al. Plasma concentration of serotonin is a novel biomarker for coronary microvascular dysfunction in patients with suspected angina and unobstructive coronary arteries. Eur Heart J 2017;38:489–96.

8. Suda A, Takahashi J, Hao K, et al. Coronary functional abnormalities in patients with angina and nonobstructive coronary artery disease. J Am Coll Cardiol 2019;74:2350–60.

9. Tearney GJ, Regar E, Akasaka T, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. J Am Coll Cardiol 2012;59:1058–72.

10. Nishimiya K, Matsumoto Y, Takahashi J, et al. Enhanced adventitial vasa vasorum formation in patients with vasospastic angina: assessment with OFDI. J Am Coll Cardiol 2016;67:598–600.

11. Ohyama K, Matsumoto Y, Takanami K, et al. Coronary adventitial and perivascular adipose tissue inflammation in patients with vasospastic angina. J Am Coll Cardiol 2018;71:414–25.

12. Virmani R, Kolodgie FD, Burke AP, et al. Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplaque hemorrhage. Arterioscler Thromb Vasc Biol 2005;25:2054–61.

13. Sato K, Kaikita K, Nakayama N, et al. Coronary vasomotor response to intracoronary acetylcholine injection, clinical features, and long-term prognosis in 873 consecutive patients with coronary spasm: analysis of a single-center study over 20 years. J Am Heart Assoc 2013;2:e000227.

14. Ong P, Athanasiadis A, Borgulya G, et al. Clinical usefulness, angiographic characteristics, and safety evaluation of intracoronary acetylcholine provocation testing among 921 consecutive white patients with unobstructed coronary arteries. Circulation 2014;129:1723–30.

15. Ishii M, Kaikita K, Sato K, et al. Acetylcholine-provoked coronary spasm at site of significant organic stenosis predicts poor prognosis in patients with coronary vasospastic angina. J Am Coll Cardiol 2015;66:1105–15.

16. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.

17. JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina). Circ J 2014;78:2779–801.

18. Beltrame JF, Crea F, Kaski JC, et al. International standardization of diagnostic criteria for vasospastic angina. Eur Heart J 2017;38:2565–8.

19. Nishimiya K, Matsumoto Y, Wang H, et al. Absence of adventitial vasa vasorum formation at the coronary segment with myocardial bridge - an optical coherence tomography study. Int J Cardiol 2018;250:275–7.

20. Ong P, Camici PG, Beltrame JF, et al. International standardization of diagnostic criteria for microvascular angina. Int J Cardiol 2018;250:16–20.

21. Nishimiya K, Matsumoto Y, Uzuka H, et al. Focal vasa vasorum formation in patients with focal coronary vasospasm -an optical frequency domain imaging study. Circ J 2016;80:2252–4.

22. Nishimiya K, Yin B, Piao Z, et al. Micro-optical coherence tomography for endothelial cell visualization in the coronary arteries. J Am Coll Cardiol Img 2019;12:1878–80.

23. Hoshino M, Yonetsu T, Yuki Y, et al. Optical coherence tomographic features of unstable coronary lesions corresponding to histopathological intraplaque hemorrhage evaluated by directional coronary atherectomy specimens. J Am Coll Cardiol Intv 2018;11:1414–5.

24. Prati F, Romagnoli E, Gatto L, et al. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. Eur Heart J 2020;41:383–91.

25. Park KH, Sun T, Diez-Delhoyo F, et al. Association between coronary microvascular function and the vasa vasorum in patients with early coronary artery disease. Atherosclerosis 2016;253:144–9.

26. Fong GH. Potential contributions of intimal and plaque hypoxia to atherosclerosis. Curr Atheroscler Rep 2015;17:510.

27. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. Eur Heart J 2014;35:1101–11.

28. Shimokawa H, Ito A, Fukumoto Y, et al. Chronic treatment with interleukin-1β induces coronary intimal lesions and vasospastic responses in pigs in vivo. The role of platelet-derived growth factor. J Clin Invest 1996;97:769–76.

29. Shimokawa H. 2014 Williams Harvey Lecture: importance of coronary vasomotion abnormalities-from bench to bedside. Eur Heart J 2014;35:3180–93.

30. Godo S, Corban MT, Toya T, et al. Association of coronary microvascular endothelial dysfunction with vulnerable plaque characteristics in early coronary atherosclerosis. EuroIntervention 2020;16:387–94.

31. Ohura-Kajitani S, Shiroto T, Godo S, et al. Marked impairment of endothelium-dependent digital vasodilatations in patients with microvascular angina: evidence for systemic small artery disease. Arterioscler Thromb Vasc Biol 2020;40:1400–12.

32. Ford TJ, Rocchiccioli P, Good R, et al. Systemic microvascular dysfunction in microvascular and vasospastic angina. Eur Heart J 2018;39:4086–97.

33. Sato K, Takahashi J, Odaka Y, et al. Clinical characteristics and long-term prognosis of contemporary patients with vasospastic angina. Ethnic differences detected in an international comparative study. Int J Cardiol 2019;291:13–8.

34. Ughi GJ, Wang H, Gerbaud E, et al. Clinical characterization of coronary atherosclerosis with dual-modality OCT and near-infrared autofluorescence imaging. J Am Coll Cardiol Img 2016;9:1304–14.

35. Lawler PR, Bhatt DL, Godoy LC, et al. Targeting cardiovascular inflammation: next steps in clinical translation. Eur Heart J 2021;42:113–31.

36. Ciliberti G, Coiro S, Tritto I, et al. Predictors of poor clinical outcomes in patients with acute myocardial infarction and non-obstructed coronary arteries (MINOCA). Int J Cardiol 2018;267:41–5.

37. Seitz A, Gardezy J, Pirozzolo G, et al. Long-term follow-up in patients with stable angina and unobstructed coronary arteries undergoing intracoronary acetylcholine testing. J Am Coll Cardiol Cardiovasc Intv 2020;13:1865–76.

38. Lee JM, Layland J, Jung JH, et al. Integrated physiologic assessment of ischemic heart disease in real-world practice using index of microcirculatory resistance and fractional flow reserve: insights from the International Index of Microcirculatory Resistance Registry. Circ Cardiovasc Interv 2015;8:e002857.

39. Tarantini G, Migliore F, Cademartiri F, et al. Left anterior descending artery myocardial bridge. J Am Coll Cardiol 2016;68:2887–99.

KEY WORDS coronary microvascular dysfunction, INOCA, OCT, spasm, vasa vasorum

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.