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Coronary Functional Abnormalities in Patients With Angina and Nonobstructive Coronary Artery Disease

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ABSTRACT

BACKGROUND Approximately one-half of patients undergoing diagnostic coronary angiography for angina have no significant coronary stenosis, in whom coronary functional abnormalities could be involved.

OBJECTIVES This study examined the significance of coronary functional abnormalities in a comprehensive manner for both epicardial and microvascular coronary arteries in patients with angina and nonobstructive coronary artery disease (CAD).

METHODS This study prospectively enrolled 187 consecutive patients (male/female 113/74, 63.2 ± 12.3 years), who underwent acetylcholine provocation test for coronary spasm and measurement of index of microcirculatory resistance (IMR) to evaluate coronary microvascular function, and followed them for a median of 893 days.

RESULTS Of all subjects, acetylcholine test identified 128 patients with vasospastic angina (VSA) (68%), and cardiac events occurred in 10 patients (5.3%) during the follow-up. Multivariable analysis revealed that IMR correlated with the incidence of cardiac events (hazard ratio: 1.05; 95% confidence interval: 1.02 to 1.09; $p = 0.002$) and receiver-operating characteristics (ROC) curve analysis identified IMR of 18.0 as the optimal cut-off value. Among the 4 groups based on the cut-off value of IMR and the presence of VSA, the Kaplan-Meier survival analysis showed a significantly worse prognosis in the group with high IMR (≥18.0) and VSA compared with other groups (log rank, $p = 0.002$). Importantly, intra-coronary administration of fasudil, a Rho-kinase inhibitor, significantly ameliorated IMR in the VSA patients with increased IMR ($p < 0.0001$).

CONCLUSIONS These results indicate that in patients with angina and nonobstructive CAD, coexistence of epicardial coronary spasm and increased microvascular resistance is associated with worse prognosis, for which Rho-kinase activation may be involved. (J Am Coll Cardiol 2019;74:2350–60) © 2019 by the American College of Cardiology Foundation.

Approximately one-half of patients undergoing diagnostic coronary angiography for typical chest pain have no significant coronary stenosis (1). In such cases with suspected angina despite nonobstructive coronary arteries, coronary functional abnormalities could be involved, including increased vasoconstrictive reactivity and/or reduced vasodilator function (2). Coronary microvessels are known to contribute to >50% of total coronary vascular resistance and regulate coronary blood flow (3). Coronary microvascular dysfunction (CMD) is typically defined as increased resistance and/or impaired vasodilatation of those microvessels, leading to inadequate increase in blood flow in response to stress with resultant myocardial ischemia (3–5). Recent studies demonstrated that patients with CMD have significantly higher rates of cardiovascular events, indicating the importance of identification of such patients (4,6,7). In the absence of flow-limiting stenosis, coronary circulation can be directly and separately assessed by coronary flow reserve (CFR) for the entire coronary tree and by index of microvascular resistance (IMR) for coronary microcirculation (7,8). Vasospastic angina (VSA) is also an important

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functional cardiac disorder caused by epicardial coronary spasm, which is caused by enhanced coronary vasoconstricting responses (2). We have previously demonstrated that Rho-kinase plays a central role in the pathogenesis of coronary spasm (2,9,10).

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Although the importance of each component of coronary functional abnormalities (VSA and CMD) has recently emerged, comprehensive evaluation of the abnormalities in the same population remains to be examined. In the present study, we thus aimed to evaluate the effect of epicardial coronary artery spasm and/or abnormal microvascular resistance on long-term prognosis and to determine if the Rho-kinase pathway is implicated in the pathogenesis of the functional coronary abnormalities.

METHODS

The present study was conducted following the ethical principles in the Declaration of Helsinki, and the protocol was approved by the Ethics Committees of Tohoku University (No.2016-1-643). All patients provided written informed consent before study entry.

STUDY POPULATION. The inclusion criteria of the present study included angina-like chest pain, nonobstructive coronary arteries, and successful performance of both coronary artery functional testing (e.g., measurement of IMR) and coronary vasoreactivity testing (e.g., provocative testing for coronary spasm) to identify the origin of their chest pain (**Figure 1**). From November 2014 to July 2017, a total of 699 patients underwent elective diagnostic coronary angiography for evaluation of chest pain and/or electrocardiographic abnormalities at our Tohoku University Hospital. Of those, 302 had no significant coronary stenosis (luminal narrowing<70% and/or fractional flow reserve [FFR] >0.8) of the major coronary arteries on control angiography. Then, 243 patients underwent acetylcholine (ACh) provocation test to assess coronary vasoconstricting responses and were also evaluated for their coronary microvascular vasodilatory function. We excluded patients with proven cardiomyopathy, significant valvular diseases (e.g., aortic stenosis), previous coronary stent implantation, relative contraindication for provocation test (e.g., bronchial asthma), renal failure, poor general condition, and unsuccessful procedures during physiological measurement and/or ACh provocation test. Finally, 187 consecutive patients who fulfilled the inclusion criteria were included in the present study (**Figure 1**).

ACH PROVOCATION TEST. The ACh provocation test was performed as previously described (9,10). Based on guidelines from the Japanese Circulation Society (11), the positive provocation test for epicardial coronary spasm was defined as the development of >90% stenosis accompanied by chest pain and ischemic electrocardiographic changes. In the present study, we defined microvascular spasm (MVS) based on the diagnostic criteria proposed by the COVADIS (Coronary Vasomotor Disorders International Study) group (5).

ABBREVIATIONS AND ACRONYMS

ACh = acetylcholine
CAD = coronary artery disease
CFR = coronary flow reserve
CMD = coronary microvascular dysfunction
IMR = index of microcirculatory resistance
MVS = microvascular spasm
VSA = vasospastic angina

CORONARY PHYSIOLOGICAL MEASUREMENTS. After ACh provocation testing, we administered ISDN intracoronarily to achieve dilatation of epicardial coronary arteries. We then performed coronary physiological measurements for FFR, CFR, and IMR in the left anterior descending coronary artery (LAD) during hyperemia induced by intravenous infusion of adenosine, as previously described (7,8). Furthermore, to evaluate the involvement of Rho-kinase, after the first measurement of CFR and IMR, we administered intracoronary fasudil (30 mg), a selective Rho-kinase inhibitor (2,12), and performed the second measurement of IMR. We calculated % changes in IMR before and after intracoronary fasudil as follows: (fasudil IMR − hyperemic IMR)/hyperemic IMR.

CLINICAL OUTCOME AND PATIENT FOLLOW-UP. We defined major adverse cardiac events (MACE) as the composite of cardiac death, nonfatal myocardial infarction, and hospitalization due to unstable angina. We only counted the number of patients with the first occurrence of an event in the MACE during the follow-up period. Long-term follow-up was performed by using a questionnaire that was sent to patients and primary physicians, in addition to the information available on the medical records or telephone surveys. The median duration of follow-up was 893 days (interquartile range [IQR]: 637 to 1,136 days).

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD or median (interquartile range), and categorical variables as number (%). Group comparisons for continuous variables were performed by the Kruskal-Wallis test for multiple groups, and the Mann-Whitney *U*-test for 2 groups. The chi-square test was used for comparisons among categorical variables. Survival rate from cardiac events was analyzed by the Kaplan-Meier method, and comparison between groups was performed by log-rank tests. Given the sample size of the original

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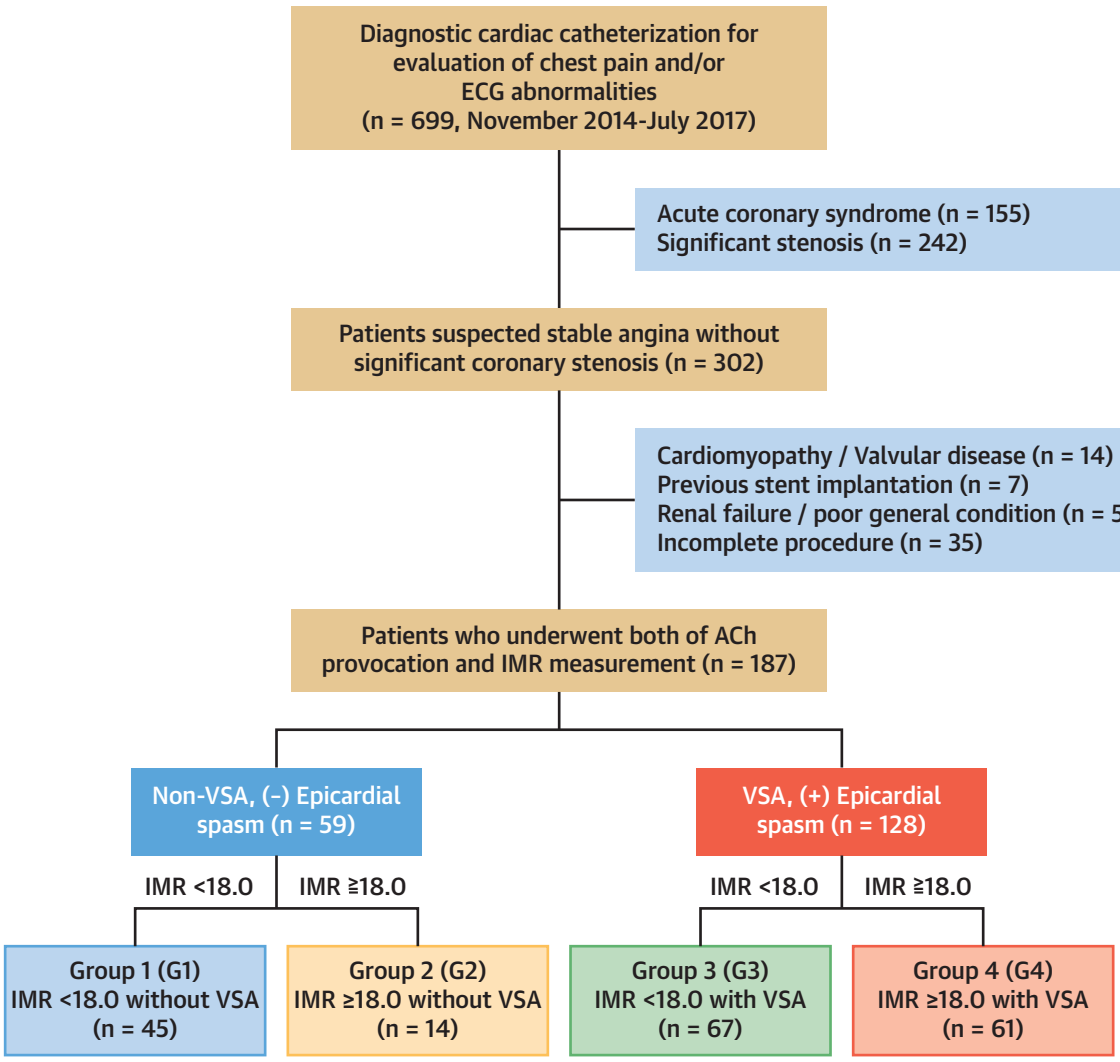
FIGURE 1 Study Flow Chart



ACh = acetylcholine; ECG = electrocardiogram; IMR = index of microcirculatory resistance; VSA = vasospastic angina.

data and the significance level = 0.05, the empirical power of the log-rank test was calculated by the method proposed by Freedman (13). Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% CIs to compare between group differences. The proportional hazards assumption of Cox regression was confirmed by the Schoenfeld residuals test implemented by the cox.zph command in R (14). Logistic regression was used to compute odds ratios (ORs) and 95% CI for the occurrence of the events. The prognostic significance of each variable was tested by univariable and multivariable logistic regression analyses. To select an optimal subset of covariates for the multivariable logistic model, the backward elimination procedure of variable selection with Bayesian information criterion was utilized. The occurrence of cardiovascular events was predicted by logistic regression models with the presence of VSA and/or high IMR relative to the reference model, and their performances were compared. The reference model was composed of age, current smoking, and dyslipidemia. Smoking and dyslipidemia were selected by stepwise variable selection from the logistic model using all candidate covariates. Age was added to the reference because it was the independent prognostic factor of MACE in the multivariable

Cox regression. C-statistics, which equal the area under the ROC curve, was used to summarize the performance of the predicted probability of the outcomes for discrimination. The improvement of fit of the models relative to the reference model was evaluated by likelihood ratio tests for the analysis of deviance table. To evaluate the improvement of the matured models relative to the reference model, integrated discrimination improvement (IDI), and continuous net reclassification improvement (NRI) with the total observations, the observations with the events and those without the event were utilized. To calculate NRI, censored participants were handled as no events (15). A p value <0.05 was considered to be statistically significant. Further information is available in the Online Methods.

RESULTS

CLINICAL PATIENT CHARACTERISTICS. The flow chart of the present study is shown in **Figure 1**. We finally analyzed 187 consecutive patients (113 men, 74 women; age 63.2 ± 12.3 years) with angina-like chest pain and nonobstructive CAD in whom we were able to complete both ACh provocation test for coronary spasm and physiological measurements of coronary microvascular functions with IMR and CFR. Clinical characteristics of the patients are summarized in **Table 1**. All patients had a stable condition, with more than one-half (56%) having symptoms at rest. Among the 187 patients, 128 (68.4%) were diagnosed as having VSA, and 22 patients (12.0%) had MVS and were categorized into the non-VSA group (Online Table 1). The median IMR value was significantly higher in the VSA than non-VSA group, whereas CFR values were comparable between the 2 groups (**Figure 2**). The distributions of patients according to IMR and CFR by each type of coexisting coronary reactivity abnormality are shown in Online Figure 1. Importantly, we found a highly negative correlation between IMR and CFR values in VSA patients, but not in non-VSA patients (**Figure 3**).

CLINICAL OUTCOMES AND PROGNOSTIC PREDICTORS. During the median follow-up period of 893 days (IQR: 637 to 1,136 days), there were 10 MACE in overall cohorts, including cardiovascular death (n = 1) and hospitalization for unstable angina (n = 9). Multivariable Cox proportional hazard analysis showed that high IMR significantly correlated with MACE in patients with chest pain and nonobstructive CAD (**Table 2**). Based on ROC curve analysis, the optimal IMR cutoff value for developing MACE was 18.0, and the area under the ROC curve was 0.76 (Online Figure 2). With this value, the sensitivity and specificity for predicting MACE were 90.0% and 63.4%, respectively, while negative predictive value was 99.1%. In multivariable logistic regression model for the presence of high IMR (≥18.0), proven VSA was the strongest correlated predictor (**Table 3**). Importantly, there were substantial overlaps of coronary functional abnormality in various combinations among VSA, low CFR (CFR <2.0), and high IMR (IMR ≥18.0) (**Figure 4**).

TABLE 1 Baseline Clinical Characteristics of Patients

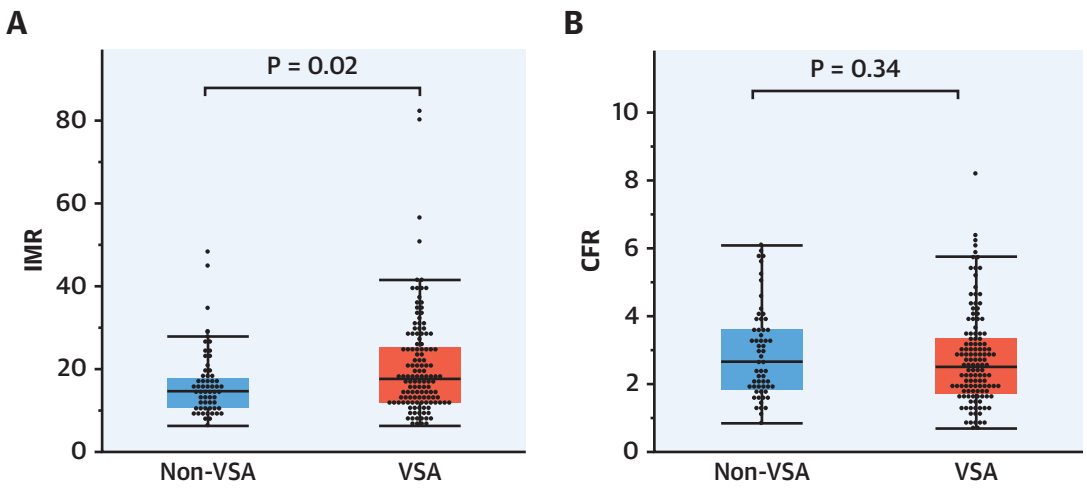
	Overall (n = 187)	Non-VSA (n = 59)	VSA (n = 128)	p Value
Age, yrs	63.2 ± 12.3	61.9 ± 14.7	63.8 ± 11.0	0.35
Male	113 (60)	38 (64)	75 (59)	0.45
Hypertension	100 (53)	33 (56)	67 (52)	0.64
Dyslipidemia	66 (35)	22 (37)	44 (34)	0.70
Diabetes mellitus	52 (28)	15 (25)	37 (29)	0.62
Current smoking	52 (28)	17 (29)	35 (27)	0.84
Family history of CAD	31 (17)	13 (22)	18 (14)	0.18
Previous MI	10 (5)	2 (3)	8 (6)	0.40
Rest angina	104 (56)	31 (54)	83 (65)	0.17
Effort angina	42 (22)	14 (24)	28 (22)	0.78
Rest and effort angina	11 (6)	2 (3)	9 (7)	0.30
eGFR, ml/min/1.73 m^2	73.1 ± 21.3	74.6 ± 27.0	72.4 ± 18.2	0.51
hs-CRP, mg/ml	0.05 (0.02–0.12)	0.07 (0.02–0.32)	0.05 (0.02–0.10)	0.17
hs-TropT, ng/ml	0.007 (0.004–0.011)	0.007 (0.004–0.013)	0.007 (0.005–0.011)	0.56
BNP, pg/ml	22.7 (9.4–46.3)	28.4 (13.8–50.3)	20.7 (8.7–42.4)	0.15
LVEF, %	65.9 ± 10.5	65.1 ± 10.7	66.3 ± 10.4	0.50
E/e′	10.3 ± 4.3	10.6 ± 4.3	10.2 ± 4.3	0.53
MVS	22 (12)	22 (37)	0 (0)	<0.0001
Physiological parameters				
FFR	0.9 (0.87–0.93)	0.90 (0.86–0.94)	0.90 (0.87–0.93)	0.85
CFR	2.54 (1.81–3.43)	2.66 (1.85–3.64)	2.51 (1.72–3.35)	0.34
IMR	16.2 (11.8–24.2)	14.7 (10.7–17.8)	17.5 (12.0–25.3)	0.02
Baseline T_{mn}, s	0.71 (0.45–1.01)	0.63 (0.40–0.96)	0.73 (0.46–1.02)	0.21
Hyperemic T_{mn}, s	0.26 (0.19–0.38)	0.24 (0.18–0.33)	0.27 (0.20–0.41)	0.03

Values are mean ± SD, n (%), or median (interquartile range).

BNP = B-type natriuretic peptide; CAD = coronary artery disease; CFR = coronary flow reserve; E/e′ = early diastolic mitral flow velocity/tissue Doppler imaging velocity; eGFR = estimate glomerular filtration rate; FFR = fractional flow reserve; hs-CRP = high sensitivity C-reactive protein; hs-TropT = high sensitivity troponin T; IMR = index of microcirculatory resistance; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MVS = microvascular spasm; T_{mn} = mean transit time.

PERFORMANCE METRICS IN RISK PREDICTION MODELS. Furthermore, as shown in **Figure 1**, we divided the patients into the following 4 groups according to the cut-off value of IMR (>18.0) and the presence or absence of VSA: G1, IMR <18.0 without VSA (n = 45); G2, IMR ≥18.0 without VSA (n = 14); G3, IMR <18.0 with VSA (n = 67); and G4, IMR ≥18.0 with VSA (n = 61). Patient characteristics of the 4 groups are shown in Online Table 2. Although there was no difference in demographic profiles except male prevalence among the 4 groups, CFR was significantly lower in G4 (VSA and high IMR). The Kaplan-Meier survival analysis showed that the patients of G4 had

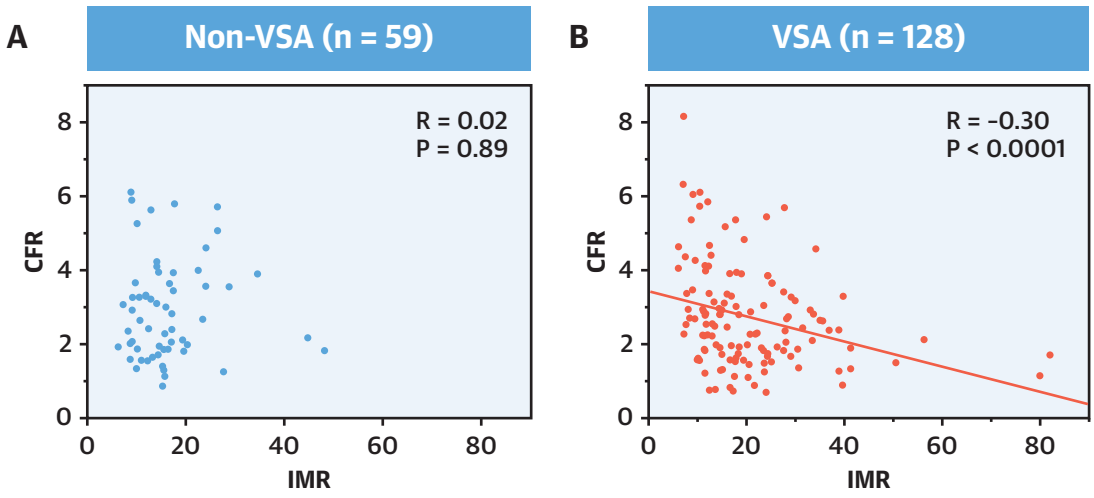
FIGURE 2 Comparison of Coronary Physiological Parameters Between Non-VSA and VSA Groups



IMR values at hyperemic state were significantly higher in the VSA group than in the non-VSA group **(A)**, whereas CFR values at hyperemic state were comparable between the 2 groups **(B)**. Results are expressed as box-and-whisker plots; 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. More extreme values are plotted individually. CFR = coronary flow reserve; other abbreviations as in Figure 1.

a significantly worse outcome compared with all other remaining patients (log-rank, p = 0.002) (Figure 5). Empirical power of the log-rank test for the occurrence of MACE in comparison with G1 and G4 was 0.87. Further logistic regression analyses on performance metrics in risk prediction models were evaluated (Table 4). C-statistics for the prediction of the occurrence of MACE significantly increased (0.75 [95% confidence interval (CI): 0.6 to 0.89] to 0.90 [95% CI: 0.83 to 0.97]; p = 0.045), when IMR and the

FIGURE 3 Correlation Between CFR and IMR Values in the Non-VSA and VSA Groups



(A) There was no significant correlation between CFR and IMR values in the non-VSA group. **(B)** There was a significant negative correlation between the 2 values in the VSA group. Abbreviations as in Figures 1 and 2.

presence of VSA were incorporated into the reference model, including age, current smoking, and dyslipidemia. The Hosmer-Lemeshow tests for all logistic regression models were not statistically significant, indicating good calibration for all models. The model with VSA and IMR achieved the highest IDI (0.10 [95% CI: 0.02 to 0.18]) and NRI all (1.14 [95% CI: 0.74 to 1.53]) compared with the reference model. The reclassification tables to evaluate the improvement in the model with VSA and IMR relative to the reference model with or without the event are presented in the Online Table 3.

AMELIORATION OF IMR BY RHO-KINASE INHIBITION WITH FASUDIL. To examine the involvement of Rho-kinase activation in the pathogenesis of coronary functional abnormalities, we examined the effects of intracoronary fasudil, a selective Rho-kinase inhibitor (2,12). Importantly, fasudil significantly ameliorated IMR in G4 (**Figure 6A**), and % changes in IMR in response to intracoronary fasudil were more evident in G4 compared with the other 3 groups (**Figure 6B**). Furthermore, there was a negative correlation between IMR and its %change after Rho-kinase inhibition in VSA but not in non-VSA patients (Online Figure 3).

DISCUSSION

The major findings of the present study are as follows. In patients with angina and nonobstructive CAD: 1) coronary functional abnormalities, including epicardial coronary spasm, reduced microvascular vasodilatation, and increased microvascular resistance, frequently coexist in various combinations; 2) IMR correlates with occurrence of MACE, and an IMR of 18.0 is the best cut-off value; 3) proven VSA is an independent predictor for high IMR (>18.0); 4) patients with high IMR and VSA have significantly poorer outcomes compared with all other remaining patients; and 5) Rho-kinase inhibition by intracoronary fasudil significantly ameliorates IMR only in patients with high IMR and VSA (**Central Illustration**). To the best of our knowledge, this is the first study that comprehensively evaluated the coronary functional abnormalities for both epicardial coronary arteries and coronary microvessels in the same patient population with chest pain and nonobstructive CAD, demonstrating that the coexistence of coronary spasm and high IMR is associated with increased risk of MACE, for which Rho-kinase activation may be involved.

IMPORTANCE OF COMPREHENSIVE ASSESSMENT OF CORONARY FUNCTIONAL ABNORMALITIES. Although the importance of coronary functional abnormalities (epicardial coronary spasm and CMD) in patients with chest pain and nonobstructive CAD has been emerging, their pathogenesis and prognostic implications remain to be fully elucidated. A recent study by Lee et al. (7) showed that integration of microvascular assessment by both CFR and IMR can improve the accuracy of prognostic prediction for patients with high FFR, although no attention was paid to epicardial coronary spasm. In the present study with a similar patient population, during the ACh provocation test, epicardial coronary spasm and microvascular spasm developed in 68.5% and 12.0% of patients, respectively. Indeed, 85.6% of our patients had an increased coronary vasoconstrictive

TABLE 2 Prognostic Factors for Cardiovascular Events in Patients With Chest Pain and Nonobstructive Coronary Arteries (Cox Proportional Hazard Model)

	Univariable Analysis		Multivariable Analysis	
	HR	95% CI	HR	95% CI
Age	0.970	0.928–1.015	0.956	0.910–1.004
Female	0.622	0.160–2.412		
Current smoking	3.989	1.125–14.139		
Hypertension	0.823	0.237–2.857		
Diabetes mellitus	0.652	0.138–3.073		
Dyslipidemia	0.406	0.086–1.917		
eGFR, ml/min/1.73 m^2	1.015	0.986–1.043		
hs-CRP, mg/ml	1.092	0.526–2.267		
LVEF, %	1.004	0.941–1.072		
BNP, pg/ml	0.993	0.974–1.013		
IMR	1.055	1.021–1.089	1.054	1.020–1.089
VSA	4.130	0.523–32.618	3.879	0.484–31.100

The satisfaction of the proportional hazards assumption of Cox regression models was confirmed by the testing using Schoenfeld residuals.

CI = confidence interval; HR = hazard ratio; VSA = vasospastic angina; other abbreviations as in Table 1.

TABLE 3 Logistic Regression Analysis for the Presence of High IMR (≥18.0) in Patients With Chest Pain and Nonobstructive Coronary Arteries

	Univariable Analysis		Multivariable Analysis	
	OR	95% CI	OR	95% CI
Age	1.021	0.995–1.047		
Female	0.855	0.469–1.558	0.511	0.254–1.029
Current smoking	0.909	0.472–1.751		
Hypertension	1.083	0.602–1.948		
Diabetes mellitus	0.812	0.420–1.572		
Dyslipidemia	0.955	0.517–1.763		
hs-CRP, mg/ml	0.896	0.564–1.423		
eGFR, ml/min/1.73 m^2	1.004	0.990–1.018		
LVEF, %	0.995	0.967–1.024		
E/e′	0.974	0.904–1.049		
BNP, pg/ml	1.000	0.996–1.003		
VSA	2.926	1.464–5.851	2.735	1.280–5.843
MVS	0.400	0.153–1.049		

MVS = microvascular spasm; OR = odds ratio; other abbreviations as in Tables 1 and 2.

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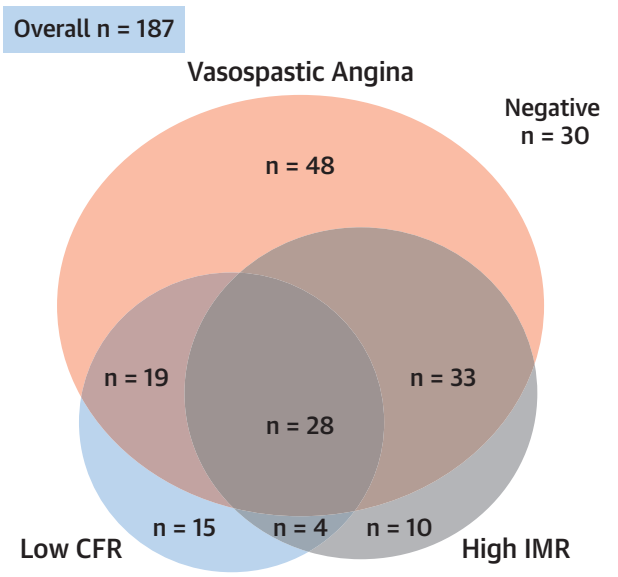
FIGURE 4 Coexistence of Coronary Functional Abnormalities

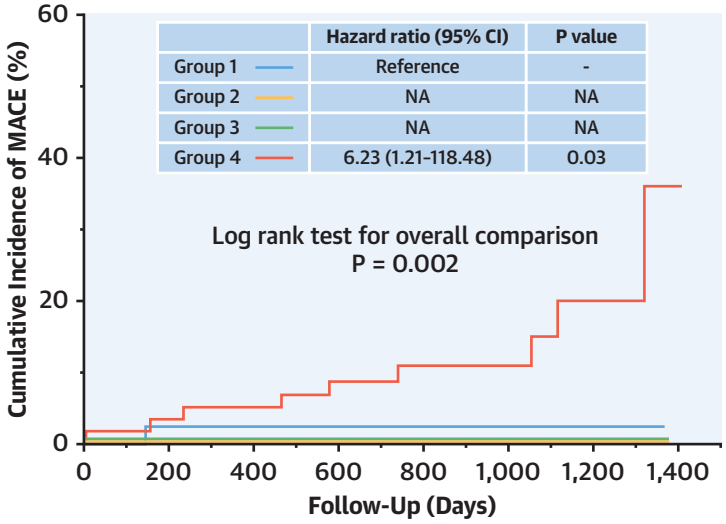


Among 187 patients, 128 (68.4%) were diagnosed as having VSA by ACh provocation test. Furthermore, 66 (35.3%) had low CFR (CFR <2.0) and 75 (40.1%) high IMR (IMR ≥18.0). Thus, more than one-half of VSA patients had microvascular functional abnormalities, including low CFR (n = 19, 10.2%), high IMR (n = 33, 17.6%), and both (n = 28, 15.0%). Abbreviations as in **Figures 1 and 2**.

reactivity, and most of them also had increased coronary resistance and/or reduced vasodilator function in the coronary microcirculation. Particularly among VSA patients, microvascular status according to IMR and CFR was highly heterogeneous (**Figure 4**, Online Figure 1). Intriguingly, median IMR value was significantly higher in VSA than in non-VSA patients despite the comparable CFR value between the 2 groups, as previously reported by Yamanaga et al. (16). Recent studies demonstrated that VSA is frequently noted in Caucasian patients with chest pain and nonobstructive CAD, and those with acute myocardial infarction and nonobstructive CAD than ever thought (17,18). Thus, attention should always be paid to possible involvement of epicardial coronary spasm in those patients. As demonstrated in **Figure 4**, coronary functional abnormalities, including enhanced coronary vasoconstrictive reactivity (VSA), reduced coronary vasodilatation (CFR <2.0), and increased coronary microvascular resistance (IMR ≥18.0), frequently coexist in various combinations in patients with angina and nonobstructive CAD. Thus, it is important to perform comprehensive assessment of those coronary functional abnormalities to elucidate the cause of angina in patients without obstructive CAD. However, almost all patients with VSA received calcium-channel blockers, nitrate and nicorandil were more frequently prescribed for the G4 patients (Online Table 4). These results indicate that the patients with MACE in the present study were at high risk even with the contemporary guideline-recommended therapies. Thus, it is important to identify the patients who are at high risk even with the intensive medical treatment by comprehensive evaluation of coronary functional abnormalities.

PROGNOSTIC IMPACT OF COMBINED MICROVASCULAR AND MACROVASCULAR CORONARY FUNCTIONAL ABNORMALITIES. It was previously reported that CMD, defined as reduced CFR, is associated with increased risk of cardiovascular events (6). However, CFR is dependent on systemic hemodynamics, myocardial contractility, and resting blood flow (3). In contrast, IMR is more specific and informative on coronary microvascular status (19), although its prognostic impact and cut-off value to indicate CMD remain to be examined (7). In the present study, we were able to elucidate, for the first time, the prognostic impact of IMR with the best cut-off value of 18.0 in patients with angina and nonobstructive CAD. The cut-off value of IMR was considerably lower than that previously reported for CMD (IMR ≥25) (19,20), while increased IMR defined as >18.0 was significantly associated with proven VSA in the linear regression model (**Table 3**). When we divided the patients into the 4 subgroups by combining the cut-off value of IMR and the presence of VSA, those with VSA and high IMR showed a worst prognosis compared with all other remaining patients (**Central Illustration**). Importantly, incorporation of both IMR value and the presence of VSA into a fully adjusted model dramatically improved the C-statistic from 0.75 to 0.90. The model with a combination of IMR and VSA also significantly increased IDI and NRI for the incidence of MACE, indicating improved risk stratification in patients with angina and nonobstructive CAD. These findings raise an important issue that patients with both enhanced coronary vasoconstrictive reactivity and reduced vasodilator function are at high risk for future MACE. It is conceivable that these patients may have an impaired compensatory system, because intact microcirculation should dilate to maintain coronary blood flow in the face of epicardial vasoconstriction (3). This notion may be supported by the present finding that a highly negative correlation between IMR and CFR values was noted only in VSA patients but not in non-VSA patients (**Figure 3**).

FIGURE 5 Kaplan-Meier Curves for MACE by Patient Group According to IMR and VSA



No. at Risk								
Negative	45	43	42	36	25	19	8	1
IMR ≥18.0 Alone	13	13	13	12	12	10	3	1
VSA Alone	67	67	67	54	36	29	10	1
VSA with IMR ≥18.0	60	59	58	50	40	28	14	2

Group 1, IMR <18.0 without VSA (n = 45); Group 2, IMR ≥18.0 without VSA (n = 14); Group 3, IMR <18.0 with VSA (n = 67); and Group 4, IMR ≥18.0 with VSA (n = 61). The long-term prognosis was significantly worse in Group 4 compared with the other 3 groups. CI = confidence interval; MACE = major adverse cardiovascular events; other abbreviations as in Figure 1.

BENEFICIAL EFFECTS OF FASUDIL ON CORONARY FUNCTIONAL ABNORMALITIES. In the present study, a close correlation was noted between coronary spasm and impaired coronary vasodilator responses in patients with chest pain and nonobstructive CAD, suggesting the presence of a common underlying mechanism for the abnormalities. Importantly, we were able to demonstrate that a selective Rho-kinase inhibitor, fasudil, significantly ameliorated impaired microvascular resistance in patients with increased IMR (≥18.0) and proven VSA compared with other 3 groups. We have previously demonstrated that Rho-kinase activation plays a central role not only for epicardial coronary spasm (9,10), but also for coronary microvascular spasm (12). Furthermore, the present study demonstrates for the first time that Rho-kinase activation is simultaneously involved in epicardial coronary spasm and increased coronary microvascular resistance. Furthermore, a negative correlation was noted between IMR and its %change after Rho-kinase inhibition only in VSA patients, indicating that increased IMR is associated with Rho-kinase activation in the

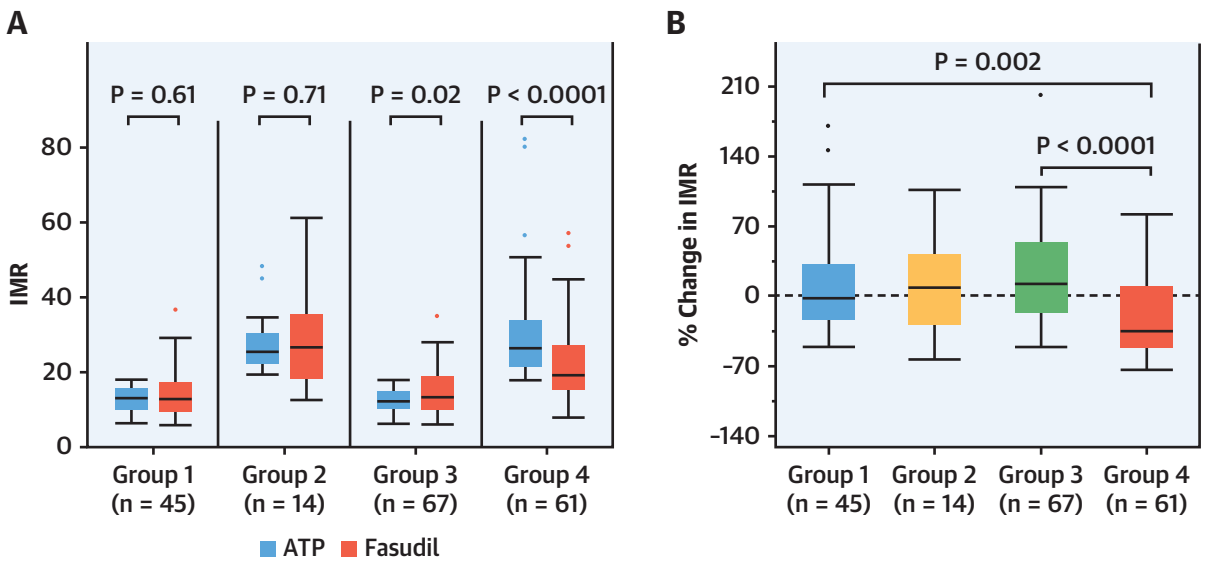
TABLE 4 Performance of the Logistic Regression Models for Cardiovascular Events

	Reference Model	Model With VSA	Model With IMR	Model With VSA and IMR
Discrimination				
C-statistics	0.75 (0.60–0.89)	0.82 (0.71–0.92)	0.90 (0.85–0.96)	0.90 (0.83–0.97)
p value	Reference	0.025	0.018	0.045
Calibration				
Hosmer-Lemeshow p value	0.788	0.698	0.910	0.975
AIC	78.409	77.235	67.768	68.510
Likelihood ratio p value	Reference	0.075	0.075	0.075
Reclassification				
IDI	Reference	0.01 (−0.03–0.05)	0.08 (0.01–0.14)	0.10 (0.02–0.18)
NRI (all)	Reference	0.45 (0.05–0.85)	1.07 (0.67–1.47)	1.14 (0.74–1.53)
NRI with event	Reference	0.80 (0.43–1.17)	0.80 (0.43–1.17)	0.80 (0.43–1.17)
NRI with no event	Reference	−0.35 (−0.49 to −0.21)	0.27 (0.13–0.41)	0.34 (0.20–0.48)

Reference model includes age, current smoking, and dyslipidemia, which were selected from age, female sex, current smoking, hypertension, diabetes mellitus, dyslipidemia, eGFR, hs-CRP, LVEF, and BNP. Model with VSA: Reference model + VSA. Model with IMR: Reference model + IMR. All p values versus the reference model.

AIC = Akaike information criterion; IDI = integrated discrimination improvement; NRI = net reclassification improvement; other abbreviations as in Tables 1 and 2.

FIGURE 6 Changes in IMR in Response to Rho-Kinase Inhibition by Fasudil

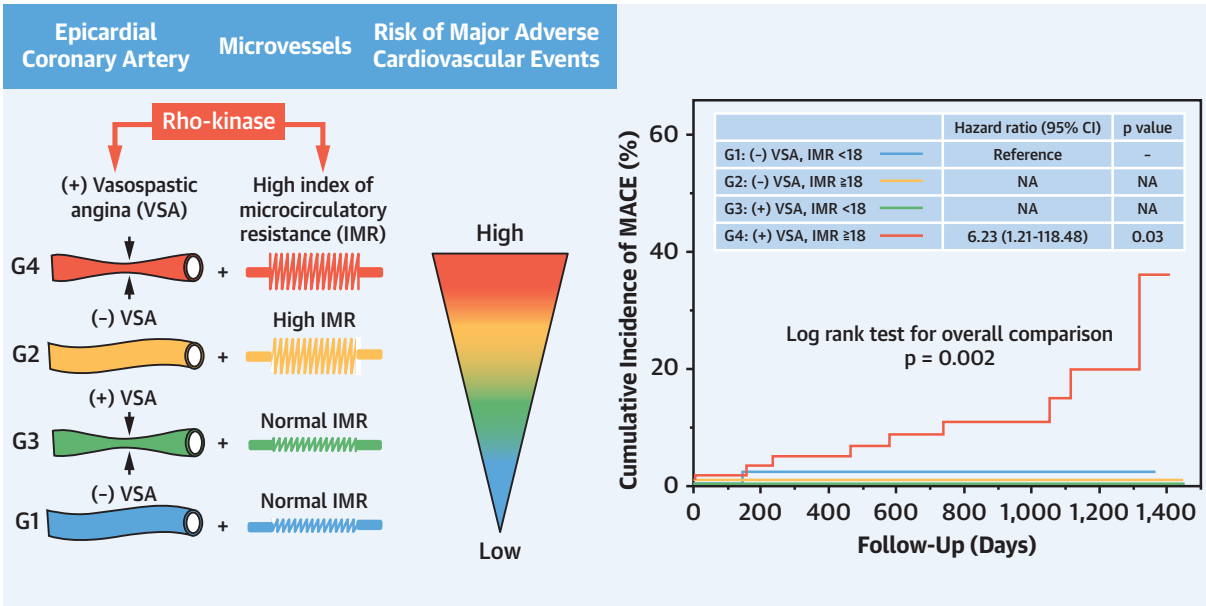


(A) Comparison of IMR levels between hyperemic state and Rho-kinase inhibition. **(B)** Comparison of %changes in IMR levels in response to Rho-kinase inhibition by fasudil. ATP = adenosine triphosphate; other abbreviations as in Figure 1.

pathogenesis of coronary functional abnormalities. Indeed, the present findings indicate that Rho-kinase is an important therapeutic target not only in VSA patients but also in those with increased IMR.

STUDY LIMITATIONS. First, the present study was a single-center and exploratory study. Thus, future multicenter validation studies are needed. Second, the small number of MACE during the follow-up period may reduce the statistical power of the present study and might have led to data overfitting. The low number of events per variable might also decrease the predictive accuracy of a logistic regression model. In addition, the majority of MACE were hospitalizations for unstable angina. However, the prevalence of hospitalization for unstable angina to total MACE in the present study (90%) was comparable with the previous studies (10,21,22). Third, we did not perform physiological measurements for the right or left circumflex coronary artery. However, because of its large myocardial perfusion area, previous studies also performed physiological measurements mainly in LAD (7,8,23). Fourth, medical treatment during follow-up was individualized at the discretion of each attending physicians on the basis of symptoms. Fifth, in the present study, only one-fourth of the subjects underwent noninvasive stress tests. Thus, it remains to be examined in future studies whether noninvasive stress tests are able to predict the functional abnormalities identified by invasive cardiac catheterization test. Sixth, 22 patients with MVS based on the diagnostic criteria by the COVADIS group were categorized into the non-VSA group. Thus, we were unable to fully evaluate their coronary microvascular hemodynamic profiles. Seventh, although it has been reported by both American and European investigators that angina pectoris without obstructive CAD is more common in female than in male patients (6), 60% of the present study population were men. Ethnic difference in male/female dominance in coronary vasomotor dysfunction may be involved in the discrepancy. Actually, in Japan, epicardial coronary spasm seems to be more frequent in male patients and MVS more frequent in female patients (21,22), whereas as Aziz et al. (24) recently reported that both epicardial coronary spasm and MVS in particular are more prevalent in women among Caucasians. Thus, our findings may not conflict with the previous study. Finally, we have no data regarding the changes in medical therapy, adherence to the therapy, and symptom and/or quality of life (e.g., Seattle Angina Questionnaire) during the follow-up. These issues also remain to be examined in future studies.

CENTRAL ILLUSTRATION **Vasospastic Angina and High Index of Microcirculatory Resistance: Prognostic Impact of Coexistence**



Suda, A. et al. J Am Coll Cardiol. 2019;74(19):2350–60.

In patients with chest pain and nonobstructive coronary artery disease, coexistence of vasospastic angina (epicardial coronary spasm) and high index of microcirculatory resistance (microvascular resistance) is associated with worse prognosis, for which Rho-kinase activation may be involved.

CONCLUSIONS

In the present study, we were able to demonstrate that in patients with chest pain and nonobstructive CAD, coexistence of epicardial coronary spasm, and increased microvascular resistance is associated with worse prognosis, for which Rho-kinase activation may be involved.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with angina and nonobstructive CAD, the coincidence of epicardial coronary spasm and increased microvascular resistance is associated with Rho-kinase activation and adverse outcomes. Rho-kinase inhibition with fasudil ameliorates microcirculatory coronary resistance in patients with vasospastic angina.

TRANSLATIONAL OUTLOOK: Future studies involving a larger number of patients and longer-term follow-up are necessary to confirm the safety and efficacy of fasudil in patients with vasospastic angina and nonobstructive CAD.

REFERENCES

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

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

3. Camici PG, D'Amati G, Rimoldi O. Coronary microvascular dysfunction: Mechanisms and functional assessment. Nat Rev Cardiol 2015;12:48–62.

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

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

6. Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary microvascular reactivity to adenosine

predicts adverse outcome in women evaluated for suspected ischemia. Results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) Study. J Am Coll Cardiol 2010;55:2825–32.

7. Lee JM, Jung JH, Hwang D, et al. Coronary flow reserve and microcirculatory resistance in patients with intermediate coronary stenosis. J Am Coll Cardiol 2016;67:1158–69.

8. Kobayashi Y, Fearon WF, Honda Y, et al. Effect of sex differences on invasive measures of coronary microvascular dysfunction in patients with angina in the absence of obstructive coronary artery disease. J Am Coll Cardiol Intv 2015;8:1433–41.

9. Kikuchi Y, Yasuda S, Aizawa K, et al. Enhanced Rho-kinase activity in circulating neutrophils of patients with vasospastic angina: a possible biomarker for diagnosis and disease activity assessment. J Am Coll Cardiol 2011;58:1231–7.

10. Nihei T, Takahashi J, Hao K, et al. Prognostic impacts of Rho-kinase activity in circulating leucocytes in patients with vasospastic angina. Eur Heart J 2018;39:952–9.

11. JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2008). Circ J 2010;74:1745–62.

12. Mohri M, Shimokawa H, Hirakawa Y, et al. Rho-kinase inhibition with intracoronary fasudil prevents myocardial ischemia in patients with coronary microvascular spasm. J Am Coll Cardiol 2003;41:15–9.

13. Freedman LS. Tables of the number of patients required in clinical trials using the log-rank test. Stat Med 1982;1:121–9.

14. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515–26.

15. Leening MJ, Vedder MM, Witteman JC, et al. Net reclassification improvement: computation, interpretation, and controversies: a literature review and clinician's guide. Ann Intern Med 2014;160:122–31.

16. Yamanaga K, Tsujita K, Komura N, et al. Single-wire pressure and flow velocity measurement for quantifying microvascular dysfunction in patients with coronary vasospastic angina. Am J Physiol 2015;308:H478–84.

17. Ong P, Athanasiadis A, Borgulya G, et al. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries: The ACOVA study (abnormal coronary vasomotion in patients with stable angina and unobstructed coronary arteries. J Am Coll Cardiol 2012;59:655–62.

18. Montone RA, Niccoli G, Fracassi F, et al. Patients with acute myocardial infarction and non-obstructive coronary arteries: Safety and prognostic relevance of invasive coronary provocative tests. Eur Heart J 2018;39:91–8.

19. Ford TJ, Corcoran D, Berry C. Stable coronary syndromes: pathophysiology, diagnostic advances and therapeutic need. Heart 2018;104:284–92.

20. Kaski JC, Crea F, Gersh BJ, et al. Reappraisal of ischemic heart disease: fundamental role of coronary microvascular dysfunction in the pathogenesis of angina pectoris. Circulation 2018;138:1463–80.

21. Takagi Y, Yasuda S, Tsunoda R, et al. Clinical characteristics and long-term prognosis of vasospastic angina patients who survived out-of-hospital cardiac arrest: multicentre registry study of the Japanese Coronary Spasm Association. Circ Arrhythmia Electrophysiol 2011;4:295–302.

22. 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;2:1–12.

23. Yang HM, Khush K, Luikart H, et al. Invasive assessment of coronary physiology predicts late mortality after heart transplantation. Circulation 2016;133:1945–50.

24. Aziz A, Hansen HS, Sechtem U, et al. Sex-related differences in vasomotor function in patients with angina and unobstructed coronary arteries. J Am Coll Cardiol 2017;70:2349–58.

KEY WORDS coronary spasm, IMR, microvascular dysfunction, nonobstructive coronary artery disease, Rho-kinase

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