Chapter 7
Diagnosis of Coronary Microvascular Dysfunction

Jun Takahashi and Hiroaki Shimokawa

Abstract Coronary microvascular dysfunction (CMD) has emerged as a third potential mechanism of myocardial ischemia in addition to coronary atherosclerotic disease (CAD) and epicardial coronary artery spasm. Since several studies indicated that CMD could be associated with increased risk of cardiovascular events, it is important to make correct diagnosis and assessment of CMD. However, in contrast with epicardial coronary arteries, the coronary microcirculation cannot be directly visualized in vivo with coronary angiography or intracoronary imaging technique. Although there are several non-invasive (e.g. transthoracic Doppler echocardiography, positron emission tomography, cardiac magnetic resonance imaging) and invasive (e.g. assessment of coronary flow reserve and microvascular resistance using adenosine, microvascular coronary spasm with acetylcholine) approaches for the evaluation of coronary microvascular function, all of them have several limitations. Currently, the interventional diagnostic procedure, which consists of acetylcholine testing for the detection of coronary spasm as well as coronary flow reserve and microvascular resistance assessment in response to adenosine using a coronary pressure–temperature sensor guidewire, could represent the most comprehensive coronary vasomotor evaluation. Furthermore, several biomarkers have recently attracted much attention as a diagnostic tool for CMD. Especially, plasma concentration of serotonin may be a novel biomarker to dissect CMD from epicardial coronary artery spasm. Correct diagnosis of the underlying cause of angina should enable us to stratify the treatment for distinct disorders, including CMD, vasospastic angina, and non-cardiac chest pain.

Keywords Non-invasive approach · Coronary vasoreactivity testing · Coronary flow reserve · Coronary microvascular resistance · Microvascular spasm · Biomarker

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H. Shimokawa (ed.), *Coronary Vasomotion Abnormalities*,
https://doi.org/10.1007/978-981-15-7594-5_7

7.1 Introduction

It has been reported that up to 40% of patients undergoing diagnostic coronary angiography for typical chest pain have no significant coronary stenosis [1]. The Women's Ischemia Syndrome Evaluation Study showed that there are at least 3–4 million patients in the United States alone who have signs and symptoms of myocardial ischemia with non-obstructive coronary artery disease (CAD), associated with poor quality of life, psychological distress, and health-care costs that approximate those of patients with obstructive CAD [2, 3]. In such cases, myocardial ischemia may be caused by different types of functional disorders involving the epicardial coronary arteries, coronary microcirculation or both [4]. Vasospastic angina (VSA) is one of the important functional cardiac disorders characterized by myocardial ischemia attributable to epicardial coronary artery spasm and a number of studies have elucidated patient characteristics, outcomes, and prognostic factors of VSA [5–7]. Furthermore, the Japanese Circulation Society guidelines describe the standard methods for the diagnosis of VSA in the current clinical practice based on the currently available evidence [8]. The Coronary Vasomotion Disorders International Study Group (COVADIS) also developed international standards for the diagnostic criteria of VSA [9]. Remarkably, the spasm provocation tests with ergonovine and acetylcholine employed in the catheterization laboratory have been established as a high-reliable diagnostic tool to detect functional disorder of the epicardial coronary artery [10, 11]. We also have recently demonstrated that Rho-kinase activity in circulating neutrophils is enhanced in VSA patients and is a useful biomarker for diagnosis and disease activity assessment of the disorder [12, 13]. On the other hand, coronary microvascular dysfunction (CMD) has emerged as a third potential mechanism of myocardial ischemia in addition to coronary atherosclerotic disease and epicardial coronary spasm [4, 14]. Indeed, it was demonstrated that CMD could be associated with increased risk of cardiovascular events, [15] indicating that it is important to make a correct diagnosis or assessment of CMD. However, in contrast with epicardial coronary arteries, the coronary microcirculation cannot be directly visualized in vivo with coronary angiography or intracoronary imaging technique. Thus, microvascular function is assessed indirectly, generally through measurements of coronary or myocardial blood flow (MBF) which is regulated by coronary arteriolar tone in healthy vessels, or detection of propensity to coronary vasoconstriction. A number of studies published in the past 2 decades have highlighted how abnormalities in the function and structure of the coronary microcirculation can interfere with the control of MBF, and contribute to the pathogenesis of myocardial ischemia [16]. In this chapter, we will briefly review the diagnostic methods and strategies for CMD.

7.2 Clinical Criteria for Suspecting Microvascular Angina Due to CMD

CMD could be developed by several pathological mechanisms. In 2007, Camici and Crea proposed the clinical and pathogenetic classifications of CMD (Table 7.1) [14]. From a pathophysiological point of view, and independently of the underlying mechanisms, CMD results in varying degrees of disruption of the normal coronary physiology. These alterations eventually impair the capacity of MBF to adapt to changes in myocardial oxygen demand. Indeed, CMD is typically suspected in patients with angina and nearly normal coronary angiograms. The term "microvascular angina" (MVA) typically describes myocardial ischemia triggered by CMD in the absence of CAD. Stable MVA is characterized by effort-induced symptoms similar to those observed in patients with angina triggered by obstructive CAD. However, MVA patients often have angina at rest and a variable angina threshold, suggestive of dynamic coronary vasomotor changes. CMD can result from a variable combination of abnormal vasodilatation and increased vasoconstriction caused by various stimuli of coronary microvessels (Fig. 7.1) [17]. Thus, the presence of both effort and rest angina suggests a possible coexistence of reduced coronary microvascular dilatory function and microvascular spasm [18]. Patients

Table 7.1 Classification of coronary microvascular dysfunction

	Clinical setting	Main pathogenic mechanism
Type 1: in the absence of myocardial diseases and obstructive CAD	Risk factors	SMC dysfunction
	Microvascular angina	Endothelial dysfunction
		Vascular remodeling
Type 2: in myocardial diseases	Hypertrophic cardiomyopathy	Vascular remodeling
	Dilated cardiomyopathy	SMC dysfunction
	Anderson-Fabry's disease	Extramural compression
	Amyloidosis	Luminal obstruction
	Myocarditis	
	Aortic stenosis	
Type 3: obstructive CAD	Stable angina	SMC dysfunction
	Acute coronary syndrome	Endothelial dysfunction
		Luminal obstruction
Type 4: iatrogenic	PCI	Luminal obstruction
	Coronary artery grafting	Autonomic dysfunction

CAD coronary artery disease, *SMC* smooth muscle cells, *PCI* percutaneous coronary intervention. (Reproduced from Crea et al. [14])

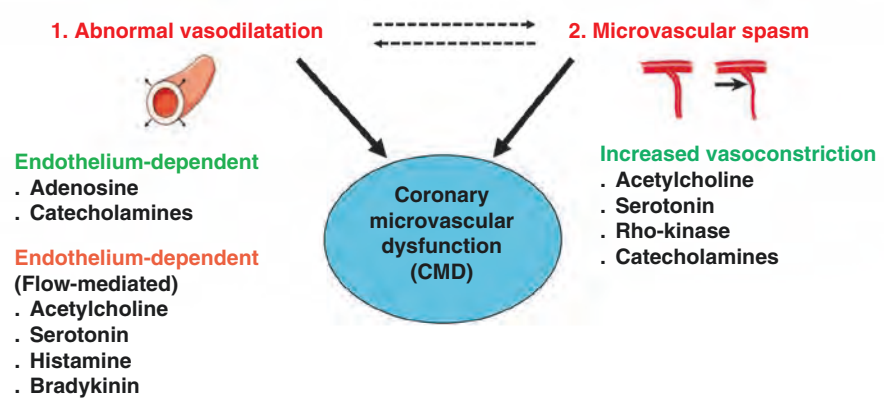

Fig. 7.1 Coronary microvascular dysfunction car result from a variable combination of abnormal vasodilatation and increased vasoconstriction caused by various stimuli

with MVA may have chest pain that can persist even after cessation of the activity [19]. Furthermore, they may not have rapid or sufficient symptom relief in response to sublingual nitroglycerin, because nitroglycerin selectively dilates larger microvessels but not arterioles [20]. Furthermore, typical and atypical chest pain does not differentiate between obstructive and non-obstructive CAD and symptom complexity may not always identify patients with CMD [21, 22]. Excluding angiographic atheroma or establishing that a stenosis has no effect on coronary physiology (e.g. normal fractional flow reserve) strongly suggests a microvascular origin of symptoms [23]. Although objective documentation of myocardial ischemia is warranted for the diagnosis of CMD, imaging modalities often give negative results despite the occurrence of ischemia. This is because, contrary to what is seen in obstructive CAD, myocardial ischemia does not follow a regional pattern in MVA and ischemia may be limited to the subendocardium in many cases [19]. Based on these clinical features of MVA, the Coronary Vasomotor Disorder Study (COVADIS) group has recently proposed the following diagnostic criteria for MVA [24]; signs and symptoms of myocardial ischemia, reduced coronary flow reserve (CFR) defined as the ratio of coronary blood flow (CBF) during near maximal coronary vasodilatation to baseline CBF, or microvascular spasm, and documented myocardial ischemia, which is not triggered by obstructive CAD but by functional or structural abnormalities at the site of the coronary microcirculation (Table 7.2). Angina occurs in approximately 30–60% of patients with CMD [22, 25–28]. Other cardinal manifestations of CMD include exertional dyspnea and possibly heart failure [29]. Patients may also manifest with a gradual decrease in exercise tolerance or dyspnea on exertion. It may represent an ischemic equivalent caused by LV diastolic dysfunction with an excessive rise in end-diastolic pressure leading to cardiopulmonary congestion. In those patients presenting with heart failure, the typical signs of elevated filling pressure, such as jugular venous distention, rales, and pedal edema, may be present.

Table 7.2 Clinical criteria for suspecting microvascular angina

1.	Symptoms of myocardial ischemia
	(a) Effort and/or rest angina
	(b) Angina equivalents (e.g. shortness of breath)
2.	Absence of obstructive CAD (<50% diameter reduction or FFR > 0.80) by
	(a) Coronary CTA
	(b) Invasive coronary angiography
3.	Objective evidence of myocardial ischemia
	(a) Ischemic ECG changes during an episode of chest pain
	(b) Stress-induced chest pain and/or ischemic ECG changes in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
4.	Evidence of impaired coronary microvascular function
	(a) Impaired coronary flow reserve (cut-off values depending on methodology use between ≤2.0 and ≤ 2.5)
	(b) Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts but no epicardial spasm during acetylcholine testing
	(c) Abnormal coronary microvascular resistance indices (e.g. IMR > 25)
	(d) Coronary slow flow phenomenon, defined as TIMI frame count >25
	CAD coronary artery disease, *CTA* computed tomographic angiography, *FFR* fractional flow reserve, *IMR* index of microcirculatory resistance, *TIMI* thrombolysis in myocardial infarction
	Definite MVA is only diagnosed if all four criteria are present
	Suspected MVA is diagnosed if symptoms of ischemia are present with non-obstructive
	CAD but only objective evidence of myocardial ischemia, or evidence of impaired coronary microvascular function alone

(Reproduced from Ong et al. [24])

7.3 Assessment for Diastolic Function of Coronary Microvasculature

Coronary microvascular function is usually assessed by measurement of coronary microvascular response to vasodilator stimuli. In many cases, the vasodilator capacity is often evaluated by CFR calculated as the ratio of CBF during maximal vasodilatation over basal CBF. Since CFR is an integrated measure of flow through both the large epicardial arteries and the coronary microcirculation, reduced CFR is a marker of CMD in the absence of obstructive stenosis of the epicardial arteries [16]. The most widely used substance to assess coronary microvascular dilator function is adenosine. Adenosine is administered at an intravenous dose of 140 μg/kg/min, as this dose has been found to achieve maximal coronary microvascular dilatation [30]. Although adenosine has possible side effects, including bradycardia due to atrioventricular or sino-atrial node blockade and bronchoconstriction, both of which are mediated by purinergic A1 receptor, relevant advantages of adenosine are its very short half-life (10 s) which enables rapid regression of side effects and repetition of the test during the same session, if necessary [31]. Another frequently used substance to assess endothelium-independent coronary microvascular dilatation is

dipyridamole, which acts by inhibiting adenosine degradation by adenosine deaminase [32]. Acetylcholine is often used as a endothelium-dependent coronary microvascular vasodilator. However, it is not the ideal substance to assess endothelium-dependent vasodilator function, since it also acts directly on smooth muscle cells (SMCs), including vasoconstriction [4]. There are several non-invasive and invasive approaches for evaluation of coronary vasodilator response, while all of them have several limitations. Although there is currently no consensus on the cut-off for the diagnosis of CMD based on imaging, a three-tiered characterization of CMD has been proposed as follows: CFR < 1.5, definite; CMD 1.5–2.6, borderline; and CMD >2.6, no CMD [33].

7.3.1 Non-invasive Techniques for Diagnosis of CMD

Transthoracic Doppler echocardiography (TTDE) can measure coronary blood flow velocity (CBFV) of the distal left anterior descending artery (LAD), which is a surrogate for CBF. CFR is measured as the ratio of peak CBFV after vasodilator to CBFV at rest in a highly reproducible fashion [34]. CFR measured by TTDE has been demonstrated to have good agreement with that measured by an intracoronary Doppler flow wire and positron emission tomography (PET) [34, 35]. Advantages of TTDE are its relatively low cost and high feasibility, but considerable intra-observer and inter-observer variability (~10%) needs to be taken into account when examining serial recordings obtained for assessing the effects of therapy [36]. Myocardial contrast echocardiography (MCE) exploits the property of intravenously administered, echogenic, gas-filled microbubbles that are similar in size and rheological properties to red blood cells [37]. MCE enables repeated, quantitative measurement of microvascular flow velocity and capillary blood volume, and provides an estimate of MBF that correlated well with that measured by PET [38]. There is a growing body of evidence that a reduced coronary flow velocity reserve index helps to identify CMD and allows risk stratification [39, 40].

PET is a well-validated technique that can provide non-invasive, accurate, and reproducible quantification of MBF and CFR in humans, and is thus used for assessment of coronary vasomotor function [41, 42]. Recent PET studies demonstrated that coronary vascular dysfunction, as defined by reduced CFR, is highly prevalent among patients with CAD, [25] increases the severity of inducible myocardial ischemia and subclinical myocardial injury, [43], and identifies patients at high risk for future cardiac events [44]. PET also has the advantage of assessing all three coronary distributions, thus allowing a more accurate assessment of microvascular dysfunction, as CMD has been shown to have a heterogenous distribution over the three vessels [45].

Cardiac magnetic resonance (CMR) has also been used to quantify myocardial perfusion following the injection of a gadolinium-based contrast agent [46]. Advantages of CMR are high spatial resolution, allowing transmural characterization of myocardial blood flow, and the lack of ionizing radiation, along with the

ability to perform a comprehensive assessment of cardiovascular structure and function. A decreased response to vasodilator is seen in the subendocardial region in CMD patients and was shown to predict prognosis [47, 48]. A gadolinium-free stress CMR approach using T1 mapping has also been recently proposed for diagnosis of myocardial ischemia with and without obstructive CAD [49].

7.3.2 *Invasive Guidewire-Based Techniques for Diagnosis of CMD*

Invasive coronary angiography, by combining the ability to exclude obstructive CAD with complementary catheter-based techniques to investigate epicardial and microvascular coronary physiology, is an attractive approach to evaluate patients with CMD [50]. It often involves an interventional procedure where a guidewire-based assessment of coronary blood flow is performed at rest and during interrogation with pharmacological probes, typically adenosine [27, 50]. The procedure is invasive by nature, requires special expertise, and can be time-consuming. However, it has been shown to be safe and effective when performed by experienced interventional operators [51]. Coronary flow reserve (CFR) reflects the ratio of hyperemic flow to basal flow and was first describe by Gould et al. in 1974 [52]. This is also termed the vasodilator capacity and reflects the ability of the coronary circulation to augment blood flow from rest. CFR is calculated using thermodilution as the resting mean transit time divided by hyperemic mean transit time, and an abnormal CFR is defined as ≤ 2 (Fig. 7.2) [25, 53]. Importantly, decreased CFR is associated with increased risk of MACE [15]. CFR reflects the combined vasodilator capacity of the epicardial coronary artery and its subtended microvasculature. Thus, there are some limitations for the use of invasively measured CFR due to its sensitivity to systemic hemodynamics, myocardial contractility, and challenges with establishing true resting coronary blood flow during invasive coronary angiography [54]. Specific

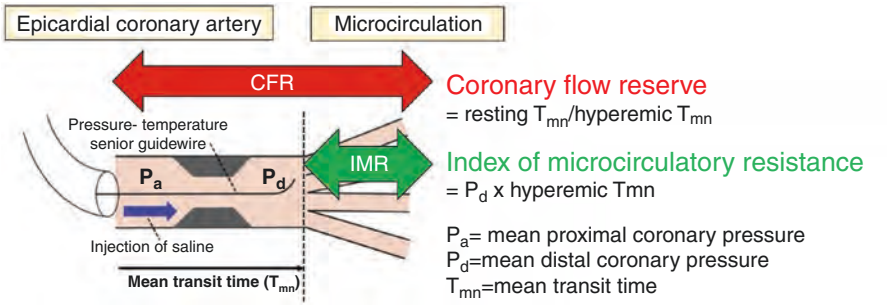

Fig. 7.2 To evaluate relaxation of the coronary artery, a guidewire-based assessment of coronary blood flow is performed at rest and during interrogation with pharmacological probes, typically adenosine. *CFR* coronary flow reserve, *IMR* index of microcirculatory resistance

measures of microvascular resistance are more reproducible and specific and are directly informative about microvascular disease [55]. Index of microvascular resistance (IMR) is calculated as the distal coronary pressure divided by the inverse of the mean transit time during maximal hyperemia [56]. It can be measured by the use of a combined pressure-temperature sensor-tipped coronary guidewire, which allows simultaneous measurement of coronary pressure and hyperemic flow (Fig. 7.2). Increased IMR (e.g. ≥25) is representative of CMD and is associated with worse cardiovascular outcomes [57, 58]. Here is the standard measurement technique of IMR [59]. Briefly, systemic administration of heparin (50 ~ 100 IU/kg) and intracoronary nitroglycerin (100 ~ 200 μg) is necessary before measuring IMR. A coronary pressure–temperature sensor guidewire is calibrated, equalized to the guide catheter pressure with the pressure sensor positioned at the tip of the catheter, and advanced to the distal two thirds of the target vessel. For an accurate thermodilution measurement, the sensor needs to be at least 6 cm into the coronary artery. A three-way stopcock and 3-mL syringe are connected to the back of the manifold. The guide catheter is flushed with saline, clearing all contrast, and an operator should pause for a minute to allow coronary flow to return to baseline. If the operator intends to calculate CFR also, then 3 mL of room-temperature saline is briskly injected through the guide catheter under resting conditions, and the console automatically calculates the mean transit time (T_{mn}) at rest. After making the resting measurement, hyperemia is induced by either infusing intravenous adenosine (140 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or by injecting intracoronary papaverine (10 ~ 20 mg). During maximal hyperemia, 3 mL of room-temperature saline is briskly injected through the guide catheter, and the hyperemic T_{mn} (T_{mn}Hyp) is measured again as described above. The system allows the operator to examine the T_{mn} curve and calculated time; if the operator is not happy, the value can be replaced with another injection. In some cases, variability in the T_{mn} values can occur, particularly if the guide catheter is moving out of the coronary ostium during saline injection. If all 3 T_{mn} values are <0.25%, then the variability can be ignored because in most cases, IMR will be in the normal range. If T_{mn} is >0.25% and ([the maximum individual T_{mn} value minus the minimum T_{mn} value]/the maximum T_{mn} value×100%) >30%, then the T_{mn} value that is furthest from the mean T_{mn} should be replaced. P_d is measured simultaneously with the same pressure wire during maximal hyperemia, and IMR is calculated as P_d multiplied by T_{mn}Hyp [60].

7.4 Objective Documentation of Coronary Microvascular Spasm

Primary reduction of coronary blood flow caused by spasm of coronary small arteries or arterioles may be the cause of angina at rest. This hypothesis is supported by the careful observations of patients with syndrome X which demonstrated that angina and ischemic ST shift were not always preceded by increments in heart rate [61]. Sinus tachycardia that had caused ischemia during exercise

testing did not develop chest pain or ECG change in most instances [61]. The variable threshold for angina symptoms during daily life suggests the presence of circadian variations in vasomotor tone and small vessel hyperconstriction [62]. Mohri et al. prospectively examined a cohort of 117 patients with angina (mostly at rest) and normal or minimally diseased epicardial coronary arteries. In 25% of the patients studied, no epicardial spasm was demonstrated during angina attack on selective coronary arteriography [63]. Chest pain which was similar to patients' previous ones developed in association with ischemic ECG changes and lactate production (an objective marker of myocardial ischemia) spontaneously or following intracoronary acetylcholine. In these patients, the pressure-rate product (an index of myocardial oxygen demand) was comparable between at rest and at the onset of angina. Thus, the decrease in coronary blood flow, rather than increased myocardial oxygen consumption, was a likely explanation for myocardial ischemia. This study suggests that coronary microvascular spasm is the cause of chest pain in a subset of patients with rest angina and normal epicardial coronary arteries. Microvascular constriction and myocardial ischemia as evidenced by ECG change were also provoked by intracoronary infusion of a peptide neurotransmitter, neuropeptide Y [64].

Acetylcholine provocation test should be performed following the guidelines of the Japanese Circulation Society [8]. Briefly, ACh was administered into the coronary artery in a cumulative manner (20, 50, and 100 μg) with careful monitoring of arterial pressure and 12-lead ECG and serial coronary angiograms at 1-min intervals. Calcium channel blockers, long-acting nitrates, and nicorandil need to be discontinued at least 48 h before the provocation test. To determine whether multivessel coronary spasm would develop, the authors first perform ACh provocation test for the LCA in a cumulative manner (20, 50, and 100 mg). If the test for the LCA is negative or ACh-induced spasms in the LCA resolves spontaneously, ACh is then injected into the right coronary artery in a cumulative manner (20 and 50 mg). When coronary spasm is induced, 5 mg of isosorbide dinitrate (ISDN) is injected into the responsible coronary artery. Additionally, to evaluate the presence of coronary microvascular spasm, lactate production during myocardial ischemia induced by ACh provocation test is recommended. Myocardial lactate extraction ratio is calculated as the ratio of the coronary arterial–venous difference in lactate concentration to the arterial concentration. Myocardial lactate production defined by negative myocardial lactate extraction ratio is considered to be highly sensitive to myocardial ischemia [65]. Microvascular spasm (MVS) is defined as myocardial lactate production despite the absence of angiographically demonstrable epicardial spasm throughout ACh provocation test or prior to the occurrence of epicardial coronary spasm following intracoronary injections of ACh [66]. At 1 min after each dose of ACh is given to LCA, paired samples of 1 mL of blood are collected from the left coronary ostium and the coronary sinus for measurement of lactate concentrations, which are immediately determined with a calibrated automatic lactate analyzer. We usually evaluate lactate production during ACh provocation test only in the LCA, as the great coronary sinus drains blood from the LCAs but not from the right coronary artery.

7.5 Biomarkers of Coronary Microvascular Dysfunction

The causes of CMD appear to be heterogeneous [14, 17]. Classical coronary risk factors are associated with impaired coronary microvascular dilatation and enhanced coronary microvascular constriction [67]. Recently, low-grade inflammation attracts much attention in the pathogenesis of CMD, as CRP levels correlate with the frequency of angina attacks and impairment of coronary microvascular dilatation in patients with syndrome X [68]. Although the importance of CMD has been emerging, reliable biomarkers for CMD still remain to be developed. Serotonin is released from aggregating platelets, causing vasoconstriction and platelet aggregation with cyclic flow reduction [69]. Several clinical studies previously addressed the relationship between systemic serotonin concentrations and coronary vasomotor dysfunction in a small number of patients with inconsistent results [70, 71]. We examined the potential usefulness of plasma concentration of serotonin to diagnose CMD [72]. CMD was defined as myocardial lactate production without or prior to the occurrence of epicardial coronary spasm during acetylcholine provocation test. Although no statistical difference in plasma concentration of serotonin [median (inter-quartile range) nmol/L] was noted between the vasospastic angina (VSA) and non-VSA groups, it was significantly higher in patients with MVS compared with those without it (Fig. 7.3). Among the four groups classified according to the

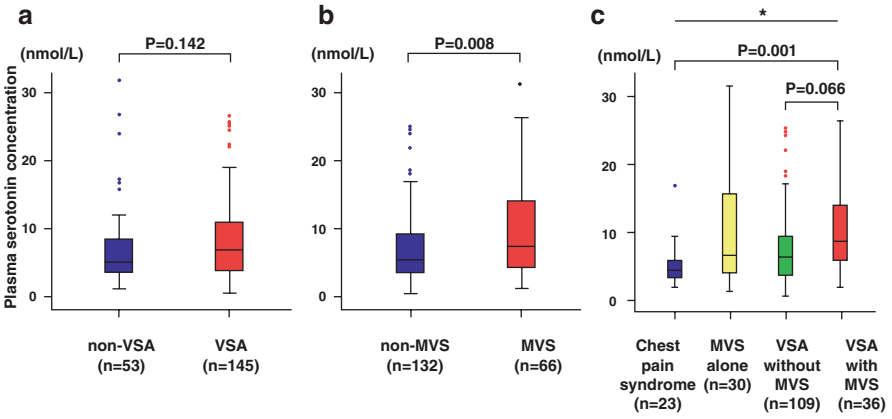

Fig. 7.3 (**a**) Plasma concentrations of serotonin were compatible between the VSA and the non-VSA groups. Results are expressed as box-and-whisker plots; the central box covers the interquartile range, with the median indicated by the line within the box. The whiskers extend to the most extreme values within 1.5 interquartile ranges. More extreme values are plotted individually. (**b**) Plasma concentrations of serotonin were higher in patients with MVS than in those without it. (**c**) Plasma serotonin concentrations of the four groups classified according to the presence or absence of VSA and MVS are shown. The serotonin concentrations were significantly higher in the VSA with MVS group than in the chest pain syndrome group by Steel-Dwass test. $*P < 0.01$ for the difference in plasma concentrations of serotonin among the four groups by Kruskal-Wallis test. *VSA* vasospastic angina, *MVS* coronary microvascular spasm. (Reproduced from Odaka et al. [72])

presence or absence of VSA and MVS, serotonin concentration was highest in the VSA with MVS group (Fig. 7.3). Importantly, there was a positive correlation between plasma serotonin concentration and baseline TIMI frame count, a marker of coronary vascular resistance [73]. The classification and regression trees analysis showed that plasma serotonin concentration of 9.55 nmol/L was the first discriminator to stratify the risk for the presence of MVS. In multivariable analysis, serotonin concentration greater than the cut-off value had the largest odds ratio in the prediction of MVS [73]. These results suggest that plasma concentration of serotonin may be a novel biomarker to dissect MVS from epicardial coronary artery spasm.

7.6 Comprehensive Evaluation of the Coronary Functional Abnormalities

Although the importance of coronary functional abnormalities (epicardial coronary spasm and CMD) in patients with chest pain and non-obstructive CAD has been emerging, their pathogenesis and prognostic implications remain to be fully elucidated. Lee et al. showed that integration of microvascular assessment by both CFR and IMR can improve the accuracy of prognostic prediction for patients with high FFR; however, no attention was paid to epicardial coronary spasm [58]. Recent studies demonstrated that VSA is frequently noted in Caucasian patients with chest pain and non-obstructive CAD and those with acute myocardial infarction and non-obstructive CAD than ever thought [74, 75]. Thus, attention should always be paid to possible involvement of epicardial coronary spasm in patients with chest pain and non-obstructive CAD. Thus, we examined the significance of coronary functional abnormalities in a comprehensive manner for both epicardial and microvascular coronary arteries in patients with angina and non-obstructive CAD [76]. Recently, the combined invasive assessment of coronary vasoconstrictor as well as vasodilator abnormalities has been titled interventional diagnostic procedure (IDP) [50, 77]. When examining patients with chest pain and non-obstructive CAD, we routinely performed intracoronary ACh testing for detection of coronary spasm as well as coronary flow reserve and microvascular resistance assessment in response to adenosine using a coronary pressure–temperature sensor guidewire. Then, we prospectively enrolled consecutive patients, who underwent ACh provocation test for coronary spasm and measurement of IMR to evaluate coronary microvascular function, and followed them. Multivariable analysis revealed that IMR correlated with the incidence of cardiac events and receiver-operating characteristics curve analysis identified IMR of 18.0 as the optimal cut-off value. Importantly, there were substantial overlaps of coronary functional abnormality in various combinations among VSA, low CFR (CFR < 2.0), and high IMR (IMR ≥ 18) (Fig. 7.4). Among the four 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 (Fig. 7.5). Importantly, intracoronary administration of fasudil, a Rho-kinase inhibitor, significantly

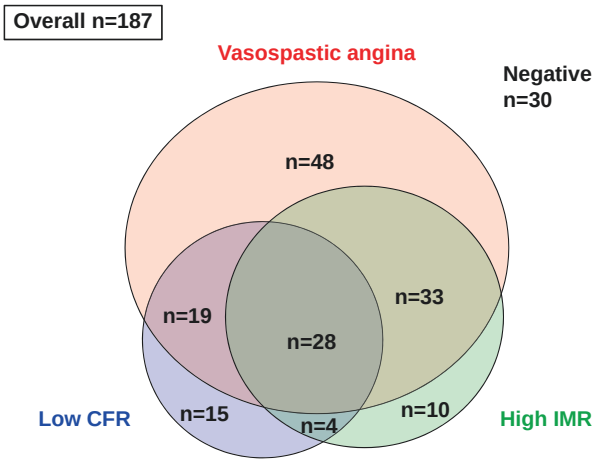

Fig. 7.4 Among 187 patients, 128 (68.4%) were diagnosed as having VSA by ACh provocation test. Furthermore, 66 (35.3%) had low CFR (CFR < 2.0) and 75 (40.1%) high IMR (IMR ≥ 18). Thus, more than half of VSA patients had microvascular functional abnormalities, including low CFR ($n = 19$, 10.2%), high IMR ($n = 33$, 17.6%), and both of them ($n = 28$, 15.0%). *CFR* coronary flow reserve, *IMR* index of microcirculatory resistance, *VSA* vasospastic angina. (Reproduced from Suda et al. [76])

ameliorated IMR in the VSA patients with increased IMR. These results indicate that in patients with angina and non-obstructive CAD, coexistence of epicardial coronary spasm and increased microvascular resistance is associated with worse prognosis, for which Rho-kinase activation may be involved. Thus, comprehensive assessment of coronary functional abnormalities, including epicardial coronary spasm and increased microvascular resistance, could be useful for risk stratification of patients with angina and non-obstructive CAD. Furthermore, Rho-kinase inhibition with fasudil may be useful for the treatment of those coronary functional abnormalities.

There is a critical missing link between the use of relevant diagnostic tests of coronary artery function and therapeutic agents with proven efficiency and health outcomes of patients with angina without obstructive CAD. This gap in evidence was recently addressed in CORonary MICrovascular Angina randomized controlled trial (CorMicA), which tested whether an IDP linked to stratified medicine improves health status in patients with ischemia but non-obstructive CAD [77]. CorMicA trial demonstrated that vasoreactivity testing with ACh and measurement of CFR and IMR can be used to guide medication therapy in patients without non-obstructive CAD. Moreover, the stratified medical therapy leads to marked and sustained angina improvement and better quality of life at 1 year following invasive coronary angiography [78]. Based on these results of CorMicA, it was suggested that the IDP could provide the most comprehensive coronary vasomotor assessment.

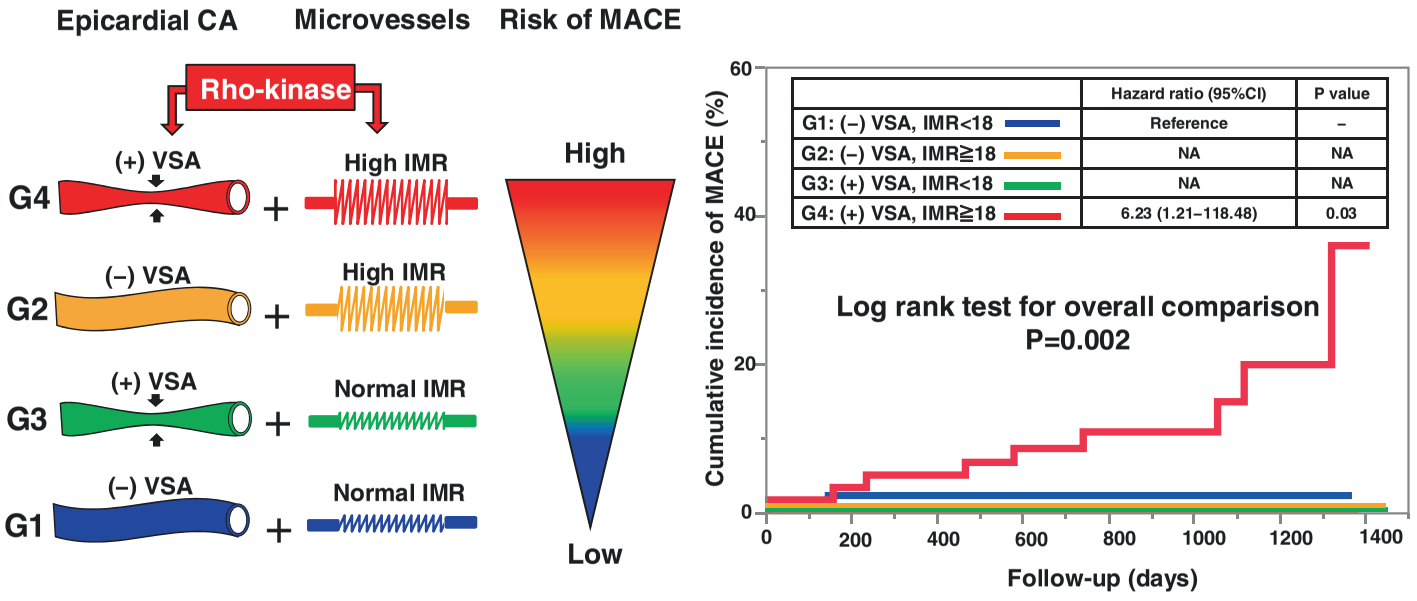

Fig. 7.5 In patients with chest pain and unobstructive CAD, coexistence of VSA (epicardial coronary spasm) and high IMR (microvascular resistance) is associated with worse prognosis, for which Rho-kinase activation may be involved. *CA* coronary artery, *IMR* index of microcirculatory resistance, *VSA* vasospastic angina. (Reproduced from Suda et al. [76])

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