# Chapter 3
# Diagnosis of Coronary Artery Spasm


**Kensuke Nishimiya, Yasuharu Matsumoto, Jun Takahashi, and Hiroaki Shimokawa**

**Abstract** Seminal clinical studies have shown that percutaneous coronary intervention (PCI) in patients with stable angina gives few benefits as compared with optimal medical therapy alone (Boden et al., N Engl J Med 356:1503–1516, 2007; Al-Lamee et al., Lancet 391:31–40, 2018). Therefore, making diagnosis of coronary vasomotion abnormalities regardless of obstructive or nonobstructive arterial segments has dramatically increased its clinical significance. Coronary artery spasm plays a key role in a wide range of ischemic heart diseases not only in vasospastic angina (VSA) but also in acute coronary syndrome and sudden cardiac death. It is of importance to have the precise diagnostic criteria for coronary artery spasm based on the clinically available evaluation methods. Particularly, recent studies have made substantial contributions to the development of new approaches that can predict the risk of future cardiovascular events in patients with VSA. Ample clinical evidence has been accumulated for elucidating the detailed mechanisms of coronary artery spasm in vivo. In this chapter, we will summarize recent advances in diagnostic methodology of coronary artery spasm.

**Keywords** Acetylcholine · Adventitia · Coronary artery spasm · the Coronary Artery Vasomotion Disorders International Study Group (COVAIDS) · Coronary microvascular dysfunction (CMD) · Ergonovine · 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) · the Japanese Coronary Spasm Association (JCSA) · Lactic acid · Optical coherence tomography (OCT) · Perivascular adipose tissue (PVAT) · Rho-kinase · Serotonin · Spasm provocation test · Vasa vasorum · Vasospastic angina (VSA).

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## 3.1 Clinical Definition and Diagnostic Criteria of Coronary Artery Spasm

Referring to the Japanese Circulation Society (JCS) guidelines for diagnosis and treatment of patients with VSA [1], definite VSA is diagnosed when ischemic changes on electrocardiogram (ECG), defined as a transient ST elevation of >0.1 mV, an ST depression of >0.1 mV, or new appearance of negative U waves in at least 2 contiguous leads, are documented during spontaneous angina attack. In case that ECG shows borderline ischemic change, definite VSA is angiographically diagnosed when transient, total, subtotal (>90% stenosis) of a coronary artery accompanied by angina pain and ischemic ECG change during the spasm provocation test with acetylcholine, ergonovine, or hyperventilation (Fig. 3.1). Following the JCS guidelines, a position paper from the Coronary Artery Vasomotion Disorders

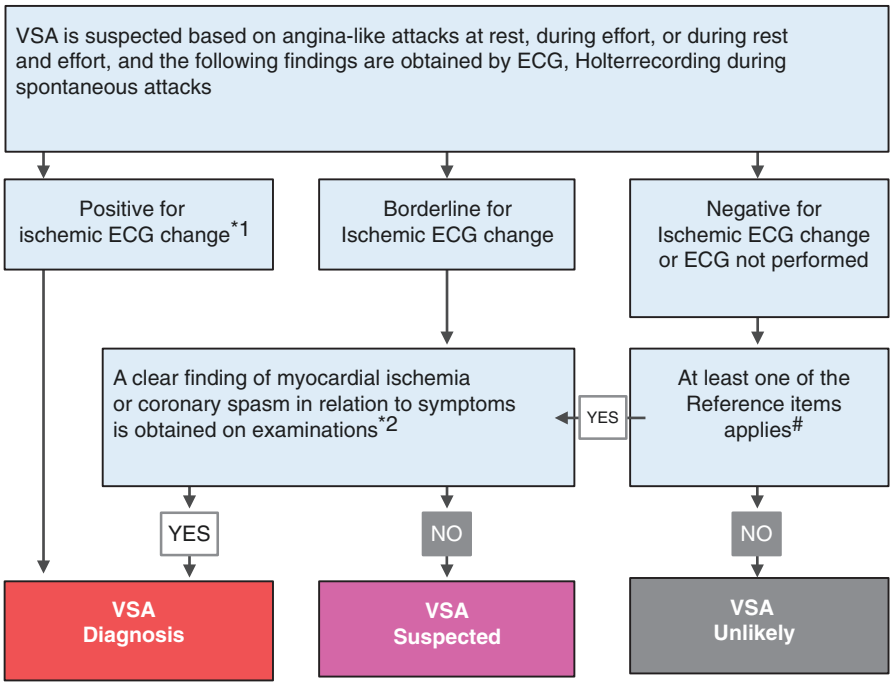


**Fig. 3.1** Diagnosis of coronary artery spasm. Diagnostic algorithm of VSA (quoted from the JCS guidelines). *1Ischemic change is defined as a transient ST elevation of 0.1 mV or more, an ST depression of 0.1 mV or more, or new appearance of negative U waves, recorded in at least two contiguous leads on 12-lead ECG. *2Examinations include the drug-induced spasm provocation test during cardiac catheterization and hyperventilation test. A positive finding for coronary artery spasm on angiography in coronary artery spasm provocation test is defined as "transient, total, or subtotal occlusion (>90% stenosis) of a coronary artery with signs/symptoms of myocardial ischemia (anginal pain and ischemic ECG change)". *VSA* vasospastic angina, *ECG* electrocardiogram. (Reproduced from JCS joint working group [1])

International Study Group (COVAIDS) depicts regarding the physical assessment of VSA that (1) subjective symptoms often appear at rest, especially between night and early morning, (2) exercise tolerance is markedly reduced in morning, (3) hyperventilation relates to the symptoms, and (4) calcium-channel blockers suppress the symptoms [2].

## 3.2 Noninvasive Evaluation Methods

ECG and Holter ECG are useful for documentation of ECG changes regardless of the presence or the absence of symptoms (Class I) [1]. The criteria for positive ECG findings include ST-segment elevation/suppression of 0.1 mV or more in at least 2 contiguous leads on 12-lead ECG. Exercise or hyperventilation test, often recommended to perform in resting condition desirably in the morning, could be an option for noninvasive assessment for coronary artery spasm. Usefulness of noninvasive cardiovascular imaging tools, such as myocardial scintigraphy and multi detector-row computed tomography (CT), remains to be determined in future guidelines.

## 3.3 Pharmacological Spasm Provocative Tests

The JCS guidelines highly recommend spasm provocation tests with acetylcholine (Class I) when a patient is negative for noninvasive VSA evaluation but is still suspected for coronary artery spasm clinically [1]. In 1986, Yasue et al. reported the usefulness of pharmacological spasm provocation test with intracoronary acetylcholine to induce coronary spasm [3]. Notably, a high diagnostic accuracy of acetylcholine provocation test for patients with variant angina (sensitivity, 90%; specificity, 99%) was reported [4]. Recent papers from the Europe demonstrated that pharmacological spasm provocation tests with acetylcholine are safe and useful for making VSA diagnosis in white patients [5, 6]. Prior to the introduction of acetylcholine, intravenous ergonovine was originally reported in 1949 [7], and was used for the first spasm provocation testing in 1972 [8]. Ergonovine provocation test is recommended if patients have a contraindication to acetylcholine due to comorbid bronchial asthma or severe atrioventricular conduction disorder [9].

In 2006, the Japanese Coronary Spasm Association (JCSA) was established, in which 85 Japanese institutes participated and registered VSA patients between September 1, 2007 and December 31, 2008 [10]. Since then, the JCSA registry has provided robust evidence, especially in the clinical presentation of coronary artery spasm. First, a study by Takagi et al. reported the safety of the spasm provocation tests and found the significant correlation between angiographic findings and long-term prognosis in 1244 VSA patients who were diagnosed with pharmacological provocation tests with either intracoronary acetylcholine or ergonovine [11]. In this study, overall incidence of arrhythmic complications, such as ventricular

tachycardia (VT) or ventricular fibrillation (VF) during the provocation tests, was 6.8%, which was comparable with those who were documented spontaneous angina attack. Patients who underwent acetylcholine provocation test showed a significant higher rate of arrhythmic complications as compared with those with ergonovine provocation test (acetylcholine 9.3% vs. ergonovine 3.2%, $P < 0.001$), which was more prominent for VT/VF (acetylcholine 4.9% vs. ergonovine 0.8%, $P < 0.001$). VSA patients with induced VT/VF during provocation test were characterized by a higher dose of acetylcholine use during the test, female, diffuse spasm in the right coronary artery, multivessel spasm, and lower prevalence of organic stenosis. When applied the logistic regression analysis, acetylcholine use during the provocation tests and diffuse spasm in the right coronary artery were strong correlated factors for the occurrence of provocation-related VT/VF. In contrast, the 5-year survival rate free from major adverse cardiac events (MACEs), including cardiac death, non-fatal myocardial infarction, hospitalization due to unstable angina pectoris and heart failure, and appropriate implantable cardioverter-defibrillator (ICD) shocks during the follow-up period, was 92%, and that of all-cause death was 98%. Importantly, MACE-free survival rate was statistically comparable between VSA patients with provocation-related VT/VF and those without them (Fig. 3.2). The multivariable Cox proportional hazard analysis showed that a mixture of focal and diffuse spasm observed in multivessels and organic stenosis were strongly correlated with MACEs, whereas no correlation between provocation-related arrhythmias and MACEs during the follow-up period was noted (Table 3.1). Thus, the JCSA study demonstrates an acceptable level of safety of the pharmacological spasm provocation test and its usefulness for the risk stratification of VSA patients [11].

Another landmark study form the JCSA registry developed the JCSA risk score that can provide comprehensive risk assessment and prognostic stratification for VSA patients [12]. A total of 7 variables, history of out-of-hospital cardiac arrest (4 points), smoking, rest angina alone, organic coronary stenosis, multivessel spasm during the spasm provocation tests (2 points each), ST-segment elevation during angina, and β-blocker use (1 point each) were chosen for the JCSA score. Intriguingly, MACE were incrementally documented in line with the low-risk, intermediate-risk, and high-risk (2.5%, 7.0%, and 13.0%, $P < 0.001$) (Fig. 3.3a). Among the 3 risk groups, clear prognostic utility of the JCSA scoring system for MACE was confirmed throughout the follow-up period (Fig. 3.3b). The study has thoroughly increased the importance of the spasm provocation test for the risk stratification of future cardiovascular events in VSA patients [12].

Although it has been believed for long time that VSA is more common in Asian countries compared with Western countries, recent studies from Germany revealed that the prevalence of VSA in Caucasians may be higher than previously thought [5, 6]. Heretofore, studies have suggested ethnic differences in the clinical manifestation and long-term prognosis of VSA patients between Japanese and Caucasians [13]. The JCSA study group recently revisited the ethnic differences in the VSA patient prognosis by comparing 1339 Japanese and 118 Caucasians [14]. The study performed by Sato et al. reported that spasm provocation tests were comparably performed in 95% of Japanese vs. 84% of Caucasians. Multivessel spasm was more

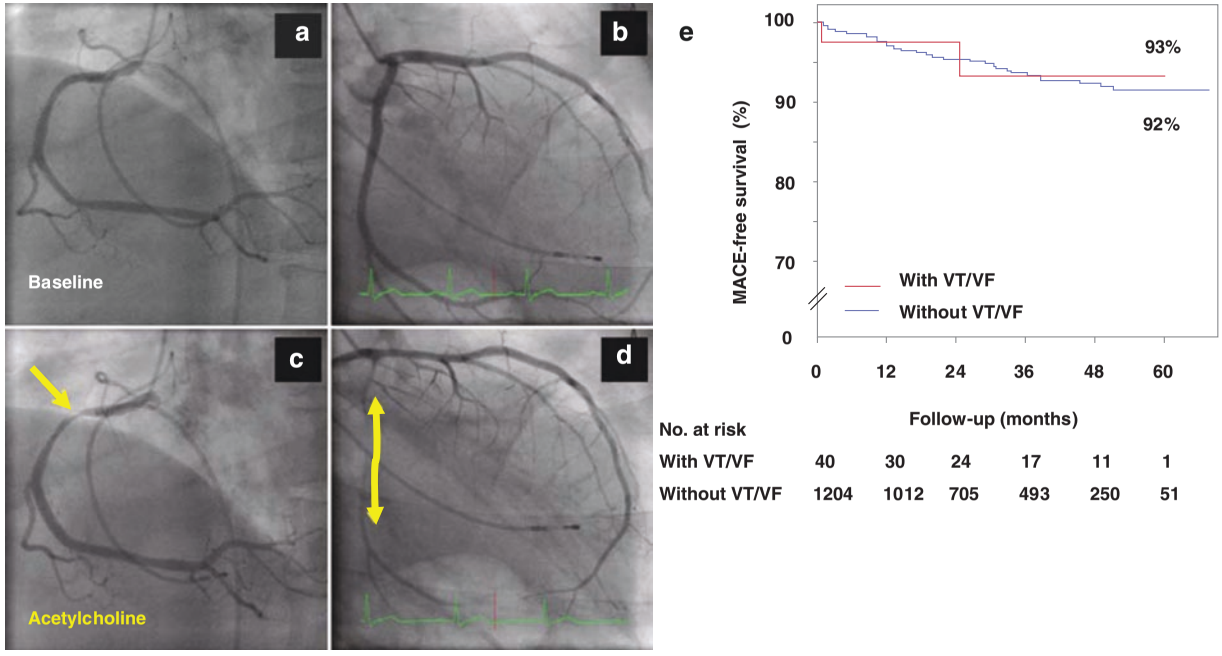


**Fig. 3.2** Acetylcholine provocation testing and its safety. Representative images of focal and diffuse mixed type, multivessel spasm (**a–d**). Baseline angiography showing no significant organic stenosis in the right and left coronary arteries (**a**, **b**). Angiography after intracoronary administration of acetylcholine demonstrating focal spasm in the proximal segment of the right coronary artery (yellow allow in **c**) and diffuse spasm along the proximal and middle segments of the left circumflex coronary artery (yellow allow in **d**). The focal spasm is defined as a discrete luminal narrowing localized in the major coronary artery. The diffuse spasm was diagnosed when luminal narrowing was observed continuously from the proximal to the distal segment of the coronary artery. The mixed type is defined as the multivessel spasm in which at least one coronary artery had focal spasm and the other had diffuse spasm. The Kaplan–Meier curve for MACE and survival in VSA patients after the diagnosis with the provocation testing (**e**). MACE-free survival rate was comparable between patients with ventricular tachycardia (VT)/ventricular fibrillation (VF) (red line, $N = 40$) and those without it (blue line, $N = 1204$) ($P = 0.90$) (**e**). MACE includes cardiac death, nonfatal myocardial infarction, hospitalization due to unstable angina pectoris and heart failure, and appropriate implantable cardioverter-defibrillator (ICD) shocks during the follow-up period. (Reproduced from Takagi et al. [11])

**Table 3.1** Factors correlated with major adverse cardiac events

| | Multivariable analysis HR | 95% CI | *P*-value |
|---|---|---|---|
| LAD spasm | 1.22 | 0.72–2.05 | 0.46 |
| LCX spasm | 0.95 | 0.55–1.64 | 0.85 |
| RCA spasm | 1.25 | 0.75–2.08 | 0.40 |
| Multivessel spasm | 1.47 | 0.89–2.41 | 0.13 |
| Type of spasm | | | |
| Focal single vessel | 1.00 | 0.45–1.74 | |
| Diffuse single vessel | 0.88 | 0.04–1.74 | 0.72 |
| Focal multivessel | 0.27 | 0.04–1.99 | 0.20 |
| Diffuse multivessel | 1.15 | 0.58–2.31 | 0.69 |
| **Mixed multivessel** | 2.84 | 1.34–6.03 | **0.006** |
| Organic stenosis | | | |
| Without stenosis | 1.00 | | |
| **Nonorganic stenosis** | 1.75 | 1.01–3.04 | **0.048** |
| **Significant stenosis** | 2.27 | 1.23–4.20 | **0.009** |
| **Provocation-related VT/VF** | 0.84 | 0.20–3.43 | 0.84 |
| **Provocation-related bradyarrhythmia** | 0.00 | 0.00–8.22 | 0.96 |

Variables were individually adjusted for age, sex, smoking, previous history of myocardial infarction, and history of out-of-hospital cardiac arrest. *LAD* left anterior descending, *LCX* left circumflex, *RCA* right coronary artery, *VT* ventricular tachycardia, *VF* ventricular fibrillation. (Reproduced from Takagi et al. [11])

prevalent in Japanese, whereas provocation-related arrhythmias were more common in Caucasians. The survival rate free from MACE, as described above, was significantly lower in Caucasians as compared with Japanese. In the multivariable analysis, the JCSA risk score, including the number of vessels positive for spasm provocation tests, was found to show good correlations with MACE rates in both Japanese and Caucasian patients, indicating the clinical importance of spasm provocation tests not only in Japan but also in Western countries.

In the context of the widespread utilization of drug-eluting stents (DES) in coronary intervention, it is fundamentally important to perform spasm provocation tests for patients with unremitting angina symptoms even after resolving the organic stenosis with DES implantation. An experimental study by Shiroto et al. demonstrated that a first-generation DES is likely to induce coronary hyperconstricting responses in response to intracoronary serotonin at the segments of proximal and distal edge of DES as compared with its platform bare-metal stents (BMS) in pigs in vivo, for which activated Rho-kinase plays an important role [15]. This finding was subsequently confirmed by a clinical study by Aizawa et al., demonstrating that pretreatment with fasudil, a selective Rho-kinase inhibitor, markedly inhibits acetylcholine-induced coronary hyperconstricting responses in patients implanted with DES in vivo [16]. More recently, a multicenter randomized control study by Tsuburaya et al. revealed that even everolimus-eluting stents, most widely used DES, could also induce coronary hyperconstricting responses at 8–10 months after implantation [17] (Fig. 3.4a, c). Intriguingly, long-term oral administration of

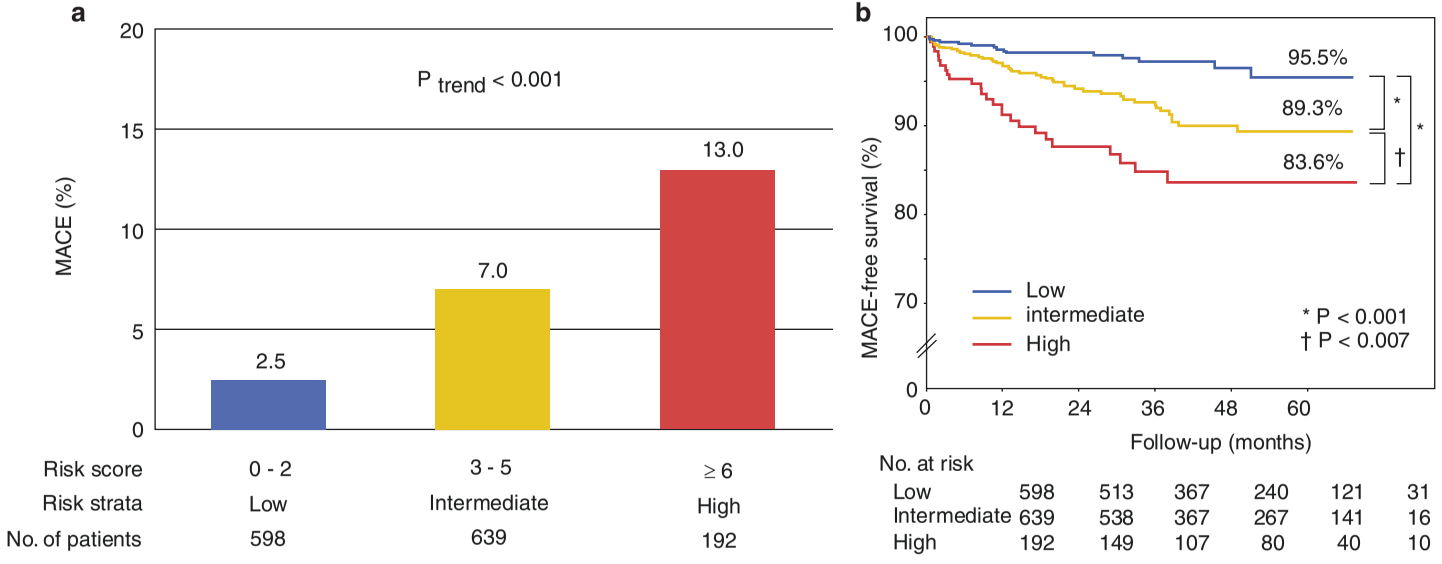


**Fig. 3.3** The Japanese Coronary Spasm Association (JCSA) risk score. In the JCSA registry, VSA patients were classified into the 3 risk groups in accordance with the risk scoring system composed of history of out-of-hospital cardiac arrest (4 points), smoking, rest angina alone, organic coronary stenosis, and multivessel spasm during the spasm provocation tests (2 points per each), ST-segment elevation during angina and β-blocker use (1 point per each). The graph (**a**) showing the incidence of MACE as described in Fig. 3.2. The Kaplan–Meier curve for MACE among the 3 risk groups showing clear prognostic utility of the scoring system throughout the follow-up period (**b**). (Reproduced from Takagi et al. [12])

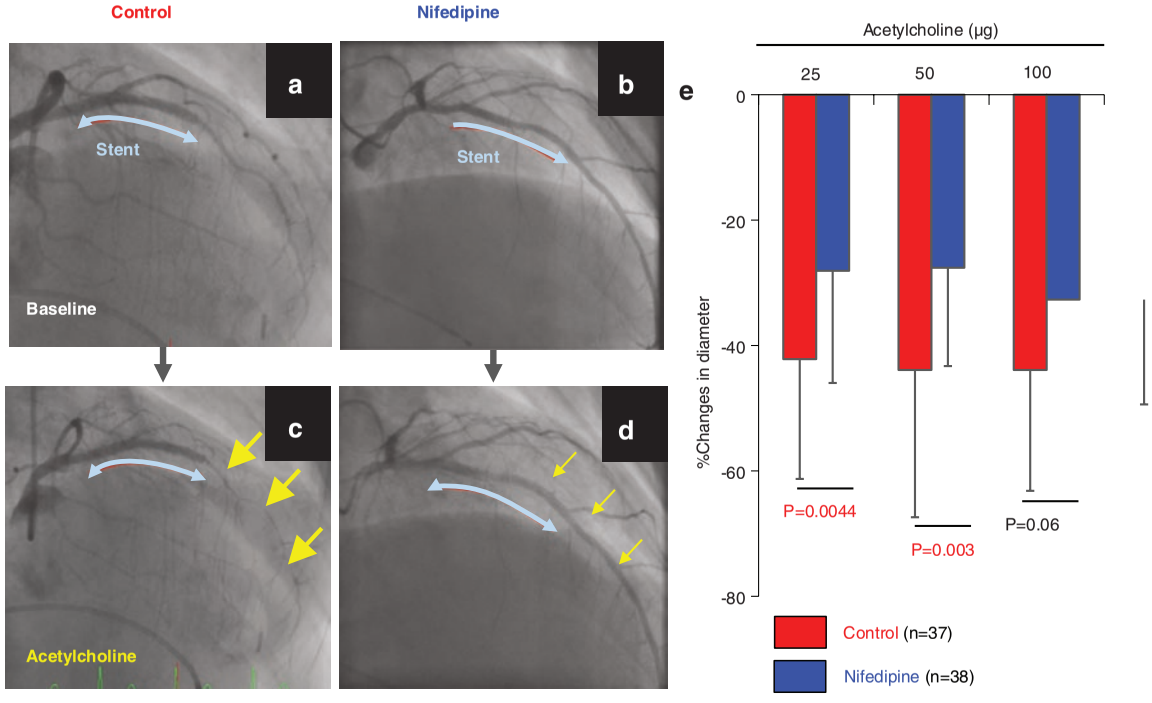


**Fig. 3.4** Inhibitory effects of long-acting nifedipine on coronary hyperconstricting responses after everolimus-eluting stents implantation in patients with stable angina pectoris. Representative angiography of patients with an implanted everolimus-eluting stent for 8 months at the timing of baseline (**a**, **b**) and that after intracoronary administration of acetylcholine (**c**, **d**). Baseline angiography showing no significant in-stent restenosis in the left coronary arteries in both control and nifedipine-treated patients (**a**, **b**). Coronary hyperconstricting responses to acetylcholine were noted in the control patient (as indicated by yellow arrows in **c**), whereas such responses were suppressed in the patient of the nifedipine group (**d**). The results of quantitative coronary angiography for % changes in diameter of the segments distal to the stents before and after intracoronary acetylcholine (**e**), showing that coronary vasoconstricting responses to acetylcholine were significantly suppressed in the nifedipine group compared with the control group. (Reproduced from Tsuburaya et al. [17])

nifedipine, a long-acting calcium channel blocker, inhibited DES-induced coronary hyperconstricting responses (Fig. 3.4b, d, e). Nishimiya et al. also reported that improved biocompatibility of polymer coating may ameliorate such coronary vasomotion abnormalities after DES [18]. Given the high rate of patients (~40%) who suffer from chest pain even after coronary intervention, spasm provocation tests are strongly recommended for those with unremitting angina especially after DES implantation [19].

## 3.4 Biomarkers for Coronary Artery Spasm

Although the JCS guidelines state that it is useful for VSA and microvascular spasm diagnosis to detect inversion of lactic acid production by measuring lactate levels at a coronary artery vs. coronary sinus (Class IIIb) [1, 20], the measurement has been hampered by its inconvenience due to the requirement of catheter insertion into the coronary sinus. Thus, we also aimed to develop novel biomarkers for coronary artery spasm that can be easily used in the clinical setting. In order to clarify the existence of genetic linkage in the pathogenesis of coronary artery spasm, the frequencies of human leukocyte antigen (HLA) were examined in 37 patients with variant angina and 236 healthy controls, and were found to show no significant differences between the patients and the controls [21]. Hizume et al. reported that sustained elevation of serum cortisol level sensitizes coronary smooth muscle to serotonin to cause coronary vasospastic responses in pigs in vivo, suggesting the cross-link between stress and coronary artery spasm [22].

We were able to demonstrate that Rho-kinase activity in circulating neutrophils, determined by the extent of phosphorylation of myosin-binding subunit (MBS, a substrate of Rho-kinase), is significantly enhanced in VSA patients as compared with controls, which is a useful noninvasive diagnostic biomarker to assess the vasospastic activity [23] (Fig. 3.5a). In this study, Rho-kinase activity in circulating neutrophils was expressed as the ratio of phosphorylated MBS (p-MBS) to total MBS (t-MBS) (Fig. 3.5a, b). A p-MBS ratio of 1.18 was identified as the best cutoff level to predict the diagnosis of VSA (Fig. 3.5b). We also demonstrated that the Rho-kinase activity is able to show the severity of angina symptoms, and the responsiveness to medical treatment [23]. We also subsequently demonstrated that Rho-kinase activity in circulating neutrophils in VSA patients was temporally enhanced after the Great East Japan Earthquake associated with disaster-related mental stress (Fig. 3.5c) [24] and that the Rho-kinase activity well corresponds to distinct circadian variation in VSA patients (Fig. 3.5d) [25]. Moreover, when VSA patients were divided by a median value of Rho-kinase activity, VSA patients with higher Rho-kinase activity ($\geq$1.20) had significantly worse prognosis (Fig. 3.6a) [26]. In this study, a p-MBS ratio of 1.24 was identified as the best cutoff level to predict future cardiac events in VSA patients (Fig. 3.6b). Of note, combination of Rho-kinase activity with the JCSA risk score dramatically enhanced the prognostic impact in VSA patients [26].

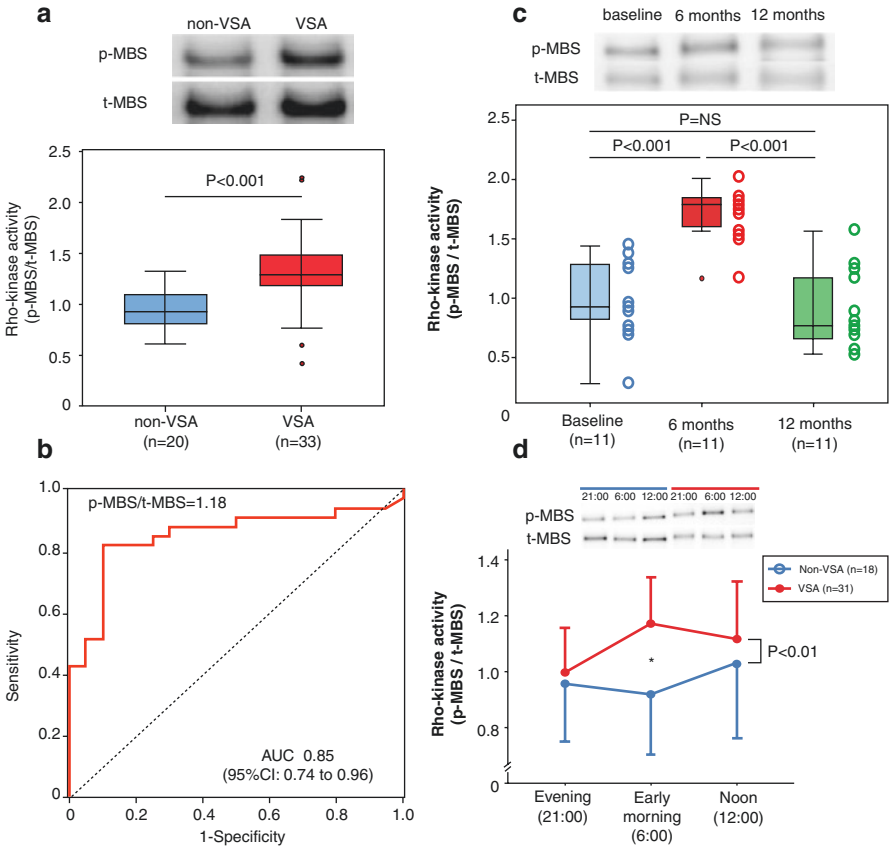


**Fig. 3.5** Rho-kinase activity in circulating leukocytes of VSA patients (diagnosis). Rho-kinase activity in circulating neutrophils is determined by the extent of phosphorylation of myosin-binding subunit (MBS, a substrate of Rho-kinase), and is expressed as the ratio of phosphorylated MBS (p-MBS) to total MBS (t-MBS) (**a**, **b**). Rho-kinase activity was significantly enhanced in VSA patients compared with controls (**a**). Receiver-operating characteristic (ROC) curve analysis confirmed that a p-MBS ratio of 1.18 was identified as the best cutoff level to predict the diagnosis of VSA (**b**). (Reprinted with permission from Kikuchi et al. [23]). Changes in Rho-kinase activity in circulating neutrophils of VSA patients after the Great East Japan Earthquake (**c**). Rho-kinase activity was significantly increased at 6 months after the Earthquake and was returned to the baseline level at 12 months. Rho-kinase activity in circulating neutrophils well corresponded to circadian variation of disease activity in VSA patients (**d**). (Reproduced from Nihei et al. [24, 25])

Coronary microvascular dysfunction (CMD) has been emerging as an aggravating factor of cardiovascular disease [27, 28]. When no flow-limiting stenosis is noted on coronary angiography, coronary microcirculation can be assessed by index of microvascular resistance (IMR) [29]. We have recently demonstrated that comorbid CMD determined by increased IMR >18 worsens the long-term prognosis of VSA patients [30] (see Chap. 8 for details). In the study by Odaka et al., we obtained blood samples from the left coronary ostia before spasm provocation tests,

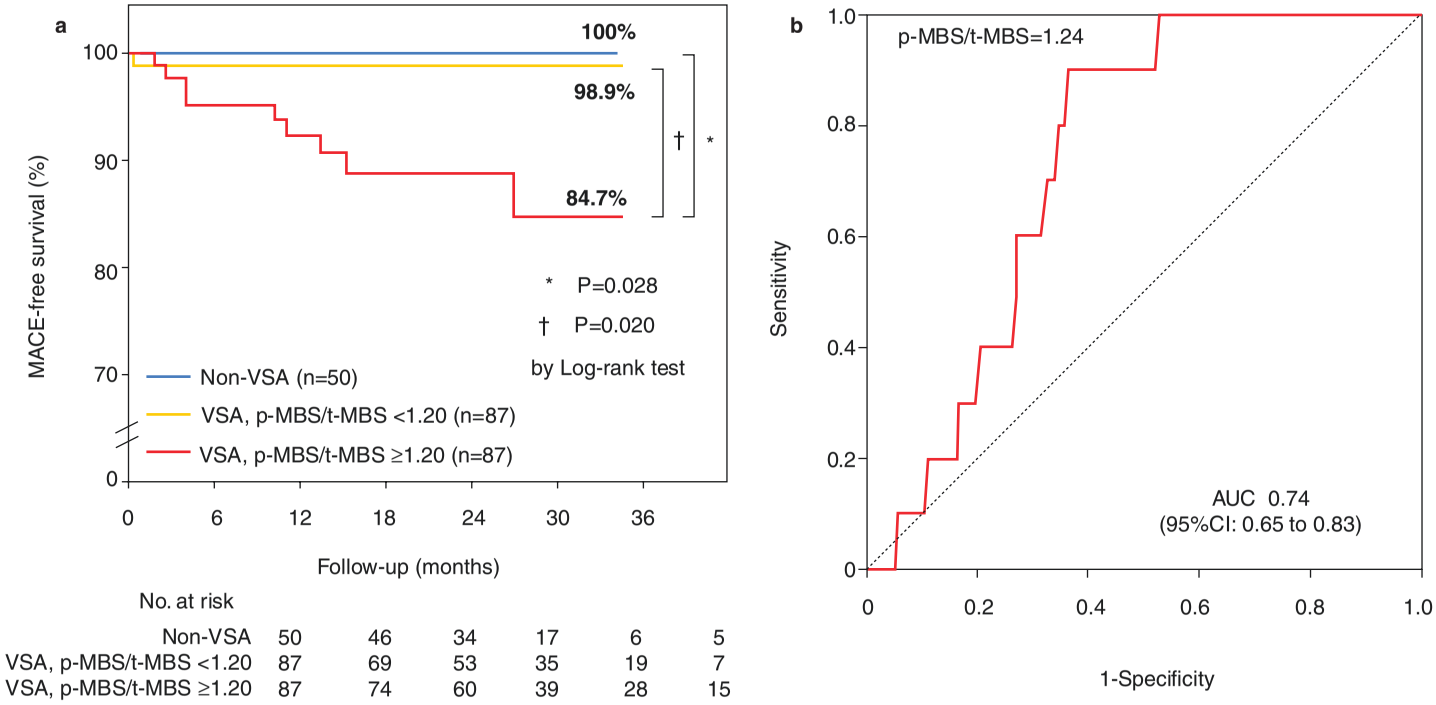


**Fig. 3.6** Prognostic impact of Rho-kinase activity in circulating leukocytes in VSA patients. The Kaplan–Meier curve for cardiac events (cardiac death, non-fatal myocardial infarction, and hospitalization for unstable angina) of VSA patients with high Rho-kinase activity (≥1.20) vs. those with low Rho-kinase activity (<1.20) vs. non-VSA patients (**a**). ROC analysis for predicting future development of cardiac events of VSA patients confirmed that a p-MBS ratio of 1.24 was identified as the best cutoff level (**b**). (Reproduced from Nihei et al. [26])

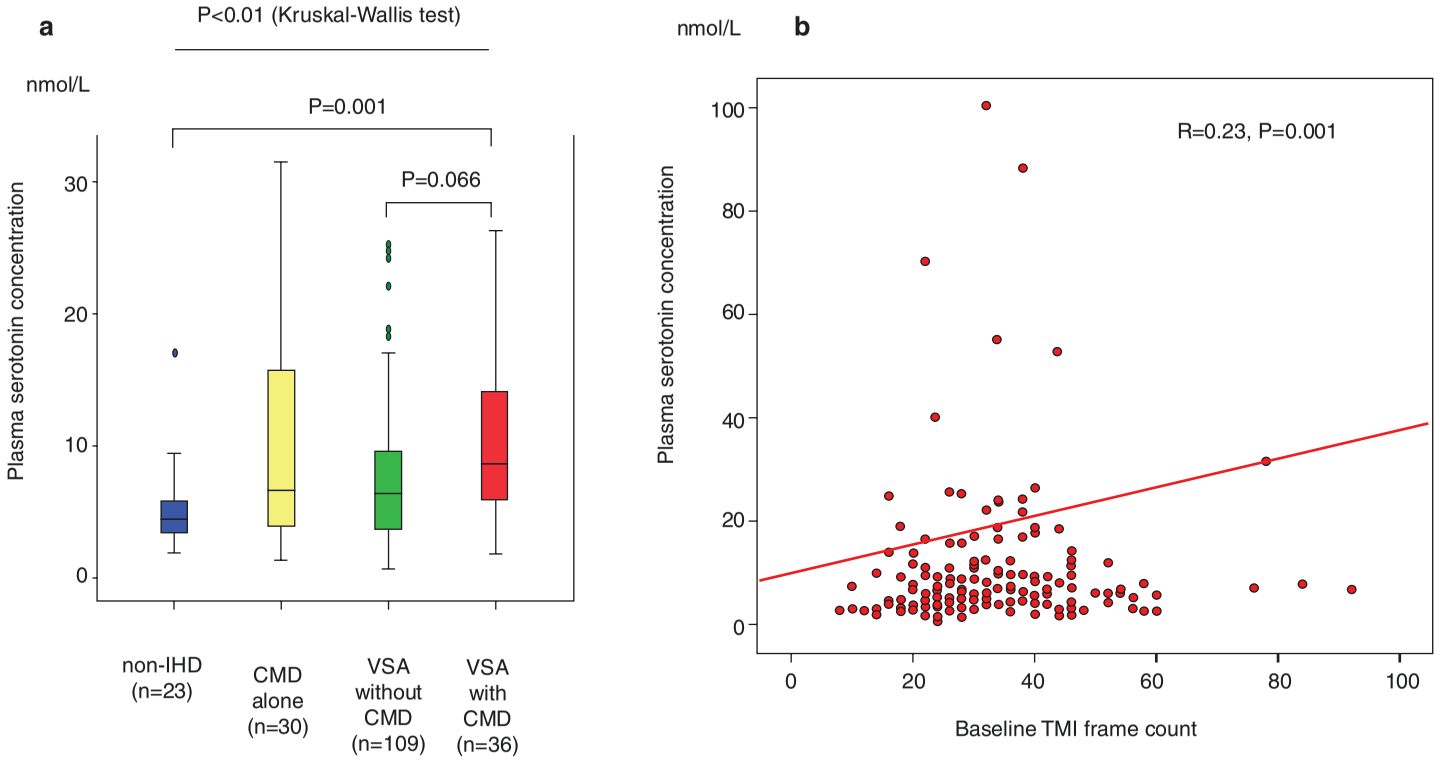


**Fig. 3.7** Plasma serotonin concentration for discrimination of VSA patients with coronary microvascular dysfunction (CMD). Plasma concentrations of serotonin by patient group classified in accordance with the diagnosis of VSA with or without CMD (**a**). CMD was defined as myocardial lactate production despite the absence of angiographically demonstrable epicardial coronary spasm. Among the 4 patient groups, serotonin concentrations were highest in the VSA with CMD group. There was a positive correlation between TIMI (Thrombolysis In Myocardial Infarction) frame count, a marker of coronary vascular resistance, and plasma serotonin concentrations. (Reproduced from Odaka et al. [25])

measured plasma concentration of serotonin, and found that VSA patients with CMD had highest serotonin concentration, while no difference was noted between VSA and non-VSA groups, associated with increased coronary vascular resistance (Fig. 3.7) [31]. Fractional flow reserve (FFR), a marker for evaluating the degree of flow limiting coronary stenotic region, may also be able to extract the high-risk population among VSA patients [32].

## 3.5 Imaging for Coronary Artery Spasm

Cardiovascular imaging could offer additional information at cellular and molecular levels on the detailed features of VSA. Intravascular imaging studies reported that atherosclerotic changes are more common in the human coronary arterial segment of focal spasm as compared with that of diffuse spasm [33, 34]. We have previously demonstrated that chronic inflammatory changes in the coronary adventitia play important roles in the pathogenesis of coronary artery spasm through Rho-kinase activation and resultant vascular smooth muscle hypercontraction [35–37]. We thus sought to develop novel imaging approaches for evaluating the extent of coronary adventitial inflammatory changes in VSA patients in vivo. First, a mode of Fourier-domain (FD) optical coherence tomography (OCT) [38] is capable of visualizing a nutrient blood vessel for coronary arterial wall linking to the intima/media, termed adventitial vasa vasorum (VV) [39, 40] in pigs and humans ex vivo. In these studies, we used the definition of adventitial area as [area outside the external elastic lamina within a distance of the thickness of intima plus media—vessel area] and the definition of adventitial VV area density calculated by [adventitial VV area/adventitial area] [39]. We were able to demonstrate that OCT-delineated adventitial VV formation was significantly enhanced at the spastic segments of VSA patients as compared with those of control subjects (Fig. 3.8a–d) [41, 43]. Adventitial VV formation was significantly enhanced in the group with high JCSA score than in that with low or intermediate score. Second, coronary perivascular adipose tissue (PVAT) volume measured by CT coronary angiography was increased at the spastic segment of VSA patients [44]. Subsequently, $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomographic (PET) imaging allows us to evaluate inflammatory changes of coronary PVAT in pigs in vivo [42]. In this study, the extent of PVAT inflammation was expressed as target to background ratio (TBR), the standardized uptake value (SUV) corrected for blood activity by dividing the average blood SUV estimated from the ascending aorta. With the novel approach of $^{18}$F-FDG PET, we demonstrated that coronary PVAT inflammatory changes were more extensive at the spastic coronary segments of VSA patients as compared with those of control subjects (Fig. 3.8e–i) [45]. Inflammatory changes measured by $^{18}$F-FDG PET were significantly suppressed after medical treatment (Fig. 3.8j). These imaging approaches may serve as a promising avenue for the fully elucidation of the pathogenesis of coronary artery spasm in living patients with VSA in vivo.

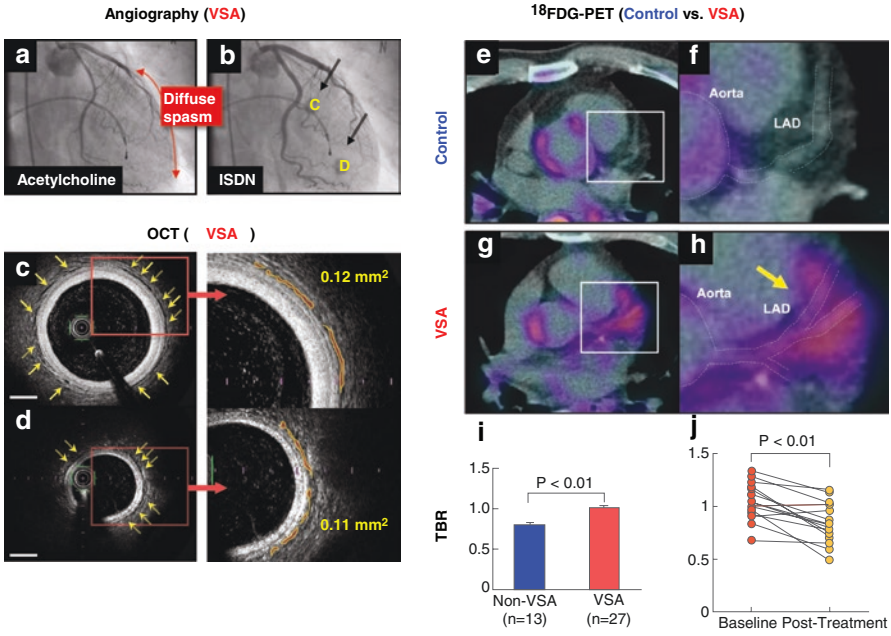


**Fig. 3.8** Imaging of coronary artery spasm. Representative coronary angiography after administration of intracoronary acetylcholine (**a**), after resolving the spasm with intracoronary administration of isosorbide-dinitrate (ISDN) (**b**), and cross-sectional images of optical coherence tomography (OCT) of a VSA patient with provoked diffuse spams (**c**, **d**). After ISDN, the coronary artery was imaged by OCT (**b**), and adventitial vasa vasorum (VV) (yellow arrows) were manually segmented on each frame. Adventitial VV area was then calculated as shown in magnified OCT images. Scale bars: 1 mm (**c**, **d**). (Reprinted with permission from Nishimiya et al. [41]). Representative $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomographic (PET) images of a non-VSA control subject and a VSA patient (**e–h**), suggesting that coronary perivascular adipose tissue (PVAT) inflammation is markedly increased at the spastic segments of the left anterior descending coronary artery (LAD) of the VSA patient (**g**, **h**). Quantitative analysis showed that TBR in coronary PVAT measured at the spastic LAD was significantly greater in the VSA group than in the non-VSA control group (**i**). TBR was significantly decreased in the VSA group after medical treatment (**j**). (Reproduced from Ohyama et al. [42])

## 3.6 Future Perspectives

A recent large-scale trial has shown that the coronary intervention for myocardial ischemia related to organic stenosis ended up showing no significant improvement in exercise time when compared with a placebo procedure [46] and may not result in the risk reduction of future cardiovascular events [46–48]. These results emphasize in part the importance of the assessment of coronary vasomotion abnormalities, including coronary artery spasm (VSA), rather than stenosis-related myocardial ischemia (Fig. 3.9). In conclusions, we strongly encourage to perform spasm provocation tests even when no organic coronary stenosis is found angiographically, and expect to possess more sophisticated approaches that can be readily used in daily

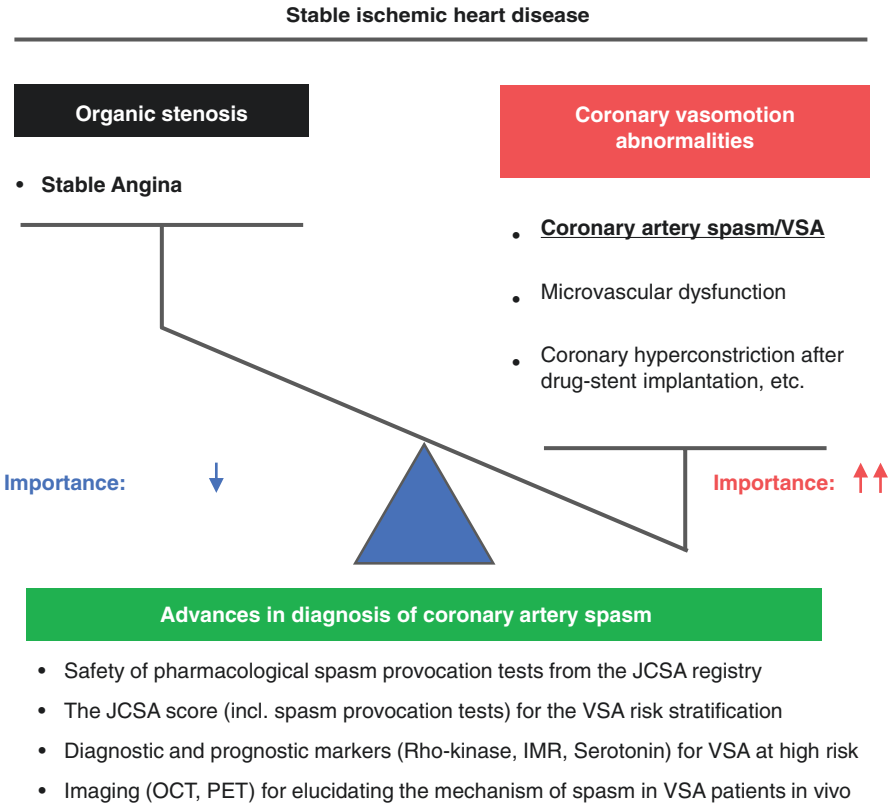


**Fig. 3.9** Recent large scale cohorts have emphasized in part the importance of the assessment of coronary vasomotion abnormalities, including coronary artery spasm (VSA), rather than stenosis-related myocardial ischemia in patients with stable ischemic heart disease. This chapter highlighted recent advances in diagnostic methodology of coronary artery spasm

clinical practice, enabling us to predict the prevalence and the disease activity of VSA.

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## References

1. JCS joint working group. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina). Circ J. 2014;78:2779–801. https://doi.org/10.1253/circj.CJ-66-0098.

2. Beltrame JF, Crea F, Kaski JC, Ogawa H, Ong P, Sechtem U, Shimokawa H, Bairey Merz CN, Coronary Vasomotion Disorders International Study Group (COVADIS). International standardization of diagnostic criteria for vasospastic angina. Eur Heart J. 2017;38:2565–8. https://doi.org/10.1093/eurheartj/ehv351.
3. Yasue H, Horio T, Nakamura N, Fujii H, Imoto N, Sonoda R, Kugiyama K, Obata K, Morikami Y, Kimura T. Induction of coronary artery spasm by acetylcholine in patients with variant angina: possible role of the parasympathetic nervous system in the pathogenesis of coronary artery spasm. Circulation. 1986;74:955–63. https://doi.org/10.1161/01.cir.74.5.955.
4. Okumura K, Yasue H, Matsuyama K, Goto K, Miyagi H, Ogawa H, Matsuyama K. Sensitivity and specificity of intracoronary injection of acetylcholine for the inductin of coronary artery spasm. J Am Coll Cardiol. 1988;12:883–8. https://doi.org/10.1016/0735-1097(88)90449-4.
5. Ong P, Athanasiadis A, Hill S, Vogelsberg H, Voehringer M, Sechtem U. Coronary artery spasm as a frequent cause of acute coronary syndrome. The CASPAR (coronary artery spasm in patients with acute coronary syndrome) study. J Am Coll Cardiol. 2008;52:523–7. https://doi.org/10.1016/j.jacc.2008.04.050.
6. Ong P, Athanasiadis A, Borgulya G, Vokshi I, Bastiaenen R, Kubik S, Hill S, Schäufele T, Mahrholdt H, Kaski JC, Sechtem U. 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. https://doi.org/10.1161/CIRCULATIONAHA.113.004096.
7. Stein L. Observations on the action of ergonovine on the coronary circulation and its use in the diagnosis of coronary artery insufficiency. Am Heart J. 1949;39:36–45.
8. Heupler FA. Provocative testing for coronary arterial spasm: risk, method and rationale. Am J Cardiol. 1980;46:335–7. https://doi.org/10.1016/0002-9149(80)90081-8.
9. Curry RC, Pepine CJ, Sabom MB, Conti CR. Similarities of ergonovine-induced and spontaneous attacks of varian angina. Circulation. 1979;59:307–12. https://doi.org/10.1161/01.cir.59.2.307.
10. Shimokawa H. 2014 William Harvey lecture: importance of coronary vasomotion abnormalities - from bench to bedside. Eur Heart J. 2014;35:3180–93. https://doi.org/10.1093/eurheartj/ehu427.
11. Takagi Y, Yasuda S, Takahashi J, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Sato T, Ogawa S, Kubo N, Momomura S, Ogawa H, Shimokawa H, Japanese Coronary Spasm Association. Clinical implications of provocation tests for coronary artery spasm: safety, arrhythmic complications, and prognostic impact: multicenter registry study of the Japanese Coronary Spasm Association. Eur Heart J. 2013;34:258–67. https://doi.org/10.1093/eurheartj/ehs199.
12. Takagi Y, Takahashi J, Yasuda S, Miyata S, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Sato T, Ogawa S, Kubo N, Momomura S, Ogawa H, Shimokawa H, Japanese Coronary Spasm Association. Prognostic stratification of patients with vasospastic angina: a comprehensive clinical risk score developed by the Japanese Coronary Spasm Association. J Am Coll Cardiol. 2013;62:1144–53. https://doi.org/10.1016/j.jacc.2013.07.018.
13. Pristipino C, Beltrame JF, Finocchiaro ML, Hattori R, Fujita M, Mongiardo R, Cianflone D, Sanna T, Sasayama S, Maseri A. Major racial differences in coronary constrictor response between Japanese and Caucasians with recent myocardial infarction. Circulation. 2000;101:1102–8. https://doi.org/10.1161/01.cir.101.10.1102.
14. Sato K, Takahashi J, Odaka Y, Suda A, Sueda S, Teragawa H, Ishii K, Kiyooka T, Hirayama A, Sumiyoshi T, Tanabe Y, Kimura K, Kaikita K, Ong P, Sechtem U, Camici PG, Kaski JC, Crea F, Beltrame JF, Shimokawa H, Japanese Coronary Spasm Association. 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. https://doi.org/10.1016/j.ijcard.2019.02.038.
15. Shiroto T, Yasuda S, Tsuburaya R, Ito Y, Takahashi J, Ito K, Ishibashi-Ueda H, Shimokawa H. Role of Rho-kinase in the pathogenesis of coronary hyperconstricting responses induced

by drug-eluting stents in pigs in vivo. J Am Coll Cardiol. 2009;54:2321–9. https://doi.org/10.1016/j.jacc.2009.07.045.
16. Aizawa K, Yasuda S, Takahashi J, Takii T, Kikuchi Y, Tsuburaya R, Ito Y, Ito K, Nakayama M, Takeda M, Shimokawa H. Involvement of Rho-kinase activation in the pathogenesis of coronary hyperconstricting responses induced by drug-eluting stents in patients with coronary artery disease. Circ J. 2012;76:2552–60. https://doi.org/10.1253/circj.CJ-12-0662.
17. Tsuburaya R, Takahashi J, Nakamura A, Nozaki E, Sugi M, Yamamoto Y, Hiramoto T, Horiguchi S, Inoue K, Goto T, Kato A, Shinozaki T, Ishida E, Miyata S, Yasuda S, Shimokawa H, Investigators NOVEL. Beneficial effects of long-acting nifedipine on coronary vasomotion abnormalities after drug-eluting stent implantation: the NOVEL study. Eur Heart J. 2016;37:2713–21. https://doi.org/10.1093/eurheartj/ehw256.
18. Nishimiya K, Matsumoto Y, Uzuka H, Ogata T, Hirano M, Shindo T, Hasebe Y, Tsuburaya R, Shiroto T, Takahashi J, Ito K, Shimokawa H. Beneficial effects of a novel bioabsorbable polymer coating on enhanced coronary vasoconstricting responses after drug-eluting stent implantation in pigs in vivo. J Am Coll Cardiol Intv. 2016;9:281–91. https://doi.org/10.1016/j.jcin.2015.09.041.
19. Crea F, Bairey Merz CN, Beltrame JF, Berry C, Camici PG, Kaski JC, Ong P, Pepine CJ, Sechtem U, Shimokawa H. Mechanisms and diagnostic evaluation of persistent or recurrent angina following percutaneous coronary revascularization. Eur Heart J. 2019;40:2455–62. https://doi.org/10.1093/eurheartj/ehy857.
20. Mohri M, Koyanagi M, Egashira K, Tagawa H, Ichiki T, Shimokawa H, Takeshita A. Angina pectoris caused by coronary microvascular spasm. Lancet. 1998;351:1165–9. https://doi.org/10.1016/S0140-6736(97)07329-7.
21. Shimokawa H, Toyoda K, Matsumoto T, Sato H, Kikuchi Y, Nakamura M. Human leucocyte antigen and coronary artery spasm. Int J Cardiol. 1986;12:362–5.
22. Hizume T, Morikawa K, Takaki A, Abe K, Sunagawa K, Amano M, Kaibuchi K, Kubo C, Shimokawa H. Sustained elevation of serum cortisol level causes sensitization of coronary vasoconstricting responses in pigs in vivo. A possible link between stress and coronary vasospasm. Circ Res. 2006;99:767–75. https://doi.org/10.1161/01.RES.0000244093.69985.2f.
23. Kikuchi Y, Yasuda S, Aizawa K, Tsuburaya R, Ito Y, Takeda M, Nakayama M, Ito K, Takahashi J, Shimokawa H. 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. https://doi.org/10.1016/j.jacc.2011.05.046.
24. Nihei T, Takahashi J, Kikuchi Y, Takagi Y, Hao K, Tsuburaya R, Shiroto T, Ito Y, Matsumoto Y, Nakayama M, Ito K, Yasuda S, Shimokawa H. Enhanced Rho-kinase activity in patients with vasospastic angina after the Great East Japan earthquake. Circ J. 2012;76:2892–4. https://doi.org/10.1016/j.jacc.2011.05.046.
25. Nihei T, Kikuchi Y, Tsuburaya R, Ito Y, Shiroto T, Hao K, Takagi Y, Matsumoto Y, Nakayama M, Miyata S, Sakata Y, Ito K, Shimokawa H. Circadian variation of Rho-kinase activity in circulating leukocytes of patients with vasospastic angina. Circ J. 2014;78:1183–90. https://doi.org/10.1253/circj.CJ-13-1458.
26. Nihei T, Takahashi J, Hao K, Kikuchi Y, Odaka Y, Tsuburaya R, Nishimiya K, Matsumoto Y, Ito K, Miyata S, Sakata Y, Shimokawa H. Prognostic impacts of Rho-kinase activity in circulating leukocytes in patients with vasospastic angina. Eur Heart J. 2018;39:952–9. https://doi.org/10.1093/eurheartj/ehx657.
27. Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U, Kaski JC, Bairey Merz CN, Coronary Vasomotion Disorders International Study Group (COVADIS). International standardization of diagnostic criteria for microvascular angina. Int J Cardiol. 2018;250:16–20. https://doi.org/10.1016/j.ijcard.2017.08.068.
28. 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. https://doi.org/10.1161/CIRCULATIONAHA.116.024534.

29. Kobayashi Y, Fearon WF, Honda Y, Tanaka S, Pargaonkar V, Fitzgerald PJ, Lee DP, Stefanick M, Yeung AC, Tremmel JA. Effect of sex differences on invasive measures of coronary macrovascular dysfunction in patients with angina in the absence of obstructive coronary artery disease. J Am Coll Cardiol Intv. 2015;8:1433–41. https://doi.org/10.1016/j.jcin.2015.03.045.
30. Suda A, Takahashi J, Hao K, Kikuchi Y, Shindo T, Ikeda S, Sato K, Sugisawa J, Matsumoto Y, Miyata S, Sakata Y, Shimokawa H. Coronary functional abnormalities in patients with angina and nonobstructive coronary artery disease. J Am Coll Cardiol. 2019;74:2350–60. https://doi.org/10.1016/j.jacc.2019.08.1056.
31. Odaka Y, Takahashi J, Tsuburaya R, Nishimiya K, Hao K, Matsumoto Y, Ito K, Sakata Y, Miyata S, Manita D, Hirowatari Y, Shimokawa H. Plasma concentration of serotonin is a novel biomarker for coronary microvascular dysfunction in patients with suspected angina and unbstructive coronary arteries. Eur Heart J. 2017;38:489–96. https://doi.org/10.1093/eurheartj/ehw448.
32. Hao K, Takahashi J, Suda A, Sato K, Sugisawa J, Tsuchiya S, Shindo T, Ikeda S, Kikuchi Y, Shiroto T, Matsumoto Y, Sakata Y, Shimokawa H. Clinical importance of fractional flow reserve in patients with organic coronary stenosis and vasospastic angina. Eur Heart J. 2019;40(Supplement_1). https://doi.org/10.1093/eurheartj/ehz745.0436.
33. Koyama J, Yamaghisi M, Tamai J, Tamai J, Kawano S, Daikoku S, Miyatake K. Comparison of vessel wall morphologic appearance at sits of focal and diffuse coronary vasospasm by intravascular ultrasound. Am Heart J. 1995;130:440–5. https://doi.org/10.1016/0002-8703(95)90349-6.
34. Kitano D, Takayama T, Sudo M, Kogo T, Kojima K, Akutsu N, Nishida T, Haruta H, Fukamachi D, Kawano T, Kanai T, Hiro T, Saito S, Hirayma A. Angioscopic differences of coronary intima between diffuse and focal coronary vasospasm: comparison of optical coherence tomography findings. J Cardiol. 2018;72:200–7. https://doi.org/10.1016/j.jjcc.2018.04.013.
35. Shimokawa H, Ito A, Fulumoto Y, Kadokami T, Nakaike R, Sakata M, Takayanagi T, Egashira K, Takeshita A. Chronic treatment with interluekin-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. https://doi.org/10.1172/JCI118476.
36. Kandabashi T, Shimokawa H, Miyata K, Kunihiro I, Kawano Y, Fukata Y, Higo T, Egashira K, Takahashi S, Kaibuchi K, Takeshita A. Inhibition of myosin phosphatase by upregulated Rho-kinase plays a key role for coronary artery spasm in a porcine model with interleukin-1β. Eur Heart J. 2017;38:489–96. https://doi.org/10.1161/01.cir.101.11.1319.
37. Masumoto A, Mohri M, Shimokawa H, Urakami L, Usui M, Takeshita A. Suppression of coronary artery spasm by the Rho-kinase inhibitor fasudil in patients with vasospastic angina. Circulation. 2002;105:1545–7. https://doi.org/10.1161/hc1002.105938.
38. Yun SH, Tearney GJ, Vakoc BJ, Shishkov M, Oh WY, Desjardins AE, Suter MJ, Chan RC, Evans JA, Jang IK, Nishioka NS, de Boer JF, Bouma BE. Comprehensive volumetric optical microscopy in vivo. Nat Med. 2006;12:1429–33. https://doi.org/10.1038/nm1450.
39. Nishimiya K, Matsumoto Y, Takahashi J, Uzuka H, Odaka Y, Nihei T, Hao K, Tsuburaya R, Ito K, Shimokawa H. In vivo visualization of adventitial vasa vasorum of the human coronary artery on optical frequency domain imaging. Validation study. Circ J. 2014;78:2516–8. https://doi.org/10.1253/circj.CJ-14-0485.
40. Nishimiya K, Matsumoto Y, Uzuka H, Oyama K, Tanaka A, Taruya A, Ogata T, Hirano M, Shindo T, Hanawa K, Hasebe Y, Hao K, Tsuburaya R, Takahashi J, Miyata S, Ito K, Akasaka T, Shimokawa H. Accuracy of optical frequency domain imaging for evaluation of coronary adventitial vasa vasorum formation after stent implantation in pigs and humans. A validation study. Circ J. 2015;79:1323–31. https://doi.org/10.1253/circj.CJ-15-0078.
41. Nishimiya K, Matsumoto Y, Uzuka H, Ohyama K, Hao K, Tsuburaya R, Shiroto T, Takahashi J, Ito K, Shimokawa H. Focal vasa vasorum formation in patients with focal coronary vasospasm. -An optical frequency domain imaging study. Circ J. 2016;80:2252–4. https://doi.org/10.1253/circj.CJ-16-0580.

42. Ohyama K, Matsumoto Y, Amamizu H, Uzuka H, Nishimiya K, Morosawa S, Hirano M, Watabe H, Funaki Y, Miyata S, Takahashi J, Ito K, Shimokawa H. Association of coronary perivascular adipose tissue inflammation and DES-induced coronary hyperconstriction responses in pigs. -$^{18}$F-FDG PET imaging study. Arterior Thromb Vasc Biol. 2017;37:1757–64. https://doi.org/10.1161/atvbaha.117.309843.
43. Nishimiya K, Matsumoto Y, Takahashi J, Uzuka H, Wang H, Tsuburaya R, Hao K, Ohyama K, Odaka Y, Miyata S, Ito K, Shimokawa H. Enhanced adventitial vasa vasorum formation in patients with vasospastic angina. J Am Coll Cardiol. 2016;67:598–600. https://doi.org/10.1016/j.jacc.2015.11.031.
44. Ohyama K, Matsumoto Y, Nishimiya K, Hao K, Tsuburaya R, Ota H, Amamizu H, Uzuka H, Takahashi J, Ito K, Shimokawa H. Increased coronary perivascular adipose tissue volume in patients with vasospastic angina. Circ J. 2016;80:1653–6. https://doi.org/10.1253/circj.CJ-16-0213.
45. Ohyama K, Matsumoto Y, Takanami K, Ota H, Nishimiya K, Sugisawa J, Tsuchiya S, Amamizu H, Uzuka H, Suda A, Shindo T, Kikuchi Y, Hao K, Tsuburaya R, Takahashi J, Miyata S, Sakata Y, Takase K, Shimokawa H. Coronary adventitial and perivascular adipose tissue inflammation in patients with vasospastic angina. J Am Coll Cardiol. 2018;71:414–25. https://doi.org/10.1016/j.jacc.2017.11.046.
46. Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, Keeble T, Mielewczik M, Kaprielian R, Malik IS, Nijjer SS, Petraco R, Cook C, Ahmad Y, Howard J, Baker C, Sharp A, Gerber R, Talwar S, Assomull R, Mayet J, Wensel R, Collier D, Shun-Shin M, Thom SA, Davies JE, Francis DP, ORBITA investigators. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. Lancet. 2018;391:31–40. https://doi.org/10.1016/S0140-6736(17)32714-9.
47. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS, COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007;356:1503–16. https://doi.org/10.1056/NEJMoa070829.
48. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, Chaitman BR, Senior R, López-Sendón J, Alexander KP, Lopes RD, Shaw LJ, Berger JS, Newman JD, Sidhu MS, Goodman SG, Ruzyllo W, Gosselin G, Maggioni AP, White HD, Bhargava B, Min JK, GBJ M, Berman DS, Picard MH, Kwong RY, Ali ZA, Mark DB, Spertus JA, Krishnan MN, Elghamaz A, Moorthy N, Hueb WA, Demkow M, Mavromatis K, Bockeria O, Peteiro J, Miller TD, Szwed H, Doerr R, Keltai M, Selvanayagam JB, Steg PG, Held C, Kohsaka S, Mavromichalis S, Kirby R, Jeffries NO, Harrell FE Jr, Rockhold FW, Broderick S, Ferguson TB Jr, Williams DO, Harrington RA, Stone GW, Rosenberg Y, ISCHEMIA Research Group. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med. 2020;382:1395–407. https://doi.org/10.1056/NEJMoa1915922.