Chapter 4
Treatment of Coronary Artery Spasm

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Abstract 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 in Asia and Western countries. In the era of widespread utilization of drug-eluting stents (DES) in the field of coronary intervention, it is important to realize the fact that patients still have unremitting angina symptoms even after resolving organic coronary stenosis with DES implantation. Although conventional management of VSA involves lifestyle modifications, use of established pharmacological therapies, further novel therapies need to be developed. Basic and clinical evidence also has been accumulated for elucidating the risk to predict future cardiovascular events, detailed mechanism of coronary artery spasm, which in turn, provides new therapeutic approach for coronary spasm. In this chapter, we will summarize the recent advances in the treatment of coronary artery spasm mainly based on our findings.

Keywords Coronary artery spasm · Vasospastic angina · Life style · Calcium channel blockers · Nitrates · Rho-Kinase inhibitors · Fasudil · Inflammation

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4.1 Importance of Treatment of Coronary Artery Spasm Worldwide

Coronary artery spasm plays an important role in a wide variety of ischemic heart disease, not only in VSA but also in other forms of angina pectoris, myocardial infarction, and sudden death [1]. Although it has been believed for a long time that VSA is more common in Asian than in Western populations [2, 3], recent studies from Germany revealed that the prevalence of VSA in Caucasians may be higher than what we expected [4, 5]. We also have recently addressed the ethnic differences in the long-term prognosis by comparing 1339 Japanese and 118 Caucasians VSA patients [6]. Multivessel spasm was more prevalent in Japanese, whereas provocation-related arrhythmias were more common in Caucasians. In the multivariable analysis, the Japanese Coronary Spasm Association (JCSA) risk score, including the number of coronary arteries positive for spasm provocation tests, was found to show good correlations with major adverse cardiac event (MACE) rates in both Japanese and Caucasian patients. Thus, these findings indicate the clinical importance of the treatment of VSA worldwide.

4.2 Management of Coronary Artery spasm

Management of VSA includes lifestyle modifications, use of pharmacological therapies, and non-pharmacological approaches [1, 7]. It is important to document suppression of both symptomatic and asymptomatic episodes with ambulatory ECG monitoring [7]. Risk stratification of future cardiovascular events in VSA patients is also important [8]. Treatment of VSA reduces the frequency of symptomatic episodes and appears to decrease the frequency of serious complications [7]. Associated with decreased disease activity and symptoms, biomarkers and cardiac images are also useful [9, 10].

4.2.1 Lifestyle Modifications for Risk Factors

We previously demonstrated that inflammatory stimuli causes upregulation of Rho-kinase leading to coronary artery spasm [11]. Notably, cigarette smoking has been shown to cause low-grade inflammation [12], which may also cause coronary spasm. Since smoking cessation removes one of the triggers for VSA and leads to a significant decrease in the frequency of episodes, at least in a short term, it should be encouraged [13]. Avoiding other risk factors for VSA, such as mental stress [14], alcohol consumption [15], and the use of pharmacological agents, such as cocaine [16], is also important in VSA patients. Indeed, we previously demonstrated that

sustained elevation of serum cortisol level sensitizes coronary arteries to cause hyperconstricting responses through Rho-kinase activation in pigs in vivo, suggesting the link between stress and coronary artery spasm [17].

4.2.2 Pharmacotherapy

Calcium Channel Blockers

Calcium channel blockers (CCBs) are the first-line therapy for VSA [7]. Indeed, CCBs effectively inhibit vasoconstriction and promote vasodilation of the coronary vasculature, thereby alleviating symptoms. Previous study demonstrated that the use of CCBs was an independent predictor of myocardial infarct-free survival in VSA patients [18].

In the era of coronary intervention with DES, it is important to realize the fact that patients have unremitting angina symptoms even after resolving organic coronary stenosis with DES implantation [19]. We have demonstrated that a first-generation DES cause coronary hyperconstricting responses in pigs in vivo in response to intracoronary serotonin at the segments proximal or distal to the DES edge, compared with its platform bare-metal stents (BMS) and that activation of Rho-kinase pathway, a molecular switch for vascular smooth muscle contraction, is involved in its pathogenesis [20]. More recently, we conducted a multicenter randomized control study that showed that even the everolimus-eluting stents, most widely disseminated DES, were able to induce coronary hyperconstricting responses at 8–10 months after DES implantation [21]. Intriguingly, nifedipine, a long-acting CCB, was able to suppress DES-induced coronary hyperconstricting responses in humans [21]. We and others also demonstrated that among the 4 major CCBs (benidipine, amlodipine, nifedipine, and diltiazem) that effectively suppress VSA attacks in general, benidipine showed the most beneficial prognostic effects than others [22, 23]. Taken together, CCBs are useful for the treatment of VSA patients with or without DES implantation.

Nitrates and Nicorandil

Long-acting nitrates are also effective in alleviating symptoms [7], although the potential nitrate tolerance makes them a less desirable first-line approach. Indeed, we addressed this important issue on the long-term efficacy of nitrate therapy in VSA patients [24]. In this study with 1429 patients with VSA, of whom more than 90 percent were receiving treatment with a CCB, a propensity score-matched analysis found that the cumulative incidence of MACE (cardiac death, nonfatal myocardial infarction, hospitalization due to unstable angina or heart failure, and appropriate implantable cardioverter-defibrillator shocks) was similar between patients with nitrate treatment and those without it (11 vs. 8% at 5 years; hazard ratio [HR] 1.28,

95% CI 0.72–2.28) [24]. Although nicorandil, one of the nitrate-like agents used in the study, had a neutral effect on clinical events (HR: 0.80; 95% CI 0.28–2.27), multivariable analysis showed a deleterious effect of the concomitant use of nitrates and nicorandil (HR 2.14; 95% CI 1.02–4.47). Thus, the long-term administration of nitrates may not improve prognosis in VSA patients who receive CCB treatment. In addition, the concomitant use of more than one nitrate formulation may increase the risk for MACE in those patients.

Rho-Kinase Inhibitors

Accumulating evidence indicates that Rho-kinase is substantially involved in the pathogenesis of coronary spasm in animals and in humans [1]. Indeed, intracoronary administration of fasudil and of hydroxyfasudil, selective Rho-kinase inhibitors, markedly inhibits coronary spasm in a porcine model with long-term treatment with IL-1β [25–27]. Importantly, the inhibition of Rho-kinase with fasudil/hydroxyfasudil was associated with the suppression of enhanced MLC phosphorylations (both MLC mono- and diphosphorylations) at the spastic coronary segments in this model [25, 26]. Subsequently, it was demonstrated that the expression and activity of Rho-kinase are enhanced at the IL-1β-induced inflammatory coronary lesions, thereby suppressing MLCPh through phosphorylation of its MBS with resultant increase in MLC phosphorylations and coronary spasm [28]. This is also the case for the hypercontractions of isolated arteriosclerotic human arteries [29].

We then demonstrated that in VSA patients, intracoronary fasudil also markedly inhibits acetylcholine-induced coronary spasm and related myocardial ischemia, demonstrating that Rho-kinase is substantially involved in the pathogenesis of coronary spasm in humans (Fig. 4.1) [30]. Severe coronary artery spasm after coronary artery bypass grafting (CABG) remains a serious complication of the surgery as it eventually results in circulatory collapse and/or death [31]. We also showed that the treatment with fasudil is useful to treat intractable and otherwise fatal coronary spasm resistant to intensive conventional vasodilator therapy after CABG (Fig. 4.2) [32]. We further conducted a clinical trial for anti-anginal effects of fasudil in patients with stable effort angina, which demonstrated that the long-term oral treatment with the Rho-kinase inhibitor is effective in ameliorating exercise tolerance in patients with adequate safety profiles [33]. Approximately half of VSA patients show abnormal responses to exercise stress tests [34]. These findings suggest that inappropriate coronary vasoconstriction may be involved even in the pathogenesis of effort angina that is effectively suppressed by Rho-kinase inhibitors.

DES-induced coronary vasomotion abnormalities even after successful PCI remains to be overcome [19]. We experienced a patient who suffered from an out-of-hospital cardiac arrest at 65 months after a sirolimus-eluting stent (first-generation DES) implantation [35]. Spasm provocation test using acetylcholine showed coronary spasm at the DES edges, whereas intracoronary pretreatment of Rho-kinase inhibitor, fasudil, markedly attenuated acetylcholine-induced vasoconstriction [35]. We also demonstrated that pretreatment with fasudil suppresses

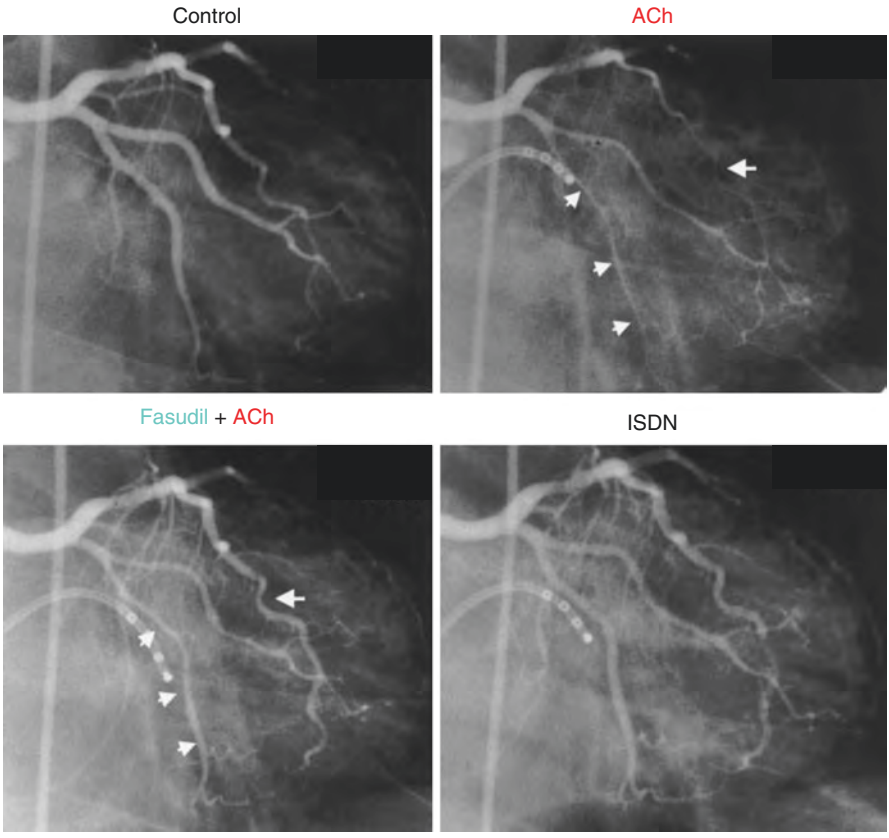

Fig. 4.1 Inhibitory effect of fasudil on coronary artery spasm. Top left, Baseline angiogram. Top right, The first ACh challenge provoked severe coronary spasm at the mid-portion of the left anterior descending coronary artery (large arrow) and diffuse spasm along the left circumflex coronary artery (small arrows). Bottom left, No epicardial spasm was provoked during the second challenge after pretreatment with fasudil. Bottom right, Angiogram after treatment with intracoronary isosorbide dinitrate (ISDN). (Reproduced from Masumoto et al. [30])

acetylcholine-induced coronary hyperconstricting responses in patients with DES implantation (Fig. 4.3) [36]. Taken together, Rho-kinase inhibitors are effective and promising drugs for the treatment of coronary artery spasm [1, 7].

Statins and Magnesium

In 64 patients who received CCB therapy, the percentage of ACh-induced coronary spasm was significantly lower in the group who received fluvastatin (30 mg/day) compared with those without it (48 vs. 79%) [37]. Magnesium deficiency may also play a role in coronary artery spasm [38]. In the previous study with 22 VSA patients, those who received intravenous magnesium (n = 14) showed coronary

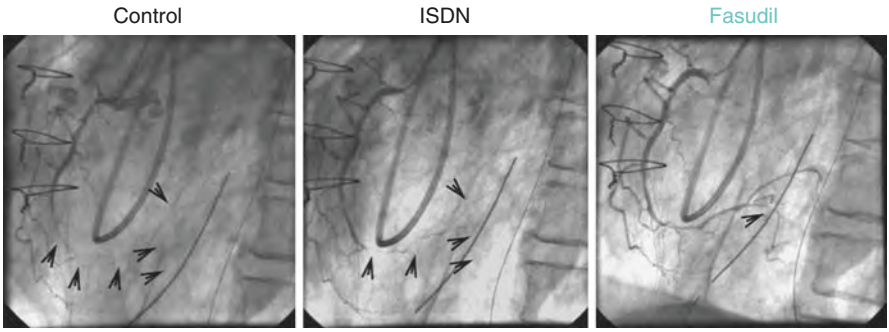

Fig. 4.2 Inhibitory effect of fasudil on intractable coronary spasm after CABG. Right coronary angiography of a patient with intractable coronary spasm after CABG. Black arrows indicate the spastic segments. Control, ISDN, and Fasudil indicate angiograms under control conditions, after intracoronary administration of isosorbide dinitrate (ISDN), and after fasudil, respectively. (Reproduced from Inokuchi et al. [32])

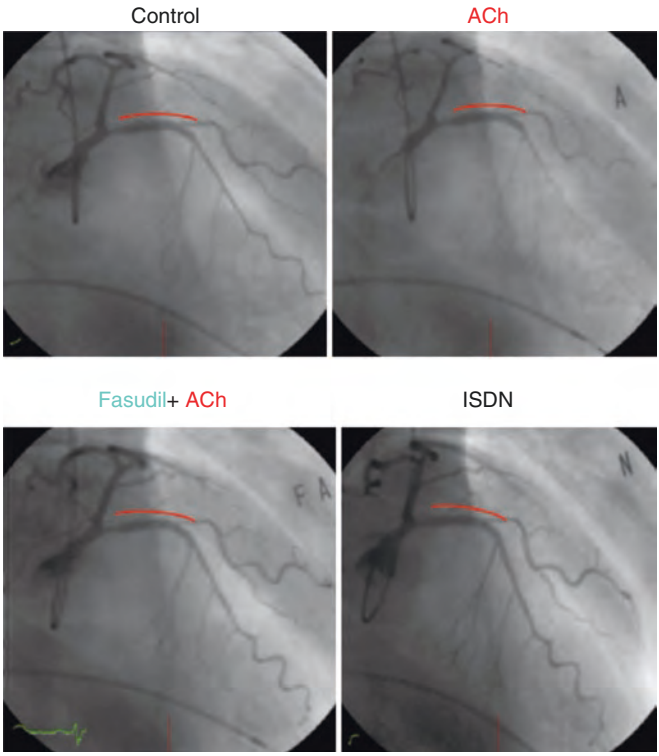

Fig. 4.3 Inhibitory effect of fasudil on drug-eluting stent-induced coronary hyperconstricting responses. *Top left*, Baseline angiogram. *Top right*, The first ACh challenge provoked severe coronary spasm at the mid-portion of the left anterior descending coronary artery (large arrow) and diffuse spasm along the left circumflex coronary artery (small arrows). *Bottom left*, No epicardial spasm was provoked during the second challenge after pretreatment with fasudil. *Bottom right*, Angiogram after treatment with intracoronary isosorbide dinitrate (ISDN). Red lines indicate the site of first-generation drug-eluting stent (Cypher™) implantation. (Reproduced from Aizawa et al. [36])

vasodilation compared with those with placebo (n = 8) [39]. Rechallenged intracoronary acetylcholine provocation tests also showed that they had less severe chest pain and ST-segment elevation. Further large studies are required to assess clinical outcomes before we recommend routine use of statins or magnesium for VSA patients.

4.2.3 Non-pharmacological Treatment

Novel non-pharmacological management of coronary vasomotion abnormalities includes, as we have recently demonstrated, catheter-based renal denervation (RDN) [40], improvement of DES polymers [41], exercise training [42], and a noninvasive low-intensity pulsed ultrasound (LIPUS) therapy [43].

The adventitia harbors a variety of components that potently modulate vascular tone, including sympathetic nerve fibers (SNF) and vasa vasorum [40]. Catheter-based RDN inhibits sympathetic nerve activity. Thus, we examined whether RDN suppresses drug-eluting stent-induced coronary hyperconstricting responses, and if so, what mechanisms are involved [40]. Pigs implanted with everolimus-eluting stents were randomly assigned to the RDN or sham group. The RDN group underwent renal ablation. At 1 month, RDN significantly caused marked damage of the SNF at the renal arteries without any stenosis, thrombus, or dissections. Notably, RDN significantly upregulated the expression of α_2-adrenergic receptor-binding sites in the nucleus tractus solitaries of the brain stem, attenuated muscle sympathetic nerve activity, and decreased systolic blood pressure and plasma renin activity. In addition, RDN attenuated coronary hyperconstricting responses to intracoronary serotonin at the proximal and distal stent edges associated with decreases in SNF and vasa vasorum formation, inflammatory cell infiltration, and Rho-kinase expression/activation. Furthermore, there were significant positive correlations between SNF and vasa vasorum and between SNF and coronary vasoconstricting responses. These results provide the first direct evidence that RDN ameliorates drug-eluting stent-induced coronary hyperconstricting responses in pigs in vivo through the kidney–brain–heart axis (Fig. 4.4) [40].

Recent studies have reported unremitting angina due to coronary vasomotion abnormalities even after successful DES implantation [19]. However, it remains to be elucidated which component of DES (metal stent, polymer coating, or antiproliferative drug) is responsible for DES-induced coronary hyperconstricting responses. We developed poly-dl-lactic acid and polycaprolactone (PDLLA-PCL) copolymer technology with higher biocompatibility that is resorbed within 3 months [41]. Four types of coronary stents were made; (1) a stent with polylactic acid (PLA) polymer coating containing antiproliferative drug (P1+ D+), (2) a stent with PLA polymer coating alone without any drug (P1+ D−), (3) a stent with novel PDLLA-PCL polymer coating alone (P2+ D−), and (4) a bare-metal stent (P−D−). These 4 stents were randomly deployed in the left anterior descending and left circumflex coronary arteries in 12 pigs. After 1 month, coronary vasoconstriction in response to

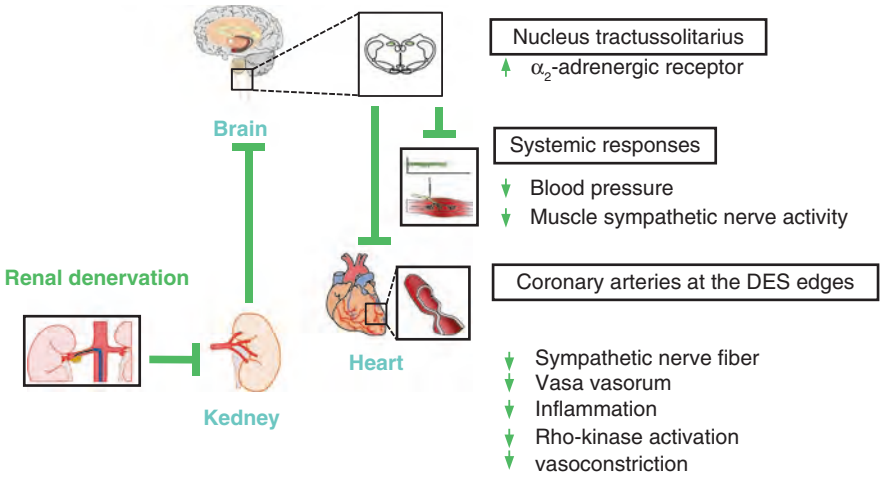

Fig. 4.4 Renal denervation as a potential novel therapeutic option for refractory coronary artery spasm. Bilateral renal denervation (RDN) ameliorates coronary hyperconstricting responses after DES implantation in pigs in vivo through suppression of the kidney–brain–heart axis, including suppressions of coronary adventitial sympathetic nerve fiber, vasa vasorum formation, inflammation, and Rho-kinase activation, suggesting that RDN is a novel therapeutic option for refractory angina. (Reproduced from Uzuka et al. [40])

intracoronary serotonin was enhanced at P1+ D+ and P1+ D− stent edges compared with P2+ D− and P−D− stent edges and was prevented by a specific Rho-kinase (a central molecule of coronary spasm) inhibitor, hydroxyfasudil. Immunostainings showed that inflammatory changes and Rho-kinase activation were significantly enhanced at P1+ D+ and P1+ D− sites compared with P2+ D− and P−D− sites. There were significant positive correlations between the extent of inflammation or Rho-kinase expression/activation and that of coronary vasoconstriction. These results indicate the causative roles of PLA polymer coating in DES-induced coronary vasoconstricting responses through inflammatory changes and Rho-kinase activation in pigs in vivo, which could be ameliorated by PDLLA-PCL copolymers (Fig. 4.5) [41].

Coronary vasomotion abnormalities could develop in both epicardial coronary arteries and intramuscular coronary microvessels. We thus examined whether vasodilator capacity of coronary microvessels is impaired in VSA patients and if so, whether exercise training could ameliorate vasodilator capacity of coronary microvessels, exercise tolerance, and angina symptoms on the top of CCB. Exercise training is effective for VSA patients in terms of improved vasodilator capacity of coronary microvessels, exercise tolerance, and angina symptoms even on the top of CCB [42].

However, a direct therapeutic approach to the coronary adventitia remains to be developed. We have developed a noninvasive, low-intensity pulsed ultrasound (LIPUS) therapy for angina, which exerts angiogenic and anti-inflammatory effects

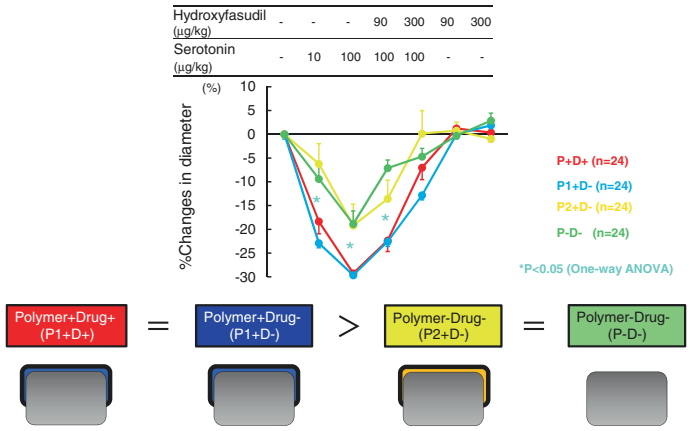

Fig. 4.5 Inhibitory effect of a novel polymer coating on coronary vasoconstricting responses at 1 month after stent implantation in pigs in vivo. Results of quantitative coronary angiography for coronary vasoconstricting response to serotonin (10 and 100 μg/kg IC) before and after hydroxyfasudil (90 and 300 μg/kg IC) at 1 month after stent implantation. Coronary vasoconstricting responses to serotonin were equally enhanced at the P1 + D+ and P1 + D− stent edges compared with the P2 + D− and P − D− stent edges. These responses were all prevented by pretreatment with hydroxyfasudil. The 4 different stents, P1 + D+, P1 + D−, P2 + D−, and P − D− (6 each), were randomly implanted in the LAD and LCX in 12 miniature pigs. At 1 month after stent implantation, animals underwent follow-up coronary angiography to assess coronary vasomotion in vivo and were then euthanized for histological and immunohistological analyses of the inflammation and expression/activity of Rho-kinase. IC = intracoronary; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; P − D− = stent without a polymer or a drug; P1 + D+ = stent with a polylactic acid polymer and a drug; P1 + D− = stent with a polylactic acid polymer but without a drug; P2 + D− stent with a poly-dl-lactic acid and polycaprolactone copolymer but without a drug; PDLLA-PCL = poly-dl-lactic acid and polycaprolactone; PLA = polylactic acid. Results are expressed as mean ± SEM. (Reproduced from Nishimiya et al. [41])

through improved coronary microcirculation. We were able to develop a noninvasive LIPUS therapy for coronary functional abnormalities caused by chronic adventitial inflammation in pigs in vivo [43].

Percutaneous coronary intervention (PCI) is not routinely indicated for patients with focal spasm and minimal obstructive disease [7]. Coronary artery spasm and lethal ventricular arrhythmias are important causes of out-of-hospital cardiac arrest (OHCA) [44]. Optimal therapy for patients resuscitated from OHCA who are not found to have structural heart disease remains to be established. In 47 consecutive OHCA survivors without structural heart disease who had fully recovered (M/F 44/3, 43 ± 13 years), we performed dual induction tests, including acetylcholine provocation test first followed by programmed ventricular stimulation after 1–2 weeks. Patients with positive coronary spasm were treated with CCB-based anti-anginal medications, and implantable cardioverter-defibrillators (ICDs) were

implanted in all patients [44]. Among OHCA survivors without structural heart disease, provokable coronary spasm and ventricular arrhythmias are common and can be seen in Brugada syndrome. No ventricular fibrillation episodes were noted in the spasm-alone patients who did not also have Brugada syndrome. Thus, patients with coronary spasm alone without Brugada syndrome may be a lower-risk group [44]. Importantly, placement of an ICD was not associated with improved survival in patients with variant angina and OHCA [45]. Thus, although there are no current guidelines for patients with VSA among OHCA survivors, an ICD should be considered based on the presence or absence of Brugada syndrome [44].

4.3 Usefulness of JCSA Risk Score for Risk Stratification of Future Cardiovascular Events

A landmark study from the JCSA registry developed the JCSA risk score that can provide comprehensive risk assessment and prognostic stratification for VSA patients [8]. A total of 7 variables, including history of OHCA (4 points), smoking, rest angina alone, organic coronary stenosis, multivessel spasm during the spasm provocation tests (2 points per each), ST-segment elevation during angina, and β-blocker use (1 point per each) were chosen for the JCSA score. Of note, MACE were incrementally documented in line with the low-risk, intermediate-risk, high-risk (2.5%, 7.0% and 13.0%, $P < 0.001$). Among the 3 risk groups, clear prognostic utility of the JCSA scoring system for MACE was confirmed throughout the follow-up period. Thus, JCSA risk score is useful for the treatment and assessment of the risk stratification of future cardiovascular events in VSA patients [8].

4.4 Biomarkers and Cardiac Imaging as a Treatment Efficacy for Coronary Artery Spasm

We previously demonstrated 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 disorder and the disease activity [9]. In this study, Rho-kinase activity in circulating neutrophils was expressed as the ratio of phosphorylated MBS (p-MBS) to total MBS (t-MBS). A p-MBS ratio of 1.18 was identified as the best cutoff level to predict the diagnosis of VSA. The Rho-kinase activity was found to show the association with the severity of angina symptoms, and was able to

correspond to the significant reduction in the disease activity after medical treatment. When we divided 174 VSA patients into 2 groups by a cutoff value (1.20), VSA patients with higher Rho-kinase activity (≥1.20) had significantly worse prognosis [46]. 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. Of note, combination of Rho-kinase activity with the JCSA risk score dramatically improved the prognostic impact in VSA patients as compared with either alone [46].

We previously demonstrated that chronic inflammatory changes in the coronary adventitia play roles in the pathogenesis of coronary artery spasm through Rho-kinase activation and resultant vascular smooth muscle hypercontraction [1, 26–28, 40, 41, 47–50]. We thus developed novel imaging approaches for evaluating the extent of coronary adventitial inflammatory changes in VSA patients in vivo. Indeed, we were able to demonstrate that optimal coherence tomography (OCT)-delineated adventitial VV formation was significantly enhanced at the spastic segments of VSA patients as compared with those of the control subjects [51, 52]. Notably, VV formation was significantly increased in the group with high JCSA score than that with the low or intermediate score. We then demonstrated that coronary perivascular adipose tissue (PVAT) volume measured by CT coronary angiography was increased at the spastic segment of VSA patients [53]. In addition, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomographic (PET) imaging allows us to evaluate inflammatory changes of coronary PVAT in pigs in vivo [54]. The extent of PVAT inflammation was expressed as a 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. Importantly, using this imaging approach with ^{18}F-FDG PET, we demonstrated that coronary PVAT inflammatory changes were more enhanced at the spastic coronary segments of VSA patients as compared with those of controls [55]. Importantly, inflammatory changes measured by ^{18}F-FDG PET were significantly suppressed after medical treatment (Fig. 4.6) and also associated with improvement of angina symptom (Fig. 4.7). Taken together, these biomarkers and imaging approaches provide better understanding of the pathogenesis and treatment efficacy of coronary artery spasm in VSA patients (Fig. 4.8) [55–57].

4.5 Future Perspectives

Although the long-term prognosis of VSA patients is usually good, refractory VSA and major cardiac events, including acute myocardial infarction and sudden cardiac death, remain important issues. Further studies are needed to improve the understanding of this pathophysiology and to develop new effective therapies.

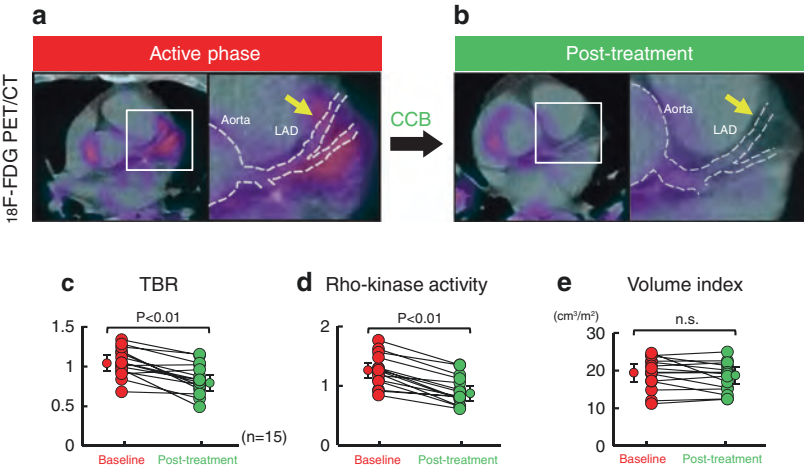

Fig. 4.6 Usefulness of ^{18}F-FDG PET/CT images and assessment of Rho-kinase activity before and after medical treatment in VSA patients(A ~ E). Representative ^{18}F-FDG PET/CT images with a VSA patient at baseline (**a**) and follow-up (**b**). Coronary perivascular FDG uptake was markedly decreased in the spastic LAD after medical treatment. Quantitative analysis showed that coronary perivascular TBR (**c**) and Rho-kinase activity (**d**) were significantly decreased after medical treatment, although coronary perivascular adipose tissue volume index (**e**) was not significantly decreased. ^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; CT = computed tomography; FDG = fluorodeoxyglucose; VSA = vasospastic angina. (Reproduced from Ohyama K, et al. [55])

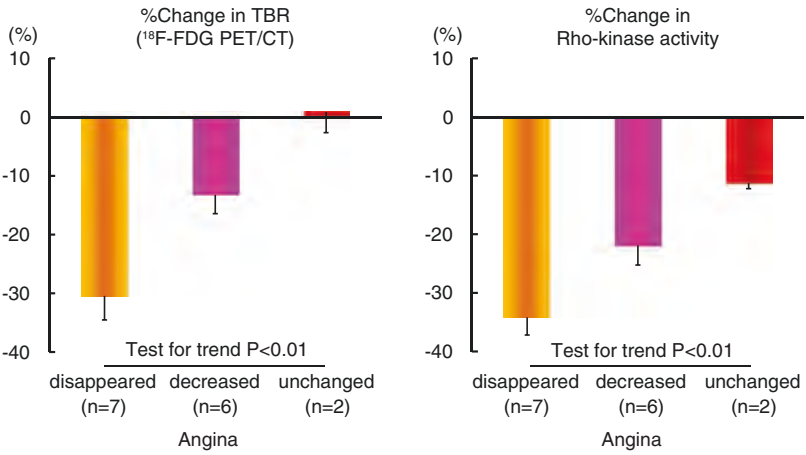

Fig. 4.7 Symptom improvement after medical treatment and changes in coronary perivascular FDG uptake and those in Rho-kinase activity. There were significant trends between the extent of symptom improvement and percent change in coronary perivascular TBR and that of Rho-kinase activity during a median follow-up of 23 months in the group with VSA. FDG = Fluorodeoxyglucose; TBR = target-to-background ratio; VSA = vasospastic angina. (Reproduced from Ohyama K, et al. [55])

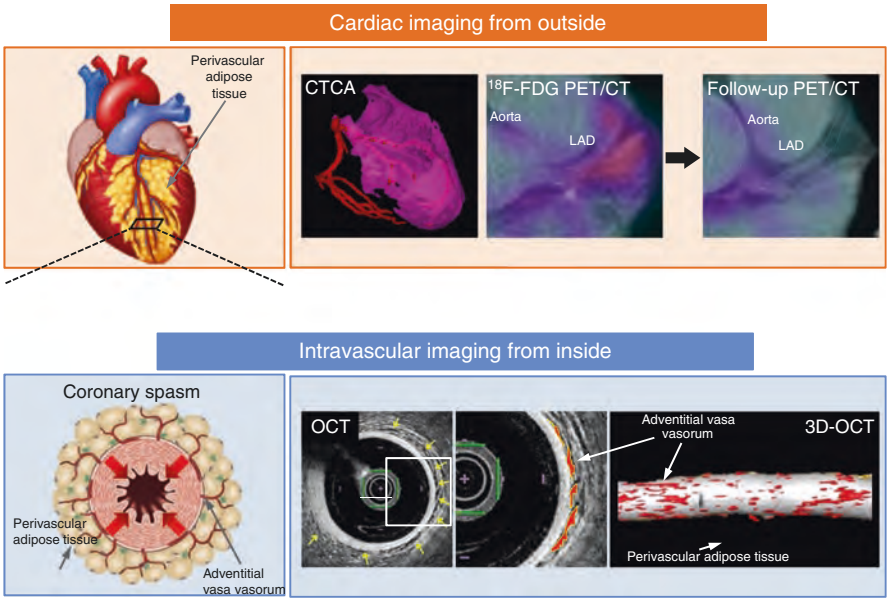

Fig. 4.8 Multimodality Imaging in VSA Patients. Coronary spasm is associated with inflammation of coronary adventitia and PVAT, as evident by ^{18}F-FDG PET/CT and OCT. In addition, ^{18}F-FDG PET/CT could be useful for disease activity assessment. FDG = Fluorodeoxyglucose; PET = positron emission tomography; OCT = optical coherence tomography; VSA = vasospastic angina. (Reproduced from Ohyama K, et al. [55])

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