Coronary Artery Spasm: Clinical Aspect

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Hiroaki Shimokawa

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H. Shimokawa (✉)
Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
e-mail: shimo@cardio.med.tohoku.ac.jp

Abstract

Vasospastic angina (VSA) is one of the important functional cardiac disorders characterized by transient myocardial ischemia due to epicardial coronary artery spasm. In this chapter, I review the clinical features of VSA including pathophysiology, diagnosis, treatments, and prognosis. Furthermore, I also refer to the evidence of microvascular angina.

Glossary of Terms

Coronary vasospasm State of functional hemodynamically relevant narrowing of a coronary artery due to hypercontraction of smooth muscle cells of the coronary artery walls.

Clinical Features

Prinzmetal's Variant Form of Angina

Angina caused by spasm of epicardial coronary arteries has been known as variant angina. By most strict definition, variant angina is a diagnosis given to patients having rest angina associated with reversible ST-segment elevation on electrocardiogram (ECG) but no evidence of myocardial necrosis as determined by serial ECGs and enzymatic analysis. This peculiar form of angina pectoris was systematically described for the first time by Myron Prinzmetal and colleagues in 1959 (Prinzmetal et al. 1959), based on the observations of 32 patients

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with rest angina associated with transient ST elevation. All characteristic clinical features that are at present well recognized were mostly reported in the Prinzmetal report. Namely, chest pain typically occurs at midnight or in the early hours of the morning and tends to be clustered. Night awakening with chest pain is common. As compared with classic angina, chest pain in variant angina is usually longer in duration and severe in intensity and frequently associated with autonomic symptoms such as nausea and cold sweating. During daytime, exercise tolerance is usually preserved. The patients do not develop angina on exertion unless obstructive coronary atherosclerosis is concomitantly present. However, exercise-induced angina does not necessarily preclude coronary artery spasm (see below). Serious ventricular tachyarrhythmias or bradycardia due to transient, high-degree atrioventricular block sometimes ensue and cause unconsciousness or fainting. Shortly after the Prinzmetal report, coronary artery spasm was angiographically documented by Gensini et al. in a patient with rest and effort angina (Gensini et al. 1962). Interestingly, these researchers used acetylcholine to induce transient cardiac arrest during which angiograms were taken.

Coronary Artery Spasm and Coronary Ischemic Syndromes

Spasm of large epicardial coronary arteries causes angina at rest associated with ST elevation (Gensini et al. 1962) or depression (Maseri et al. 1977; Yasue et al. 1981). In addition to rest angina, coronary artery spasm plays a pivotal role in a broad spectrum of coronary ischemic syndromes, including exercise-induced angina, silent myocardial ischemia, pre-infarction (unstable) angina, acute myocardial infarction, postinfarction angina, syncope, and sudden cardiac death (Fig. 1) (Maseri et al. 2009).

Coronary angiography during anginal attacks in patients suffering from recurrent angina at rest revealed a wide range of coronary artery disease from normal coronaries to severe three-vessel disease (Maseri et al. 1977). ST-segment elevation was caused by a transient occlusion of the major coronary artery, whereas ST-segment depression was caused by incomplete occlusion of coronary branches and invariably associated with the extensive coronary artery disease and rich collateral networks. Coronary collaterals develop with or without coronary artery disease (Yasue et al. 1981;

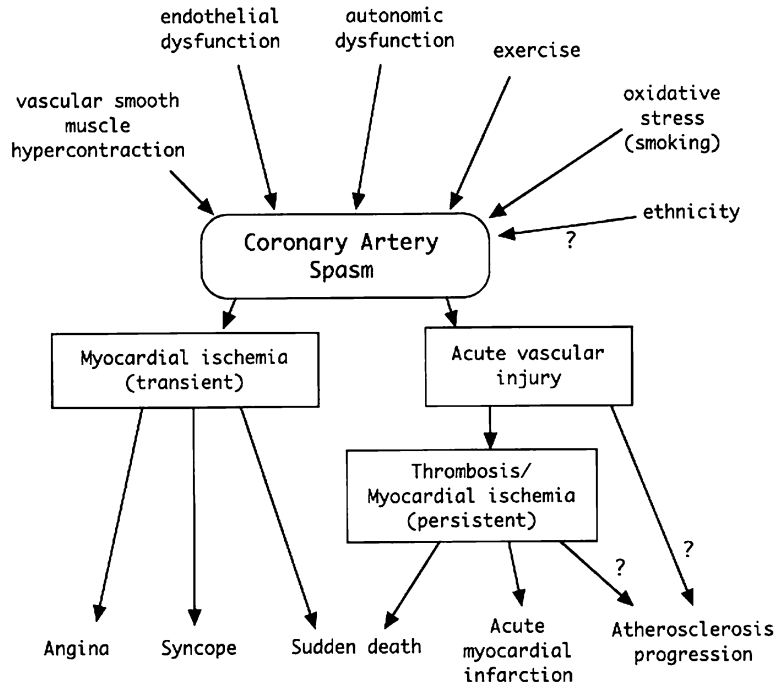

Fig. 1 Schematic diagram of pathophysiology of coronary artery spasm in relation to clinical manifestations of coronary ischemic syndromes. See text for detail

Takeshita et al. 1982) and can modify the extent and severity of myocardial ischemia.

Coronary artery spasm can also be the cause of effort angina. It had been generally believed that exercise-induced angina was caused by increased myocardial demand for oxygen in the presence of flow-limiting organic stenosis and that ST elevation during exercise testing indicated the presence of severe organic stenosis. Coronary angiograms taken during exercise in the cardiac catheterization laboratory clearly demonstrated that exercise provoked coronary artery spasm leading to total obstruction of major coronary artery at the site of no significant organic stenosis at baseline (Yasue et al. 1979; Specchia et al. 1979). The elevation or depression of ST segment during exercise may be determined by the severity and extent of coronary artery spasm, the underlying coronary artery disease, or both (Yasue et al. 1981; Boden et al. 1981; Kaski et al. 1986a). It should be noted that patients with vasospastic angina often exhibit a marked variability of exercise capacity even in the same day. The circadian variation in angina threshold is an important diagnostic clue to suspect the involvement of coronary spasm in ischemic manifestations. It was shown that epicardial coronary artery tone as well as the sensitivity of coronary arteries to vasoconstrictor stimuli (e.g., ergonovine) varied substantially in the morning and in the afternoon (Yasue et al. 1979; Waters et al. 1984). The underlying mechanism of the circadian variation is not fully understood, but may be related, at least partly, to the changes in the activity of autonomic nervous system (Takusagawa et al. 1999; Lanza et al. 1996) and possibly endothelial function (Kawano et al. 2002).

The results based on the 24-h ambulatory ECG monitoring have shown that silent myocardial ischemia is frequently observed in patients with variant angina. It was reported that approximately 80 % of myocardial ischemia with transient ST elevation was asymptomatic (Araki et al. 1983). Silent myocardial ischemia was associated with malignant ventricular tachyarrhythmias and may cause cardiac sudden death (see below).

Coronary artery spasm is responsible for acute coronary thrombosis, resulting in pre-infarction unstable angina and acute myocardial infarction in a subset of patients. It was previously reported that intracoronary nitroglycerin was effective to recanalize the occluded vessel by relieving spasm in 6 of 15 patients with acute myocardial infarction (AMI) within 12 h after the onset (Oliva and Breckinridge 1977). In all of the six patients, spasm was superimposed on the high-grade atherosclerotic stenosis (Oliva and Breckinridge 1977). The result suggested that coronary spasm might be the primary cause of acute coronary occlusion or, at least, the secondary event to sustain flow impairment. Not rarely, AMI develops in the absence of significant organic stenosis (Maseri et al. 1978; Fukai et al. 1993; Ong et al. 2008). It was also shown that coronary spasm could be provoked at 4 weeks after onset in 75 % of patients with AMI and no significant organic stenosis in Japan (Fukai et al. 1993). These patients were characterized by the presence of pre-infarction and/or postinfarction angina at rest, the occurrence of multivessel spasm, and smaller infarct size (Fukai et al. 1993). It was reported from Germany that when the frequency of coronary spasm in patients with acute coronary syndrome (ACS) and unobstructed coronary arteries was examined by intracoronary acetylcholine provocation test, every forth patients with ACS had no culprit lesion and almost 50 % of the patients who underwent a provocation test had proof of coronary spasm (Ong et al. 2008).

In general, postinfarction angina is a predictor of adverse outcomes after AMI (Mueller et al. 1992). However, coronary spasm is the cause of postinfarction angina in a subset of patients with cyclic ST elevation. These patients may have no critical coronary stenosis on angiography (Nakamura and Koiwaya 1983; Koiwaya et al. 1982) and be effectively treated with calcium channel blockers (CCBs). The prognosis is generally favorable with CCBs in this population (Nakamura and Koiwaya 1983; Koiwaya et al. 1982). Provocation test frequently provokes coronary spasm in patients with AMI. When the relationship between provoked coronary spasm and clinical course of patients with AMI was examined, the frequency of major adverse cardiac event-free survival was significantly lower in the positive group than in the negative group,

indicating that provoked coronary spasm is a significant independent predictor of poor prognosis in AMI patients (Wakabayashi et al. 2008).

Sudden Cardiac Death in Variant Angina

Syncope is an important manifestation of vasospastic angina and is caused by ventricular tachyarrhythmias or bradycardia due to transient conduction disturbances. It is commonly preceded by anginal pain, but not always (Maseri 1982). The development of arrhythmias is not related to the frequency of angina and concurs with symptomatic as well as asymptomatic myocardial ischemia (Araki et al. 1983; Myerburg et al. 1992). More importantly, sudden cardiac death can ensue as a result of coronary artery spasm (Roberts et al. 1982; Miller et al. 1982), even in patients with silent myocardial ischemia (Myerburg et al. 1992; Chevalier et al. 1998). In a subgroup of survivors of out-of-hospital cardiac arrest (OHCA), coronary spasm and silent myocardial ischemia were identified as a likely cause of their fatal arrhythmias (Myerburg et al. 1992; Chevalier et al. 1998). Additionally, in the current era, a substantial number of patients with OHCA survived without neurological deficits due to the increasing use of bystander cardiopulmonary resuscitation, implantable cardioverter-defibrillator (ICD), and subsequent hypothermia therapy, and a higher portion of them are found to have coronary spasm (Takagi et al. 2009). Documented serious dysrhythmias (ventricular tachycardia/fibrillation, high-degree atrioventricular block, and asystole) during hospitalization were associated with the risk of future sudden death (Holmes et al. 1981). Indeed, in patients with vasospastic angina who died suddenly from cardiac causes, multivessel spasm and angina-related arrhythmias had been documented in the initial evaluation, but the presence of fixed coronary stenosis did not predict sudden cardiac death (Koyanagi et al. 1989). As mentioned earlier, silent ischemia is frequently observed in patients with variant angina (Araki et al. 1983; Aoki et al. 1990) and may play a role in sudden cardiac death (Myerburg et al. 1992; Chevalier et al. 1998). The nationwide multicenter study conducted by the Japanese Coronary Spasm Association found that VSA patients who survived OHCA are particularly a high-risk population, even in the current era with long-acting calcium channel blockades (Takagi et al. 2011). Although a recent study with a small number of patients reported that ICD therapy combined with medication is appropriate for this high-risk VSA population (Matsue et al. 2012), further studies are needed to determine whether ICD therapy improves the long-term prognosis of VSA patients who survived OHCA.

Risk Factors for Coronary Artery Spasm

Cigarette smoking has been identified as a risk factor for coronary artery spasm in different groups of patients including premenopausal women (Sugiishi and Takatsu 1993; Scholl 1986; Caralis et al. 1992; Nobuyoshi et al. 1992). The Japanese Coronary Spasm Association study found that when the patients with vasospastic angina were divided into three groups by age [young (<50 years), middle-aged (50–64 years), and elderly (≥65 years)], the survival was significantly lower in the younger female group (young, 82 %; middle-aged, 92 %; elderly, 96 %; $P < 0.01$), where a significant interaction was noted between age and smoking (Kawana et al. 2013). Cessation of smoking is associated with spontaneous remission of angina (Tashiro et al. 1993). High LDL cholesterol and insulin resistance were suggested to be a risk factor for vasospastic angina in selected patients (Nobuyoshi et al. 1992; Shinozaki et al. 1995), but were not confirmed by others. It was previously reported that serum levels of hsCRP were elevated in VSA patients than in non-VSA patients (Itoh et al. 2007) and that 6-month treatment with a statin significantly reduced the disease activity of VSA along with the decrease in hsCRP levels (Yasue et al. 2008). These results suggest that low-grade inflammation caused by risk factors including hyperlipidemia and smoking is involved in the pathogenesis of VSA and that hsCRP is useful for disease activity assessment of VSA.

Racial Difference

For decades, many researchers have suspected that there may be a racial difference in the prevalence of angina caused by coronary artery spasm (Beltrame et al. 1999). For example, variant angina appears to be relatively common in Japan. However, there have been very few studies to systematically compare the incidence of angina due to coronary spasm between different countries, and it remains to be determined whether the ethnicity actually is a risk factor for coronary artery spasm. In addition to the prevalence, there also seems to be variations in clinical and angiographic characteristics between the Japanese and Caucasian patients. The former group of patients has lower incidence of concomitant fixed atherosclerotic stenosis in epicardial coronary arteries, which may be the basis for better prognosis associated with fewer myocardial infarction during follow-up (Nakamura et al. 1987; Shimokawa et al. 1988). Angiographic studies have shown that basal coronary tone as well as vascular reactivity to exogenous constrictor stimuli are diffusely increased, both at spastic and non-spastic arteries, in the Japanese patients, whereas the hyperreactivity is confined to the spastic segment in the Caucasian (Beltrame et al. 1999). Multivessel spasm is also common in the Japanese population. However, since a recent study on a Caucasian demonstrated a high positive rate of provocation test in patients with stable angina pectoris and unobstructed coronary arteries (Ong et al. 2012), it is conceivable that the racial difference between Asian and Caucasian patients may not be so high as has been previously considered.

Coronary Artery Spasm vs. Vascular Injury and Atherosclerosis Progression

In most cases of variant angina, impairment of coronary blood flow is transient, and coronary artery spasm does not persist long enough to cause myocardial cell necrosis. However, a single or repeated episodes of spasm may injure the vascular wall. As immediate sequelae, vascular hyperconstriction may cause endothelial damage, plaque rupture, intramural hemorrhage, and acute thrombosis. Furthermore, the progression of coronary atherosclerosis may ensue as a consequence of acute vascular injury. The authors have developed a porcine model of coronary artery spasm (Shimokawa et al. 1983; Nakamura 1991), demonstrating that agonist-induced spasm could cause structural changes of endothelial cells ("squeezing") and promoted adhesion of leukocytes at the spastic site (Nagasawa et al. 1989). In addition, intra-plaque hemorrhage was induced by repetitive spasm, leading to the rapid progression of coronary atherosclerosis and the development of AMI (Nagasawa et al. 1989; Kuga et al. 1993a). In patients with variant angina, coronary spasm was shown to increase soluble P-selectin production in the coronary circulation (Kaikita et al. 1995). The result may suggest that coronary spasm induces leukocyte adhesion which may result in vascular/myocardial damages in patients as well. It was also reported that plasma concentration of fibrinopeptide A was increased during anginal attacks in patients with variant angina (Oshima et al. 1990; Ogawa et al. 1989; Irie et al. 1989). Elevated fibrinopeptide A levels were not due to myocardial ischemia per se, because patients with stable effort angina had normal fibrinopeptide A levels on treadmill exercise testing (Irie et al. 1989). Furthermore, it was demonstrated that subcutaneous heparin suppressed an increase in plasma fibrinopeptide A levels, but not vasospastic attacks (Ogawa et al. 1989), suggesting that elevated fibrinopeptide A was the consequence, but not the cause, of coronary artery spasm. Thus, coronary spasm seems to activate the coagulation pathway, probably because of local blood stasis, and may contribute to intravascular thrombus formation.

It is an important question whether the acute functional and/or structural alterations at spastic segment of the coronary artery accelerate the process of coronary atherosclerosis for longer periods of time. Several studies were conducted to address this question but have yielded conflicting results. One group put forward this hypothesis by reporting a case in whom fixed atherosclerotic coronary stenosis developed at the site where spasm had been previously documented

(de Caterina et al. 1984). A retrospective analysis of 239 patients undergoing coronary angiography and ergonovine testing showed that coronary spasticity was a strong predictor for future progression of coronary artery disease (Chierchia et al. 1984). A similar result was reported from a Dutch group (Ozaki et al. 1995). In the latter study, persistent vasospastic activity was reportedly associated with atherosclerosis progression, and suppression of vasospastic activity lead to stenosis regression in some patients. In contrast, other group reported a negative result as they followed 10 patients with variant angina in whom the disease remained active over relatively long periods and observed that atherosclerosis progression was infrequent (Kaski et al. 1992). The discrepancy of these studies is due, at least partly, to variations in the number and clinical backgrounds, including ethnicity, of enrolled patients and the duration of follow-up. These studies are retrospective and suffer from bias of patient selection. Thus, it remains to be examined whether coronary artery spasm is a risk factor for atherosclerotic coronary artery disease itself.

Pathophysiology

In his report of 1959, Prinzmetal hypothesized a temporarily increased "tonus" at the narrowed, atherosclerotic segment of the epicardial coronary artery as a cause of myocardial ischemia with ST elevation (Prinzmetal et al. 1959). Within this context, MacAlpin suggested in his so-called geometric theory that a small, physiological increase in vascular tone could seriously impair coronary blood flow if it is superimposed on the atherosclerotic severe stenosis (MacAlpin 1980). Now, a plethora of clinical observations (Maseri et al. 1977; Takagi et al. 2011; Ong et al. 2012) as well as experimental studies (Shimokawa et al. 1983, 1985) have demonstrated that spasm occurs not only at segments with significant organic stenosis but also at angiographically normal or minimally diseased segments. Thus, coronary artery spasm cannot be explained by the geometric theory alone. Although the pathogenesis of coronary artery spasm remains to be fully elucidated, a primary hyperreactivity of vascular smooth muscle cell and endothelial dysfunction are considered to be the underlying main mechanisms (Maseri et al. 2009; Lanza et al. 2011). In the following paragraphs, possible mechanisms will be briefly discussed, including vascular hyperreactivity, endothelial dysfunction, and other possible contributing factors in the pathogenesis of coronary spasm in clinical situations (Fig. 1). Basic aspects of coronary artery spasm derived from experimental studies using animal models are discussed in the second part of this section.

Vascular Hyperreactivity

A number of endogenous vasoconstrictor substances/systems have been considered to be causatively involved in coronary artery spasm, including catecholamine (α-adrenoceptors), serotonin, histamine, dopamine, and constrictor prostaglandins such as thromboxane A2. However, blockade of any of these agonist-receptor interactions failed to suppress the spasm (de Caterina et al. 1984; Chierchia et al. 1982, 1984; Robertson et al. 1983). These lines of evidence have led to the concept that coronary artery spasm is not caused by abnormalities of specific agonist-receptor interaction but an enhanced reactivity (hyperreactivity) of the vessel to a generalized stimulus (Kaski et al. 1986a; Shimokawa et al. 1985; Robertson et al. 1983). Hyperreactivity may be defined as exaggerated constrictor response to a small dose of a certain agonist that would not cause hyperconstriction in healthy vessels (Kaski et al. 1989; Maseri et al. 1990). Limited availability of endogenous vasodilator substances and vascular smooth muscle cell hypersensitivity may contribute to vascular hyperreactivity and will be discussed below. In particular, the authors had accumulated evidence that a major mechanism of vascular smooth muscle cell (VSMC) hypersensitivity was represented by an increase in Rho-kinase activity, an enzyme that controls contraction and relaxation of VSMC independently of intracellular Ca^{2+} concentration (Somlyo and Somlyo 1994). Activated Rho-kinase enhances myosin light

chain phosphorylation through inhibition of myosin-binding subunit (MBS) of myosin phosphatase, leading to hyperconstriction of VSMC (Shimokawa and Takeshita 2005). Moreover, the authors have demonstrated that Rho-kinase pathway plays a central role in the molecular mechanism of coronary artery spasm in animal models (see the second part) (Shimokawa et al. 1999; Kandabashi et al. 2000). Importantly, the Rho-kinase inhibitor, fasudil, has been shown to prevent acetylcholine-induced coronary artery spasm in patients with vasospastic angina, suggesting that the Rho/Rho-kinase pathway actually plays an important role in the clinical setting (Masumoto et al. 2002).

Endothelial Dysfunction

The endothelium is lining on the inner surface of the vessels and synthesizes a number of vasoactive substances that are secreted intravascularly and abluminally. Among those substances, nitric oxide (NO) is a powerful vasodilator and plays a pivotal role in regulating local vascular tone. The bioavailability of NO has been shown to be decreased under certain pathological conditions (Shimokawa 1999; Mohri and Takeshita 1999). Furthermore, coronary artery spasm occurs, either spontaneously or following provocative agent such as ergonovine, preferentially at the atherosclerotic site of the coronary artery. The degree of atherosclerosis is not necessarily advanced and can represent only wall irregularities or minimal narrowing on arteriography. Such early atherosclerotic lesions are believed to be accompanied with endothelial dysfunction. It was thus reasonable to hypothesize that altered metabolism of NO may play a role in the genesis of coronary artery spasm. This hypothesis has been proposed based on the following observations: (1) flow-dependent vasodilation (Kugiyama et al. 1997) and constrictor response to N^G-monomethyl-L-arginine (Kugiyama et al. 1996) were decreased at spastic segments and (2) the gene mutation of endothelial NO synthase was present in a subset of patients with variant angina (Yoshimura et al. 1998; Nakayama et al. 1999). However, the authors currently are of opinion that endothelial dysfunction does not play a central role in the pathogenesis of coronary artery spasm for the following reasons. First, NO-dependent coronary dilatation, as tested with intracoronary acetylcholine, bradykinin, and substance-P, is well preserved at the spastic segment to the degree comparable with that of the non-spastic segment (Egashira et al. 1992; Kuga et al. 1995; Yamamoto et al. 1992; Okumura et al. 1992). Second, long-term treatment with fish oil (eicosapentaenoic acid) improved endothelial dysfunction but failed to prevent coronary artery spasm (Yamamoto et al. 1995). Third, basal release of NO as estimated by constrictor response to intracoronary administration of NO synthase inhibitor (N^G-monomethyl-L-arginine) was actually preserved between spastic and non-spastic arteries (Egashira et al. 1996). Fourth, coronary risk factors such as aging, hypertension, hypercholesterolemia, diabetes, and smoking are all known to impair NO-dependent vasodilation, but the prevalence of vasospastic angina is apparently much less than is estimated by the number of subjects having these risk factors. Finally, the reported prevalence of the gene mutations is low even among patients with variant angina and seems to be unable to account for the occurrence of coronary artery spasm in most cases. Collectively, these lines of evidence suggest that hypersensitivity of VSMC, rather than endothelial dysfunction, is the primary cause of coronary artery spasm. Deficient NO may possibly be a modifying factor predisposing to exaggerated vascular constriction. Furthermore, Rho-kinase activation described above had been reported to be associated with the regulation of endothelial NO synthase (Takemoto et al. 2002). A series of experimental studies using the animal model of coronary artery spasm in the authors' laboratory support this notion (see the second part).

Other Factors

It has been recognized by many physicians that anginal attacks occur in the early morning hours in many patients with variant angina. Although the presence of circadian variation in coronary vasospasticity suggests a possible contribution of

the autonomic nervous system, there is still no consensus even in recent publications with regard to the roles of sympathetic or vagal function. Vasospastic attacks in variant angina were reported to be associated with increased sympathetic activity (Yamasaki et al. 1996; Miwa et al. 1998), reduced sympathetic activity (Takusagawa et al. 1999), increased vagal tone (Saitoh et al. 1998), or vagal withdrawal (Lanza et al. 1996; Tsuchiya et al. 1996). The sympathovagal imbalance may be a trigger in selected patients but appears not to be the primary cause of coronary artery spasm.

Vitamin E is a potent, naturally occurring antioxidant and may contribute to preventing LDL oxidation. Oxidized LDL increases vascular reactivity and impairs endothelial function in vitro. It was reported that plasma vitamin E levels were decreased in patients with variant angina and that the supplementation with vitamin E acetate was effective to suppress anginal attacks (Miwa et al. 1996; Motoyama et al. 1998). Magnesium deficiency was also associated with the disease activity of variant angina (Satake et al. 1996). However, it is unknown in how much proportion of patients with variant angina these abnormalities are responsible for the occurrence of coronary artery spasm.

Diagnosis, Treatments, and Prognosis

It is relatively easy to make a diagnosis of variant angina in subjects having typical symptoms. Carefully taking a history of clinical symptoms is of diagnostic importance. Anginal attacks that preferentially occur in the early morning hours and preserved exercise tolerance in the daytime strongly suggest a significant contribution of coronary artery spasm. The 24-h ambulatory ECG monitoring is of particular help, especially when the disease activity is high. Transient and repetitive ST elevation is a reasonably reliable and easily recognizable hallmark (Maseri 1982). Exercise ECG testing is normal unless coronary artery disease or exercise-induced spasm is concomitantly present. In some patients, coronary artery spasm may be the cause of effort angina, with or without fixed organic stenosis (Yasue et al. 1979, 1981; Specchia et al. 1979; Boden et al. 1981; Kaski et al. 1986a). Exercise-induced ST elevation is observed only in patients with significant coronary artery disease, whereas ST depression is exclusively in those with normal or insignificant stenoses (Kaski et al. 1986a). When repeated exercise testing is normal in the patients having ST elevation, it is suggested that coronary artery spasm substantially contributes to effort angina in those patients. In patients with variant angina and positive exercise testing, diltiazem, when taken 2 h before exercise, prevented ischemic ECG changes during exercise in most patients without significant organic stenosis. In contrast, all patients with significant stenosis had a positive response even after diltiazem. Thus, exercise ECG testing done with the pretreatment of diltiazem had a high sensitivity (96 %) and specificity (100 %) in detecting severe fixed stenosis in patients with variant angina (Araki et al. 1986). It has been recently demonstrated that Rho-kinase activity (as evaluated by the ratio of phosphorylated to total form of Rho-kinase) in circulating leukocytes of 1.18 is the best cutoff level to predict the diagnosis of VSA, and it was significantly decreased after 3-month medical treatment with CCBs (Kikuchi et al. 2011). These results indicate that the noninvasive measurement of Rho-kinase activity in circulating leukocytes may be useful for diagnosis and disease activity assessment in patients with vasospastic angina (Kikuchi et al. 2011).

In addition to noninvasive diagnostic testing, coronary arteriography and provocation testing may be indicated when (1) 24-h ambulatory ECG fails to document ischemic ST-segment shifts because of infrequent occurrence of anginal attacks; (2) angina occurs both at rest and on effort; (3) angina is refractory to medical treatments; (4) angina is accompanied with unconsciousness; or (5) the patient feels a considerable anxiety for symptoms and the origin of chest pain needs to be determined. Cardiac catheterization and coronary arteriography can accurately evaluate the presence or absence of concomitant coronary artery disease, serious arrhythmias or conduction disturbances during attack, and multivessel spasm, all of

which are significant predictors for future cardiovascular events such as AMI and sudden cardiac death (Miller et al. 1982; Nakamura et al. 1987; Yasue et al. 1988). Provocation test should be done in the cardiac catheterization laboratory.

Provocation Tests

Various kinds of non-pharmacological maneuvers and pharmacological stimuli have been used to provoke coronary artery spasm. The former include hyperventilation with or without Tris-buffer infusion, cold pressor, and handgrip, and the latter include ergonovine, acetylcholine, serotonin, histamine, dopamine, and norepinephrine (Kaski et al. 1986a; Beltrame et al. 1999). The sensitivity is generally higher with vasoactive agents such as ergonovine than with non-pharmacological perturbations. The diagnostic accuracy is dependent not only to the maneuver/agent selected but also the activity of the disease. Vasomotor response to the same stimulus can be variable even in the same individual. Circadian variation in the sensitivity of testing was also reported (Waters et al. 1984). Ergonovine and acetylcholine have been widely used in the cardiac catheterization laboratory as a provocative agent, and it has been shown that the sensitivity and specificity of testing with either agent are high (Kaski et al. 1986a; Okumura et al. 1988). Ergonovine can be administered either intravenously or intracoronarily; however, intracoronary route requires only a small dose and is safer because of fewer side effects on systemic circulation. More importantly, the intracoronary route is preferable to avoid the occurrence of multivessel spasm that sometimes results in catastrophic hemodynamic collapse. Ergonovine-induced anginal attacks are similar to spontaneous ones in terms of the characteristics of chest symptoms, ECG changes, hemodynamics, and the site of spasm (Curry et al. 1979). Acetylcholine is also given as a provocative stimulus. It is metabolized within seconds and needs intracoronary infusion. Since acetylcholine could cause marked bradycardia and/or transient cardiac arrest, a temporary pacing catheter should be placed in the right ventricle. Acetylcholine-induced spasm is rather diffuse in the coronary artery trees as compared with that induced by ergonovine. Acetylcholine stimulates the release of NO from the endothelium, and therefore, vasomotor behavior induced by acetylcholine may reflect the net effects of endothelial function and reactivity of vascular smooth muscle cells. However, these spasm provocation tests are thought to have a potential risk of serious arrhythmic complications including ventricular tachycardia or fibrillation and bradyarrhythmias. According to a recent study of Japanese VSA patients who underwent spasm provocation tests with either ergonovine ($n = 497$) or acetylcholine ($n = 713$), the incidence of arrhythmic complications during the provocation tests was 6.8 %, which was comparable with those during spontaneous angina attack (Takagi et al. 2013a). Furthermore, the study provided the novel finding that mixed-type multivessel spasm at provocation tests had a significant correlation with future cardiac events. These results suggest that the coronary spasm provocation tests have an acceptable level of safety, and the evaluation of spasm type may provide useful information for the risk stratification of VSA patients (Takagi et al. 2013a). Thus, it is recommend to perform such spasm provocation tests to adequately diagnose vasospastic angina.

Coronary Artery Tone

Diagnostic coronary arteriography is done in patients with all cardiovascular medications withdrawn before the study. The difference between the coronary arterial diameter obtained at baseline and after the administration of nitrates (nitroglycerin or isosorbide dinitrate) represents the degree of tonic arterial constriction and is often termed as "basal tone." If the tone is basally increased at a given segment, the segment will be dilated by nitrates to the greater degree. Increased basal tone may be related to the spasticity of the coronary artery and therefore the disease activity (Kuga et al. 1993b; Ozaki et al. 1996). Whether basal tone is increased at the spastic segment as compared with the non-spastic segment has been examined by

different investigators, and there appears to be a difference between the Japanese and Caucasian patients. In the Japanese patients with variant angina, basal tone is diffusely increased both at spastic and non-spastic segments as compared with subjects having no coronary spasm (Kuga et al. 1993b; Hoshio et al. 1989). This may be related to the higher prevalence of multivessel or multiple segment spasm in the Japanese patients. Thus, increased basal tone may be a diagnostic clue for coronary artery spasm in this population (Beltrame et al. 1999). However, the absence of increased tone does not preclude the occurrence of spasm (Kuga et al. 1993b). In the Caucasian patients, increased basal tone at the spastic segment was also demonstrated and correlated well with the disease activity over years in one study (Ozaki et al. 1996), but not in the other (Kaski et al. 1991).

Managements

Calcium channel blockers (CCBs) are very effective in preventing coronary artery spasm and thereby angina attacks in patients with variant angina (Opie 1996). There appears to be no difference in the efficacy between short- and long-acting preparations. Sudden cessation of CCBs is known to be associated with AMI and sudden cardiac death (Nakamura et al. 1987). Thus, the dose of CCBs should be gradually tapered with caution when necessary. Ambulatory ECG monitoring should help to recognize the rebound of spastic activities. CCBs are also effective for post-infarct angina due to spasm (Nakamura and Koiwaya 1983; Koiwaya et al. 1982). However, it should be noted that CCBs should not be given routinely in post-MI patients, because this class of agents is known to increase mortality in certain subsets of patients (The Multicenter Diltiazem Postinfarction Trial Research Group 1988; Yusuf 1991). β-blockers without calcium channel blockers may be detrimental in patients with variant angina, because they might induce coronary artery spasm and aggravate myocardial ischemia by unopposing α-adrenoceptor-mediated vasoconstriction (Robertson et al. 1982). Furthermore, calcium channel blockers may reduce sudden cardiac death caused by coronary artery spasm (Myerburg et al. 1992). As stated earlier, smoking is a major risk factor for coronary spasm and should be quitted in all patients (Tashiro et al. 1993).

The majority of patients with variant angina can be safely managed with CCBs, and it is rare to require further interventional approaches. Variant angina that is refractory to full medication including high doses of CCBs can be effectively treated by balloon angioplasty with and without intracoronary stenting (Gaspardone et al. 1999; Kultursay et al. 1996). These patients usually have spasm that is superimposed on a medium-degree organic coronary stenosis.

Long-Term Prognosis and Its Determinants

In general, the prognosis of variant angina is good, especially with use of CCBs (Miller et al. 1982; Koyanagi et al. 1989; Takagi et al. 2011; Nakamura et al. 1987; Shimokawa et al. 1988; Yasue et al. 1988; Waters et al. 1983; Severi et al. 1980). Adverse outcomes are related to the extent of coronary artery disease of >90 % diameter stenosis as determined by coronary arteriography (Nakamura et al. 1987; Shimokawa et al. 1988; Yasue et al. 1988; Waters et al. 1983), left ventricular dysfunction (Waters et al. 1983), high disease activity such as accelerating angina (Nakamura et al. 1987; Yasue et al. 1988; Waters et al. 1983), disuse or sudden discontinuation of CCBs (Nakamura et al. 1987; Yasue et al. 1988; Waters et al. 1983), extensive myocardial ischemia caused by multivessel spasm (Koyanagi et al. 1989; Yasue et al. 1988), and documented serious arrhythmias or conduction disturbances (Koyanagi et al. 1989; Shimokawa et al. 1988; Yasue et al. 1988). The presence of concomitant organic coronary artery disease increases the risk of future myocardial infarction, whereas multivessel spasm or documented arrhythmias predicts sudden cardiac death (Nobuyoshi et al. 1992). To apply those various prognostic factors in clinical practice, the assessment of their accumulation in individual patients

should be taken into consideration. Thus, a novel scoring system, the JCSA (Japanese Coronary Spasm Association) score, which consists of seven predictors of major adverse cardiac events, including history of out-of-hospital cardiac arrest (four points), smoking, angina at rest alone, organic coronary stenosis, multivessel spasm (two points each), ST-segment elevation during angina, and b-blocker use (one point each) was developed. The JCSA risk score provides the comprehensive risk assessment and prognostic stratification for management of patients with vasospastic angina (Takagi et al. 2013b).

Coronary Microvascular Spasm

Syndrome of Chest Pain and Normal Coronary Arteriograms

As much as ~30 % of patients with suspected angina pectoris who undergo coronary arteriography are found to have normal or minimally diseased epicardial coronary arteries and no epicardial spasm. Chest pain and normal coronary arteriograms have been a dilemma both for patients and physicians, and its nature seems heterogeneous (Mohri and Takeshita 1999; Kaski 1998). Importantly, some patients with angina and normal coronary arteriograms have a limited microvascular dilator reserve in response to physiological and pharmacological stimuli and are given a generic diagnosis of microvascular angina or cardiac syndrome X (Cannon 1988; Likoff et al. 1967; Kaski et al. 1995; Camici and Crea 2007; Lanza and Crea 2010). Limited flow reserve may result in oxygen demand-supply imbalance under the condition of increased myocardial oxygen demand and would therefore account well for angina during exercise (Opherk et al. 1981; Greenberg et al. 1987).

Angina Caused by Coronary Microvascular Spasm

Patients with microvascular angina often suffer from chest pain at variable levels of effort or even at rest (Mohri et al. 1998; Kaski et al. 1986b). The reduced coronary flow reserve due to inadequate microvascular dilator capacity would not be the cause of myocardial ischemia that was not associated with exercise. Primary reduction of coronary blood flow caused by spasm of small coronary arteries or arterioles may be the cause of angina at rest. This hypothesis is supported by the careful observations of patients with syndrome X, demonstrating that angina and ischemic ST shift were not always preceded by increments in heart rate (Kaski et al. 1986b). Sinus tachycardia that had caused ischemia during exercise testing did not develop chest pain or ECG change in most instances (Kaski et al. 1986b). The variable threshold for angina symptoms during daily life suggests the presence of circadian variations in vasomotor tone and small vessel hyperconstriction (Lanza et al. 1997). The authors prospectively examined a cohort of 117 patients with angina (mostly at rest) and normal or minimally diseased epicardial coronary arteries. In 25 % of the studied patients, no epicardial spasm was demonstrated during angina attack on selective coronary arteriography (Mohri et al. 1998). Chest pain that 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 (Fig. 2). 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 (Mohri et al. 1998). Importantly, the high prevalence of microvascular spasm in Caucasian patients with stable angina and unobstructed coronary artery had been recently demonstrated (Ong et al. 2012). Microvascular constriction and myocardial ischemia as evidenced by electrocardiographic change were also provoked by intracoronary infusion of a peptide neurotransmitter, neuropeptide Y (Clarke et al. 1987).

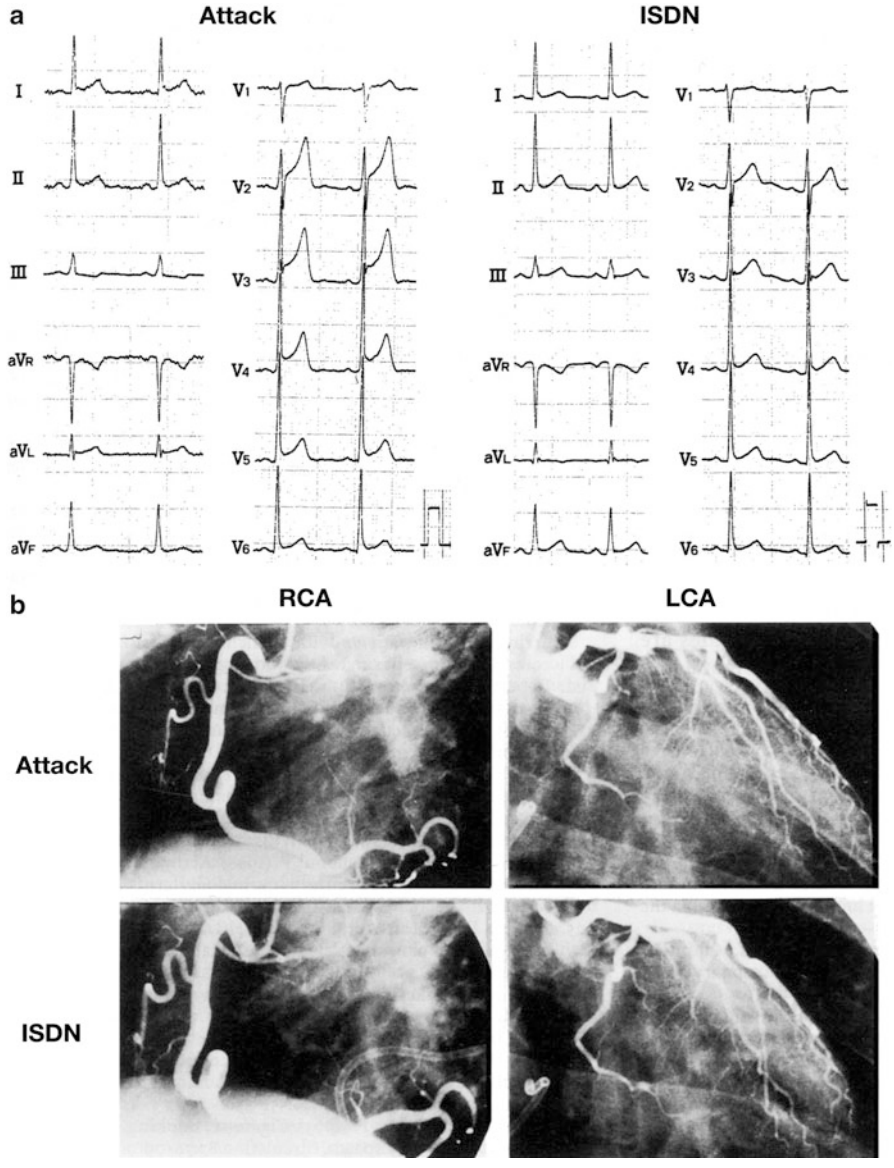

Fig. 2 12-lead ECG (**a**) and coronary arteriograms (**b**) of a 39-year-old man with history of angina on exertion and at rest. Angina occurred spontaneously in the catheterization laboratory in association with ST-segment elevation in leads I, aVL, and V2–6. No epicardial spasm was observed in the right or left coronary artery. Intracoronary isosorbide dinitrate relieved chest pain and normalized ECG. Paired arterial and coronary sinus blood sampling confirmed myocardial lactate production during attack (From Mohri et al. (1998) with permission)

Unsolved Questions

There are many questions to be solved, including the prevalence, pathogenesis, and treatments of microvascular angina. Microvascular angina is reportedly more common among postmenopausal women (Kaski et al. 1995; Ockene et al. 1980). The reason of female predominance is largely unknown and may be related, at least in part, to estrogen deficiency (Rosano et al. 1996). NO has been documented to be deficient in patients with this syndrome (Motz et al. 1991; Egashira et al. 1993). Impaired NO-dependent vasodilation may increase small vessel tone and predispose to

Table 1 Pathogenesis of angina by sites of the coronary artery

Large epicardial coronary arteries
Atherosclerotic (fixed) stenosis: effort angina (classical angina)
Spasm (dynamic stenosis): variant angina
Coronary microvessels
Reduced dilator reserve: effort angina
Spasm: rest angina

hyperconstriction in response to acetylcholine or to other neurohumoral stimuli. Contribution of VSMC hypercontraction to the pathogenesis of microvascular disorders has also been suggested by the animal model with chronic inhibition of NO synthesis (Kadokami et al. 1996; Ito et al. 1995). These animals develop functional and structural abnormalities of coronary microvessels. Importantly, these microvessels showed hypersensitivity to vasoactive substances such as serotonin (Kadokami et al. 1996). Thus, reduced availability of NO, VSMC hypercontraction, or both at the level of coronary microvessels may cause coronary microvascular spasm. Finally, effective management of these patients has not been established. Conventional treatments with β-blockers, nitrates, or CCBs seem to be of limited efficacy (Lanza et al. 1994, 1999). Several agents that increase endothelium-derived NO availability are now under investigation. These include estrogen preparations, angiotensin-converting-enzyme inhibitors, HMG-CoA reductase inhibitors (statins), and NO donors, some of which have been shown to be effective in selected cases with microvascular angina.

Fixed and dynamic stenoses of the large epicardial arteries are responsible for exercise-induced and variant angina, respectively (Table 1). Impaired dilator reserve of small coronary vessels has been revealed as a possible cause of myocardial ischemia in selected cases with effort angina and normal coronary arteriograms. There is now evidence suggesting that primary hyperconstriction of small coronary vessels is involved in a subset of patients with rest angina. Further studies are needed to establish an effective strategy to manage these patients.

Summary

Coronary artery spasms have been associated with multiple risk factors responsible for a transient myocardial ischemia causally related to the clinical syndromes of angina, syncope or less frequently sudden death. Provocation tests have been shown valuable to allow prognostic stratification and to guide treatment. The overall prognosis is good, particularly in patients treated with CCBs, low JCSA score level and limited plaque burden. Microvascular spasms appear to be related to impaired NO- dependent vasodilation, yet effective treatment still remains to be established.

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