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REVIEW ARTICLE

Coronary artery spasm—Clinical features, diagnosis, pathogenesis, and treatment

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Summary Coronary (artery) spasm plays an important role in the pathogenesis of ischemic heart disease, including stable angina, unstable angina, myocardial infarction, and sudden death. The prevalence of coronary spasm differs among populations, is higher in Japan and Korea than in the Western countries probably due to genetic as well as environmental factors. Coronary spasm occurs most often from midnight to early morning and is usually not induced by exercise in the daytime. The attacks of coronary spasm are associated with either ST segment elevation or depression, or negative U wave on ECG. Patients with multi-vessel coronary spasm may suffer from lethal arrhythmia, including advanced AV block, ventricular tachycardia or fibrillation, or even sudden death, and they are often resistant to conventional medical therapy including Ca-channel blockers (CCBs). Endothelial nitric oxide (NO) activity is reduced and markers of oxidative stress are elevated in patients with coronary spasm. Thrombogenesis is enhanced and plasma levels of hsCRP and P-selection are elevated in patients with coronary spasm. Thus, patients with coronary spasm have endothelial dysfunction and are suffering from a low-grade chronic inflammation. Polymorphisms of endothelial NO synthase, smoking, and low-grade inflammation are the most important risk factors for coronary spasm. Coronary spasm is a hyper-contraction of coronary smooth muscle triggered by an increase of intracellular Ca^{2+} in the presence of an increased Ca^{2+} sensitivity. It has been shown that RhoA/ROCK pathway is involved in Ca^{2+} sensitivity and that the reduced endothelial NO activity results in increased Ca^{2+} sensitivity through enhanced RhoA/ROCK pathway. Accordingly, it is possible that in addition to CCBs, RhoA/ROCK pathway blockers may prove to be useful for the treatment of coronary spasm.

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Contents

''CORONARY SPASM—The hypothesis, once widely accepted, that active constriction of the coronary arteries is the chief mechanism of angina pectoris is no longer valid.''

Harrison and Reeves [7, p. 52].

Angina pectoris is caused by transient myocardial ischemia due to an imbalance between myocardial oxygen demand and supply [1,2]. Classical or stable effort angina is characterized by (1) the attack is induced by exertion and relieved by rest or nitroglycerin administration, and (2) the attack is associated with transient ST segment depression in the electrocardiogram [1—3]. This form of angina has been well known for more than 200 years since its description by Heberden [4] and its pathogenesis has been explained by increased myocardial oxygen demand in the presence of fixed organic stenosis of epicardial coronary arteries [1—3]. This concept was based on the fact that the majority of patients with angina were found to have severe and extensive atherosclerotic narrowing in their coronary arteries. Beta-adrenergic blocking agents, which reduce myocardial oxygen demand, have been widely used for the treatment of angina. The efficacy of nitroglycerin has been attributed chiefly to its venodilatatory effect, which results in pooling of blood in the venous system leading to decreased myocardial work rather than to its direct effect on the coronary arteries [5].

In 1959, Prinzmetal et al. [6] described a new form of angina pectoris which differed sharply from the classical angina and named it ''variant form of angina pectoris.'' The characteristics of this syndrome were: the attack associated with ST segment elevation on ECG occurred at rest and was not induced by exertion. However, this syndrome drew little attention among the cardiologists at that time probably because it was usually not induced by exercise in the daytime and the concept of increased myocardial oxygen demand as a cause of angina pectoris prevailed [1,7].

With the introduction of coronary angiography by Sones and Shirey in 1959 [8] and its widespread use, spasm of an epicardial coronary artery or coronary spasm was documented angiographically during the attack of variant angina at several institutions in the early 1970s [9—11]. Thus, coronary spasm was established as the cause of variant angina [10—12]. With the introduction of ambulatory ECG monitoring for myocardial ischemia and its widespread use, many cases of variant angina have been reported, particularly in Japan [13,14].

It is now known that coronary spasm plays an important role in the pathogenesis not only of

variant angina but also of ischemic heart disease in general, including effort angina, unstable angina, acute myocardial infarction and sudden death [15—18], and thus the postulation of Harrison, cited above [7] is no longer valid. Thus, variant angina is only one aspect of the wide spectrum of myocardial ischemic syndromes [15] caused by coronary spasm. Angina caused by coronary spasm is now usually called ''coronary (vaso) spastic angina'' and the name ''variant angina'' is less often used [18].

Coronary constriction and spasm

Coronary arteries are able to contract and relax via various mechanisms. Thus, coronary constriction is a normal phenomenon and not necessarily pathological. Under certain disease conditions, however, coronary constriction becomes more dominant than in the healthy population and may contribute to symptoms such as angina pectoris [19]. The degree of coronary constriction may differ considerably in different syndromes and different patients. Indeed, in certain patients coronary constriction may be only slightly increased and hence no symptoms may occur at rest; however, the increased coronary tone may significantly alter the threshold for angina during exercise in these patients [20,21]. On the other hand, coronary constriction may be so severe that myocardial ischemia occurs even at rest in some patients with angiographically normal coronary arteries. Under such conditions, a near-total or total occlusion, or severe diffuse constriction of the coronary artery can be demonstrated. Some authors have emphasized the difference between increased constriction and total occlusion of a coronary artery and have restricted the expression ''coronary spasm'' to the latter condition [22]. However, increased constriction contributes to a various spectrum of ischemic heart disease and the same patients may have different degree of coronary constriction at different times. Thus, the difference between hyperconstriction and total occlusion is gradual and the distinction between coronary spasm and hyperconstriction is artificial [19,23]. Indeed, hyperconstriction usually involves the entire coronary artery, although the degree of constriction may differ among segments of the artery, resulting in total occlusion in some cases.

We define coronary spasm as an abnormal contraction of an epicardial coronary artery resulting in myocardial ischemia [14,18]. With this definition, there are no limits on the degree of lumen diameter reduction required to diagnose coronary spasm since ischemia must accompany the changes of vessel size.

Prevalence of coronary spasm

There are not enough data on the prevalence of coronary spasm both in the Eastern and Western countries, probably because it is difficult to examine coronary spasm systematically at the each time of coronary angiography. The prevalence rate may also vary depending on the interest and eagerness on the part of the investigators. Bertrand and co-workers reported in 1982 that coronary spasm was provoked by ergonovine in 20% of patients with recent myocardial infarction and in 15% of patients who complained of chest pain in 1089 consecutive patients undergoing coronary angiography [24]. Coronary spasm has become less frequent in the Western countries recently. This is probably due to the facts that Ca-channel blockers (CCBs), which are specifically effective in suppressing coronary spasm, have been widely used for chest pain and/or hypertension, and/or better nitrate regimens have been developed and used. Also, many cardiologists are now not much interested in coronary spasm and provocation tests for it are less often performed [25]. Coronary spasm is, however, still prevalent and provocation tests for it are routinely performed at many institutions in Japan [26] and perhaps in Korea [27]. The recent survey on the prevalence of coronary spasm at multi-institutions in Japan showed that coronary spasm was documented in 921 (40.9%) of the 2251 consecutive patients with angina pectoris who underwent coronary angiography [26]. Thus, there seems to be a racial difference in the prevalence of coronary spasm between the Japanese and Caucasians. Indeed, a recent report showed a major racial difference in coronary constrictor response between Japanese and Caucasians [28]. However, the frequency has become less frequent also in Japan probably because of the prevalent use of CCBs for hypertension as well as for ischemic heart disease and the decreased incidence of smokers [29]. Increased medications of aspirin, statins, ACE inhibitors, or angiotensin II receptor blockers may also have contributed to the reduction of coronary spasm [30]. It is also possible that cardiologists now may be more interested in patients who are in need of percutaneous coronary intervention (PCI) and do not want to be bothered with coronary spasm. Many cardiologists consider the provocation test for coronary spasm too cumbersome and time-consuming for the busy invasive-interventional laboratory and think that a

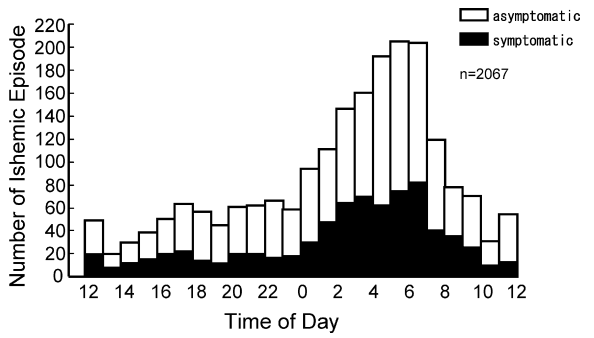

Figure 1 Diurnal distribution of the ischemic episodes in patients with variant angina. The attacks occur most often from midnight to early morning. To be noted is that the number of asymptomatic attacks was larger than that of symptomatic attacks. (From Yasue and Kugiyama [18].)

trial of CCBs may be enough for the evaluation of possible spasm [18].

Clinical manifestations

Circadian variation

Coronary spasm occurs usually at rest, particularly from midnight to early morning [6,12—19] (Fig. 1). Although Prinzmetal et al. [6] emphasized that variant angina is not induced by exercise, coronary spasm can often be induced even by mild exercise in the early morning [20,31]. However, it is usually not induced in the afternoon even by strenuous exercise. Thus, there is a circadian variation in the exercise capacity in the patients with coronary spasm [20]. It is now known that the attacks of all forms of ischemic heart disease including acute myocardial infarction and sudden death occur most often in the early morning [13,17,18,32]. This may be related at least partially to the fact that the tone of an epicardial coronary artery is increased in the early morning, whereas it is decreased in the afternoon [20].

The causes of the circadian variation of coronary spasm remain to be elucidated. Because coronary spasm can be induced by intracoronary injection of acetylcholine (ACh) [33], the neurotransmitter of the parasympathetic nervous system, changes in the activity of the autonomic nervous system may be involved in the circadian variation of coronary spasm [34]. Coronary spasm can also be induced by stimulation of alpha-adrenergic receptors [10]. Circadian variations of the production of various hormones including cortisol, vasopressin, melatonin, growth hormone, and insulin or inflammatory cytokines including TNF-alpha or IL-1, may also be related to the circadian variation of coronary spasm.

Symptoms and the ECG changes

The commonly associated manifestations of myocardial ischemia due to coronary spasm are chest pain and ST segment changes on the ECG. Chest pain is similar in quality to that of stable effort angina, but is often more severe and prolonged, accompanied by cold sweat, nausea or vomiting, and sometimes by syncope. It should be noted, however, that myocardial ischemia due to coronary spasm often occurs without accompanying symptoms [18,34]. Indeed, the incidence of silent myocardial ischemia caused by coronary spasm is more than two times higher than that of symptomatic ischemia (Fig. 1) [18].

The ECG changes that occur during the attack of coronary spasm include ST segment elevation and/or depression, peaking and/or increase in amplitude of the T wave, a delay in the peak and an increase in the height and width of the R wave resulting in fusion of R wave with T wave, and a decrease in magnitude or disappearance of the S wave. The negative U wave may also appear at the beginning or near the end of the attack, and is often associated with ST segment changes in the anterolateral leads. It may be the only ECG change that occurs during a mild attack when spasm is less severe and does not cause the total obstruction of a coronary artery. Total or subtotal occlusion of a major coronary artery by spasm, results in ST segment elevation in the leads that represent the area of myocardium supplied by the artery. The ST segment elevation is usually accompanied by reciprocal ST segment depression in the opposite leads. It is therefore important to record electrocardiograms in multiple leads. The magnitude of ST segment elevation varies and corresponds roughly to the degree of acute myocardial ischemia. As the attack proceeds, the magnitude of ST segment elevation increases and, in association with an increase in magnitude and widening of the R wave in the same lead, may form a ''monophasic curve'' at the peak of the attack. This ''monophasic curve'' is usually not seen during the attack of acute myocardial infarction and is characteristic of a severe attack of coronary spasm occluding the proximal segment of a major coronary artery. The ST segment elevation appears in the leads corresponding to the distribution of one major coronary artery. The leads in which ST segment appears are usually the same during each attack in the same patient, indicating that spasm usually appears at the same coronary artery in the same patient. However, it is

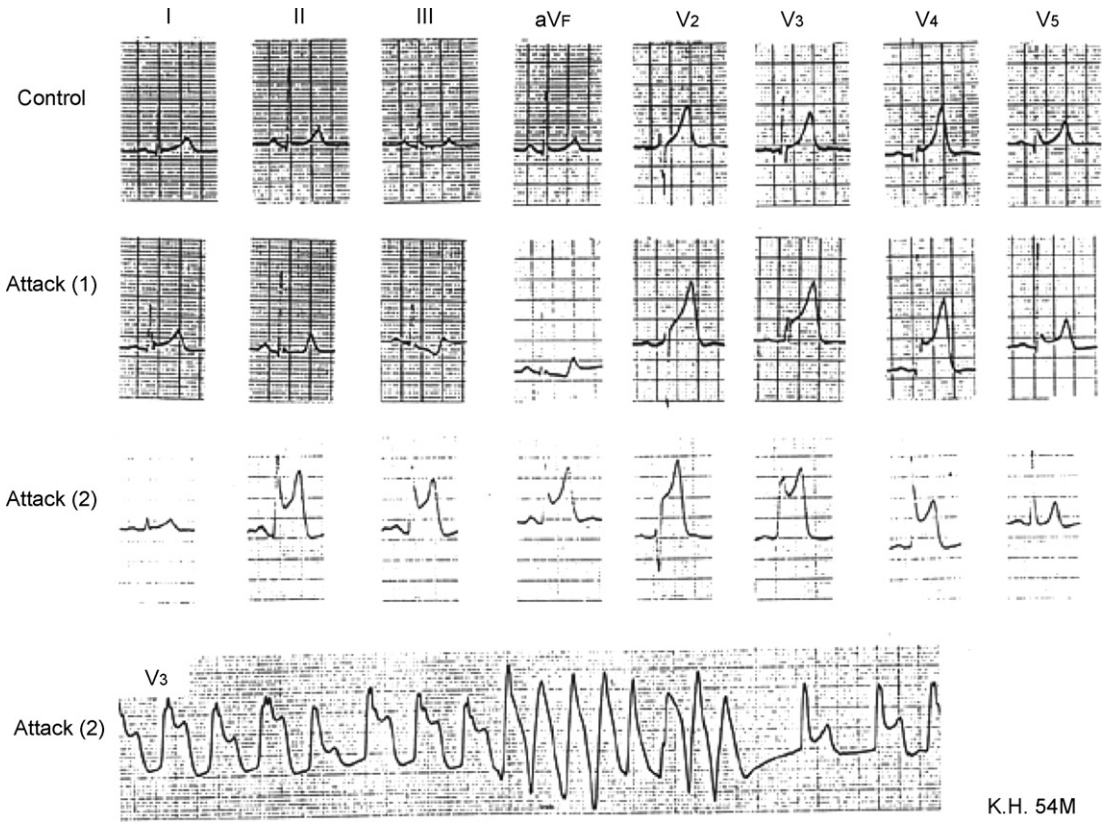

Figure 2 The ECG changes during the attacks of multi-vessel coronary spasm. During the spontaneous attack, ST segment elevation appeared in the chest leads (leads V_{2-5}) and ST segment depression in the inferior leads (leads II, II, and aVF). During the attack induced by exercise, ST segment elevation appeared in both the anterior and inferior leads (leads II, III, aVF, and V_{2-4}). Ventricular tachycardia also appeared during the attack as shown at the bottom.

not rare that ST segment elevation occurs in the anterior leads during one attack and in the inferior leads in another in the same patients. There are also patients in whom ST segment elevation occurs simultaneously both in the anterior and inferior leads (Fig. 2). These are patients with simultaneous multi-vessel coronary spasm and the attacks often result in ventricular tachycardia and/or fibrillation (Fig. 2) [17,18,35]. There is not much difference in the incidence of ST segment elevation between the anterior leads and inferior leads. The ECG may be unchanged at the beginning of an attack or when the attack is mild. Occasionally, pseudonormalization of a previously depressed ST segment may appear.

Coronary spasm may also cause ST segment depression instead of elevation in the leads that represent the distribution area of the spasm artery. The ST segment depression indicates less severe (non-transmural or sub endocardial) myocardial ischemia than does ST segment elevation, which represents transmural myocardial ischemia. The ST segment depression occurs: when (1) spasm of a major artery is less severe (subtotal and/or diffuse; (2) a major artery receiving collaterals is completely occluded; or (3) a small artery is completely occluded [23]. The direction and extent of ST segment change may vary from one episode to another and that ST segment elevation and depression can occur in the same patient or even in the same lead within minutes or hours [15].

Various forms of arrhythmia often appear during attacks of coronary spasm associated with ST segment elevation. These include ventricular arrhythmias such as ventricular premature contractions or ventricular tachycardia, bradyarrhythmias, atrioventricular block, and supraventricular arrhythmias. Ventricular fibrillation may also appear rarely.

Ventricular arrhythmias appear more often when ST segment elevation occurs in the anterior leads. Bradyarrhythmias appear more frequently when ST segment elevation occurs in the inferior leads. The high-degrees of bradyarrhythmias are often associated with hypotension, and sometimes with syncope. Lethal arrhythmias such as ventricular tachycardia, ventricular fibrillation and complete AV block may appear particularly during an attack of

multi-vessel spasm (Fig. 2) [17,18,35,36]. There is a good correlation between the incidence of arrhythmia and the degree of ST segment elevation).

Coronary angiographic and hemodynamic changes

Coronary spasm has been thought to occur at a site of organic stenosis of a major coronary artery [6]. However, coronary spasm appears in angiographically normal arteries as well as those with organic stenosis [18,36—38]. Of the 179 patients with coronary spasm at our institution [18], 126 (70%) had normal or near normal coronary arteries. Spasm may be diffuse or diffuse plus focal [39] and may even migrate from site to site. Spasm occurs not only at one large coronary artery but also at two or three large arteries separately or simultaneously in the same patients. Multi-vessel spasm was demonstrated in 93 (52%) of the patients (Fig. 3) and 77 (83%) of these patients had normal or near-normal coronary arteries [18].

The patients with multi-vessel coronary spasm have the following characteristics: (1) most of them have angiographically normal coronary arteries; (2) they are resistant to treatment and often require larger amounts of CCBs to suppress the attacks, which often recur on cessation of the drugs; (3) they are more likely to have lethal arrhythmias such as ventricular tachycardia or ventricular fibrillation and are more likely to suffer from sudden death [18].

There is no consistent increase in heart rate, blood pressure or dP/dt before the onset of ST segment elevation. The most typical and early hemodynamic pattern observed in the initial phase of coronary spasm is a reduction of positive and negative peak dP/dt and elevation of endo-diastolic pressure of the left ventricle [15]. These hemodynamic changes occur before the appearance of ST segment elevation. Subjective symptoms always follow ST segment and hemodynamic changes. Myocardial ischemia alters not only the contractile properties of the heart, but also impairs ventricular relaxation. The combination of incomplete myocardial relaxation and depressed contractility leads to elevated ventricular filling pressure. Thus, the appearance of wall motion abnormalities is the

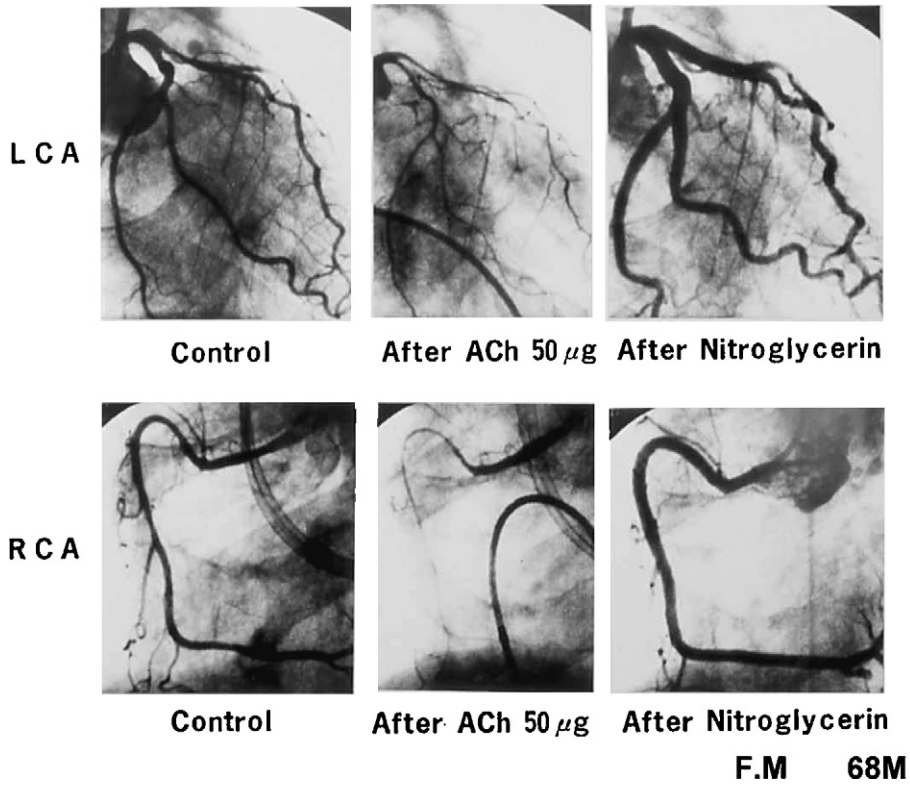

Figure 3 Coronary angiograms in a patient with multi-vessel coronary spasm. Injection of acetylcholine (ACh) into the left coronary artery (top left) and the right coronary artery (bottom left) induced spasm in each of the artery separately. Please note that spasm appeared in all three major arteries (the left anterior descending artery, left circumflex artery and right coronary artery). Spasm was reversed after intracoronary injection of isosorbide dinitrate (ISDN, top right and bottom right). There was no significant organic stenosis in the arteries.

most sensitive marker of myocardial ischemia and this can easily be detected by echocardiograms [27,40,41]. The appearance of wall motion abnormalities of the left ventricle during the attack has also been demonstrated by ventriculography [11].

Precipitating factors

There are several factors which may precipitate coronary spasm. These may be divided into physiological factors and pharmacological agents.

Coronary spasm occurs most often at rest, particularly from midnight to early morning. However, in the early morning, even mild exertion may induce coronary spasm [18]. Physical and/or mental stress, particularly the latter, for several weeks or months may precipitate coronary spasm, particularly at rest [18,42]. Exposure to cold [43], Valsalva maneuver and hyperventilation [40,44—46] may also precipitate coronary spasm. Magnesium deficiency is also associated with coronary spasm [46,47]. Coronary spasm itself often induces coronary spasm, thus making vicious circle [18].

Pharmacological agents include catecholamines (epinephrine, norepinephrine, isoproterenol, dopamine, dobutamine) [10,48,49] parasympathomimetic agents (acetylcholine, methacholine, pilocarpine) [33,34], anticholinesterase agents (neostigmine, etc.) [50], ergonovine [27,51—53], serotonin [54], histamine [55], beta-adrenergic blocking agents [34,56], withdrawal from chronic exposure to nitroglycerin [57], cocaine [58], smoking [59,60], and alcohol [61,62]. Particularly to be noted in the daily life is alcohol ingestion. Heavy drinking after stressful situations often induces coronary spasm, usually not immediately but after several hours when blood levels of alcohol may have disappeared.

These factors or agents may induce coronary spasm singly. However, when several of these factors are combined, the possibility of occurrence of coronary spasm is high [18].

Coronary spasm and coronary thrombosis

Coronary thrombosis is now known to be the cause of acute coronary syndromes including acute myocardial infarction, unstable angina and ischemic sudden death [63—65]. Coronary spasm may also be involved in the pathogenesis of acute coronary syndromes [15—18]. Plasma levels of fibrinopeptide A, a marker of thrombin generation, are increased after attacks of coronary spasm [66,67] and there is a circadian variation in the levels in parallel with that of the attacks of coronary spasm (Fig. 4) [67]. Plasma levels of plasminogen activator inhibitor 1 also show a circadian variation in parallel with that of the attacks of coronary spasm [68]. Platelets also are activated after attacks of coronary spasm but not after those of stable effort angina [69]. These findings indicate that coronary spasm can trigger coronary thrombosis and may play an important role in the pathogenesis of acute coronary syndromes. Indeed, coronary thrombosis has been demonstrated by angioscopy in patients with variant angina [70].

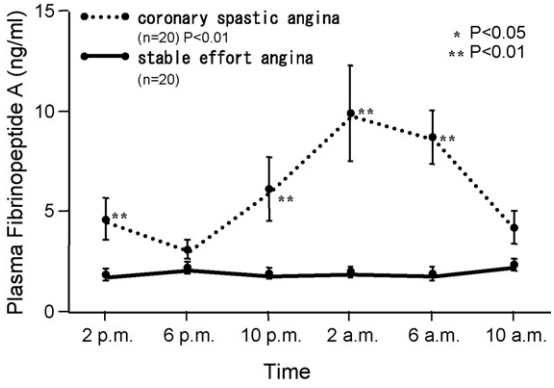

Figure 4 Circadian variation of plasma levels of fibribopeptide A in patients with variant angina and those with stable exertional angina. Plasma levels of fibrinopeptide A are increased and show marked circadian variation with a peak appearing from midnight to early morning in patients with variant angina. In contrast, the levels are not increased and do not show a circadian variation in patients with stable exertional angina. $^{*}p < 0.05$, $^{**}p < 0.01$, difference of the levels between patients with variant angina and those with stable effort angina at each sampling time. (From Ogawa et al. [67].)

Diagnosis of coronary spasm

The diagnosis of coronary spasm is not necessarily easy. In contrast to stable effort angina, which is reproducibly induced by exercise testing, coronary spastic angina is usually not induced by exercise, particularly in the afternoon and occurs usually at rest, particularly from midnight to early morning [18,20]. The attack is transient, often lasts only a few seconds, and is unpredictable. Thus, ambulatory monitoring of ECG is extremely important to detect the attack [13,18]. However, even with ambulatory monitoring of ECG, the attack may not appear during the monitoring periods, especially when the attack is not frequent. Moreover, ECG does not provide a direct evidence of coronary spasm.

It is for these reasons that provocation tests for coronary spasm have been developed. These afford an opportunity to induce an episode of coronary

spasm at a chosen time, when the patient is adequately monitored in a laboratory well equipped for appropriate documentation of this phenomenon. Several provocative tests for coronary spasm have been developed. Of these ACh and ergonovine tests are most often used [24,27,33,36,51—53]. Coronary arteries involved in spasm are super-sensitive to ACh and ergonovine. Ergonovine is an ergot alkaloid that stimulates both alpha-adrenergic and serotonergic receptors and the intracoronary injection of doses ranging from 10 to 80 μg in total are used at most institutions. However, spasm involving both the right and left coronary artery may not be demonstrated with this route of administration, because nitroglycerin must be administered to relieve spasm after its demonstration in the infused artery and spasm cannot be provoked in the other remaining artery.

The intracoronary injection of ACh in doses of 10—100 μg is used for provocation of coronary spasm [33,36]. Duration of the action of injected ACh is very short and the induced spasm usually disappears spontaneously within 2—3 min without the need of nitrates administration. Thus, this method allows provocation of spasm separately in the left and right coronary arteries and is useful to demonstrate multi-vessel spasm (Fig. 3) [36]. The intracoronary injection of ACh into the right coronary artery often induces bradyarrhythmias, particularly and insertion of a standby temporal pacemaker is obligatory.

Coronary spasm can also be induced by hyperventilation, which causes respiratory alkalosis [44—46]. The sensitivity of this test is 65% and the specificity is 100% [45]. It may thus be safely said that coronary spasm exists when an ischemic attack is induced by hyperventilation. However, there is a danger of inducing simultaneous multi-vessel spasm with this method of provocation. Histamine [55], epinephrine [10], dopamine [48], dobutamine [49], serotonin [54], exercise in the morning [20,31], and the cold pressor test [43] can all induce coronary spasm, but all of these tests is less sensitive than ergonovine or ACh.

There are daily, monthly and yearly as well as circadian variations in the attack of coronary spasm [13,18] and the sensitivity of the tests depends on the disease activity of the time. Thus, a false negative test may often be obtained in patients with established coronary spasm when the disease activity is low.

Although the provocation tests for coronary spasm by ACh or ergonovine are usually safe, a number of complications may occur. These include various arrhythmias, hypertension, hypotension, abdominal cramps, nausea, vomiting, and other non-specific complications. Rarely, serious complications such as ventricular fibrillation, myocardial infarction, or even death may occur [17,35]. Therefore, the tests should be conducted only by qualified physicians and in a setting where appropriate resuscitation and other measures can promptly be done.

Strictly speaking, the diagnosis of coronary spasm must be made on the basis of coronary angiographic findings during the attack. However, it is not possible to perform coronary angiography during the attack in every patient and there is no need for this.

Angina pectoris that is relieved promptly by sublingual administration of nitroglycerin may be diagnosed as coronary spastic angina even without angiographic evidence, if one of the following characteristics is found.

These characteristics are:

1. The attack occurs at rest, particularly from midnight to early morning.
2. There is marked circadian variation of exercise capacity, the attack easily induced by exercise in the morning but not by even vigorous exercise in the afternoon.
3. The attack is associated with ST segment elevation on the ECG.
4. The attack is induced by hyperventilation.
5. The attack is suppressed by CCBs, but not by beta-blockers.

Risk factors for coronary spasm

Coronary spasm is mostly a disease of middle- and old-aged men and post-menopausal women [18,60]. The disease rarely occurs in the young men and pre-menopausal women. Age, LDL-cholesterol, hypertension, diabetes mellitus, and smoking are all known to be a significant risk factor for stable effort angina or coronary atherosclerosis [2,3,71]. On the other hand, age, smoking, high sensitivity C-reactive protein (hsCRP), and remnant lipoproteins are a significant risk factor for coronary spasm [59,60,72—76]. The incidence of cigarette smoking is significantly higher among patients with coronary spastic angina than among those with stable effort angina [59,60]. These facts suggest that the pathogenesis of coronary spasm may differ from that of coronary atherosclerosis, which is closely related to abnormalities of LDL-cholesterol metabolism. Cigarette smoking is thus, a crucial risk factor for coronary spasm and highlights the fact that the high incidence of cigarette smoking may be one of the factors for the high prevalence of coronary spasm in the Japanese.

In addition to cigarette smoking and other environmental factors, genetic factors may also be involved in the pathogenesis of coronary spasm as will be described in the next section.

Pathogenesis of coronary spasm

The exact mechanisms by which coronary spasm occurs remain to be elucidated.

The endothelial dysfunction and oxidative stress

The vascular endothelium was once thought as a simple passive barrier between circulating blood and surrounding tissues. However, recent evidence indicates that it is a multifunctional organ the integrity of which is essential to normal vascular physiology, and its dysfunction can be critical for the pathogenesis of vascular disease [77].

ACh causes vasodilation by releasing nitric oxide (NO) from the endothelium and in humans, intracoronary infusion of ACh induces coronary vasodilation in young healthy subjects, whereas it causes vasoconstriction in patients with coronary atherosclerosis [77—79]. Coronary arteries in patients with coronary spastic angina are highly sensitive to the vasoconstrictor effect of intracoronary injection of ACh, resulting in spasm [33,36]. Intracoronary injection of ACh is thus used as a provocative test for coronary spasm [33,36]. Coronary spasm can also be induced by ergonovine, serotonin, or histamine, all of which are endothelium-dependent vasodilators by releasing NO.

On the other hand, nitrates including nitroglycerin, are endothelium-independent vasodilators and cause vasodilation by being converted into NO in vivo, which stimulates soluble guanylate cyclase, resulting in increased cyclic GMP [79,80]. The coronary arteries in patients with coronary spasm are highly sensitive to the vasodilator effect of nitrates [39,81]. It is thus possible that super-sensitivity of spasm arteries to nitroglycerin is due to the deficiency of endogenous NO activity in these arteries [80—86].

NO is synthesized from L-arginine by way of NO synthase (NOS) and NO synthesis is specifically blocked by L-monomethyl-arginine (L-NMMA) [79,80]. The coronary artery diameter decreases in response to intracoronary infusion of L-NMMA in the control subjects, whereas it does not change significantly in patients with coronary spasm [84]. These observations indicate that NO is released in the basal state and is involved in the regulation of basal vascular tone in normal humans and that NO activity is deficient in the coronary artery in patients with coronary spasm. There is a significant positive correlation between the response to L-NMMA and that to nitroglycerin, i.e. the smaller the response to L-NMMA, the larger the response to nitroglycerin, indicating that the super-sensitivity to nitroglycerin is related to the deficiency of endogenous NO activity in the coronary artery in patients with coronary spasm [81,85]. NO-mediated flow dependent dilation is also impaired in patients with coronary spasm [86].

NO is also known to suppress the production of endothelin 1 and angiotensin II which are potent vasoconstrictors and proliferators of vascular smooth muscle and deficiency of NO may enhance the synthesis of these potent vasoconstrictors [87,88]. Indeed, there are intimal thickening and hyperplasia in the coronary arteries involved in spasm [89,90].

The deficiency of NO activity may be due to either a decrease in production or an increase in degradation of NO before it can produce its effect on smooth muscle, or both.

Polymorphisms of eNOS gene

Endothelial NO is synthesized by endothelial NOS (e-NOS) which is constitutively expressed in the endothelium [79]. We have recently found the polymorphisms of Glu298Asp in the exon 7 and $T^{-786}C$ in the 5′-flanking region of the e-NOS gene and have shown that these polymorphisms are significantly associated with coronary spasm [91,92]. These findings strongly suggest that the e-NOS gene polymorphisms compromise the endothelial NO production and predispose the patients with these alleles to coronary spasm. Further more, not only coronary arteries but also the peripheral arteries are deficient in NO activity in patients with coronary spasm [93—95], suggesting that deficiency of NO activity may occur not only in the coronary arteries but also in the entire vascular system in these patients. However, NO polymorphisms are found in only one-third of the patients and thus other genes or factors may also be involved in the pathogenesis of coronary spasm.

Oxidative stress

Oxygen free radicals degrade NO and cause vasoconstriction [79,80]. Both basal and ACh-induced endothelial dysfunction in coronary arteries are improved by intracoronary injection of antioxidants such as vitamin C or glutathione, in patients with

coronary spasm [96—98]. Plasma levels of vitamin E, another antioxidant, are low and those of thioredoxin, a marker of oxygen species, are high in patients with coronary spastic angina [99—101]. Coronary spasm rarely occurs in pre-menopausal women except those who smoke [18] and estrogens have antioxidant activity and suppress the attack in post-menopausal women with coronary spastic angina [102]. Interestingly, there is a menstrual cyclic variation of the attack in association with changes of plasma levels of estrogen in pre-menopausal women with coronary spastic angina [103]. Coronary spasm is significantly associated also with polymorphism of the gene for paraoxonase I, which has an antioxidant effect [104] and the plasma level of thioredoxin, a marker of oxidative stress, is increased in patients with coronary spasm [101]. Coronary spasm is more prevalent among smokers than in non-smokers [59,60] and endothelial function is impaired both in coronary and brachial arteries and is improved by vitamin C infusion in smokers [105,106]. Cigarette smoke extract markedly suppresses the ACh induced endothelium-dependent relaxation and the suppression is prevented by antioxidants in isolated arteries [107,108]. All of these findings indicate that smoking degrades NO by way of oxygen radicals.

Multiple regression analysis reveals that smoking as well as e-NOS and paraoxonase I polymorphisms is a highly significant risk factor for coronary spasm [59,60,91,92,104]. Increased NO degradation by oxygen radicals or both may play an important role in the pathogenesis of coronary spasm.

However, there are still some controversies regarding endothelial dysfunction in patients with coronary spasm and some workers report that there is no endothelial NO deficiency and dysfunction in patients with coronary spasm [109].

Chronic low-grade Inflammation

Shimokawa and his coworkers [110] has developed the swine mode of coronary spasm by chronically applying IL-β to the coronary artery of the animal. Adhesion-molecule such as P-selection is increased in the coronary artery involved in spasm [111]. Plasma levels of hsCRP, a sensitive marker of inflammation, are also increased in patients with coronary spasm as compared with those of non-coronary spasm patients [72,73]. Chronic smoking, a number one risk factor for coronary spasm, is associated with chronic low-grade inflammation [112]. These findings indicate that chronic low-grade inflammation plays an important role in the pathogenesis of coronary spasm.

Hypercontractility of coronary smooth muscle

Contraction and relaxation of vascular smooth muscle are regulated by myosin light chain (MLC) kinase (MLCK) and myosin light chain phosphatase (MLCP) through phosphorylation and dephosphorylation of MLC [113]. The classical pathway through which contracting stimuli induce MLC phosphorylation is an increase of the free intracellular Ca^{2+} concentration. The complex of Ca^{2+} and calmodulin then activates MLCK, leading to increased MLC phosphorylation [114]. Coronary spasm may be regarded as hyper-contraction of coronary smooth muscle triggered by an increase of intracellular Ca^{2+} and CCBs, which block the entry of Ca^{2+} into cells, are highly effective in suppressing coronary spasm [14,31,53].

It has recently shown that Ca^{2+}-independent regulation also occurs through the inhibition of MLCP and that the level of MLC phosphorylation is determined by a balance between MLC phosphorylation by MLCK and dephosphorylation by MLCP [115—119]. Accumulating evidence indicates that small GTPase RhoA and its downstream effector, ROCK/Rho-kinase, inhibit MLCP, leading to augmentation of MLC phosphorylation and Ca^{2+} sensitization in response to vasoconstrictor stimuli. Studies showed that RhoA/ROCK activity is enhanced in the rat arteries with hypertension and vasospasm [115—119].

Shimokawa and colleagues [110,119] have developed swine models of coronary spasm and have shown that ROCK activity is enhanced in smooth muscles of the coronary artery involved in spasm in these animals. They also showed that specific inhibitors of ROCK relieved coronary spasm in humans [120]. Statins, which block the RhoA/ROCK pathway [121], also suppress coronary spasm [122]. It is thus quite probable that enhanced Ca^{2+} sensitization via enhanced Rho/ROCK activity as well as increased intracellular Ca^{2+} may play a critical role in the genesis of coronary spasm. The precise mechanisms by which the activity of Rho/ROCK pathway is increased remain to be elucidated. Recent studies show that cGMP-dependent protein kinase inhibits RhoA-induced Ca^{2+} sensitization of contraction in vascular smooth muscle [123,124]. Decreased endothelial NO activity has been shown to increase Rho/ROCK activity in the coronary arteries [119,124—127].

These new findings thus, connect the activity of RhoA/ROCK to endothelial NO and are in agreement with the clinical observations that spasm arteries are super-sensitive to both vasoconstrictor agonists and nitrates [39,83]. Enhanced phospholipase C activity may also be involved in coronary spasm

through enhanced contraction of vascular smooth muscle cells [128,129].

Magnesium

Magnesium is said to be an endogenous calcium antagonist, and infusion of magnesium suppresses hyperventilation-induced attack in patients with coronary spasm [46]. There is magnesium deficiency in 45% of the patients with variant angina and magnesium deficiency may be related to the genesis of coronary spasm in some of the patients [47,62].

Treatment

Acute attack

The attack of coronary spasm can usually be promptly relieved by the sublingual administration or oral spray of nitroglycerin or isosorbide dinitrate (ISDN). In refractory spasm, intravenous or intracoronary injection of the drugs may be necessary. Nitrates are converted in vivo to NO [79,80] and the administration of nitrates may be regarded to be a replacement therapy for deficiency of endogenous endothelial NO in patients with coronary spasm. Indeed, coronary arteries involved in spasm are highly sensitive to nitrates [39,82,83].

Prevention of coronary spasm

Though the sublingual administration of nitroglycerin or ISDN rapidly relieves the attack, the duration of actions of these drugs is short and less than an hour. For the prevention of attack, long-acting drugs are needed and CCBs are very effective for this purpose. CCBs inhibit inflow of Ca^{2+} into the smooth muscle cell through voltage-sensitive Ca^{2+} channels, thereby causing vasodilation [18]. The efficacy of these drugs against the attack of coronary spasm is often dramatic.

It is to be noted that timing of the administration of these drugs is important because the attacks of coronary spasm usually occur from midnight to early morning. These drugs should then be given before going to bed in the night. Doses should also be gradually increased in the individual patient, paying due attention to the side effects. In patients with multi-vessel coronary spasm, CCBs should not be withdrawn even if the symptomatic attacks occur rarely because silent myocardial ischemia often occurs [18] and there is a danger of sudden death from lethal arrhythmias in these patients [17,18,35].

Long-acting nitrates (oral or transdermal) are also useful for preventing coronary spasm. However, the potency of nitrates is reduced by nitrate tolerance [130—132]. In the clinical practice, intermittent therapy with a nitrate-free window of at least 8 h has been recommended. Nicorandil, a nitrate and K-channel activator, is also effective in suppressing coronary spasm [133].

For refractory coronary spasm, larger doses and combination of different classes of CCBs, together with nitrates may be necessary. In addition, magnesium [46], statins [122], antioxidants such as vitamin C and E, ACE-inhibitors, ARBs, anti-inflammatory agents as aspirin, or estrogen in post-menopausal women, may also have beneficial effects on coronary spasm [94,96—100]. Because contraction of vascular smooth muscle is under the dual control of intracellular Ca^{2+} and RhoA/ROCK activity, inhibitors of RhoA/ ROCK pathway may also prove useful for the treatment and prevention of coronary spasm in the future [119—122]. There are, however, some patients with coronary spasm whose attacks are refractory to and cannot be completely controlled even by these medications [17,18].

General measures

Because patients with coronary spasm have endothelial dysfunction [82,84], the elimination or control of the factors which may impair endothelial function or increase oxidative stress, particularly smoking, is very important. Thus, elimination or control of all the risk factors for coronary atherosclerosis [2,71], is also necessary in the case of coronary spasm. Drinking alcohol may induce attacks of coronary spasm usually not immediately but several hours after drinking in susceptible patients [61]. Strenuous exercise in the daytime may also induce the attacks in the midnight or in the early morning [18]. Emotional stress is a very important substratum for the attacks and anger or fear may induce the attacks. The attacks often disappear without any medications by hospitalization alone probably because the patients are shielded from social stress. Magnesium, which is an endogenous calcium antagonist, must be supplied in the patients deficient in this element [46,47,62]. Drugs that may induce coronary spasm must be avoided. Such drugs include catecholamines, muscarinic agonists, ergot alkaloids, prostaglandins, alcohol and propranolol. In post-menopausal women with refractory coronary spasm, estrogen replacement therapy may be useful [102].

Prognosis

The natural history of variant angina or coronary spasm is generally characterized by periods of recurrent attacks lasting for 3—6 months alternating with the periods in which the patient is asymptomatic. Long-term survival is usually good so long as patients are on CCBs and avoid smoking [134—137].

The predictors for prognosis are the number of coronary artery with significant organic stenosis, medication of CCBs and multi-vessel coronary spasm [135]. In many patients, the attack tends to diminish with time after a few months of recurrent attacks. There is still no definite answer as to how long the administration of CCBs should be continued. It is our opinion that patients with multivessel patients should be on CCBs indefinitely because these patients often have lethal arrhythmias (ventricular tachycardia, ventricular fibrillation, high-degree AV block, or asystole) and are at high risk of sudden death [17,18,35,36], even though they may be asymptomatic. They also require high doses of CCBs to suppress the attacks. They should be closely watched and followed by a knowledgeable physician.

Clinical perspective

The incidence of coronary spasm seems to be decreasing throughout the world, including Japan, probably because of the wide use of medications such as CCBs, statins, ACE-inhibitors, ARBs, and aspirin for cardiovascular disease [29]. The decreasing of smoking habit also may have contributed to the reduced incidence of coronary spasm. Many cardiologists, particularly the young, are now much interested in PCI and pay less attention to coronary spasm. Multi-detector computed tomography scan are increasingly applied for evaluation of coronary heart disease in place of coronary angiography. Under these circumstances, it is possible that there will be less and less cardiologists who are familiar with coronary spasm in the future. Because there are not a few patients with coronary spasm who are refractory to the conventional medications and who may suffer from lethal arrhythmias or sudden death, and because PCI is not the right answer to the problem of coronary spasm [138], it is quite important for every clinician to be alert to the presence of coronary spasm, which may be silent and lethal. Coronary spasm is a hypercontraction of coronary smooth muscle triggered by an increase of intracellular Ca^{2+} in the presence of an increased Ca^{2+} sensitivity. It has been shown that RhoA/ROCK pathway is involved in Ca^{2+} sensitivity and that the reduced endothelial NO activity results in increased Ca^{2+} sensitivity through enhanced RhoA/ROCK pathway. Accordingly, it is possible that, RhoA/ROCK pathway blockers including statins or fasudil may prove to be useful in addition to CCBs for the treatment of coronary spasm [119,121]. Further studies are required to elucidate the pathogenesis of this intriguing disease of coronary artery and develop more effective, disease-modifying, and long-lasting treatments for it.

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